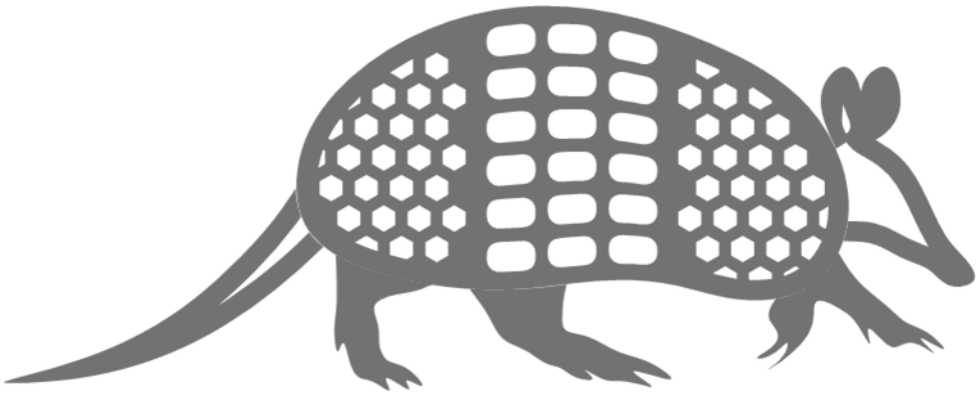
Aalto University
School of Arts, Design
and Architecture

Affordable Bionic Semi-Patient-Specific Cranial Implants for Low- and Middle-Income Countries and Conflict Zones

Yulia Kulkova



THESIS

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ABSTRACT

Background: Expensive-to-treat conditions in low-income and low-to-middle-income countries (LMICs) are generally unmitigated, as the world's health aid is mainly focused on transmissible diseases whose treatment costs are low. Cranioplasty is a neurosurgical procedure to reconstruct cranial defects. In LMICs, the most common reconstruction material is the autologous bone, although the complication rate is high. Other treatment modalities are often too expensive. Therefore, an affordable solution is needed to raise a standard for cranial reconstructions in emergency cases, conflict zones, developing countries and/or rural areas.

Objective: The objectives of this thesis are to formulate a design of a set for the creation of modular cranial semi-patient specific implant (semi-PSI) and demonstrate its clinical potential as an affordable solution for on-the-spot cranial reconstructions in LMICs and conflict zones.

Materials and Methods: As the main approach, this thesis project employs a Concurrent Engineering. The thesis is combining empirical and experimental research in every iteration phase of the workflow.

Results: In this thesis, a design concept of a set for the creation of a modular cranial semi-PSI is formulated together with the group of prominent Finnish neurosurgeons. This concept is based on a set of stackable geometrical modules, which can be clicked together akin to LEGO and placed in different configurations to match the shape of various cranial defects. In mechanical testing, the prototypes of the modular cranial semi-PSI did not disintegrate and were capable of mechanical performance in line with the Food and Drug Administration requirements in the United States. Clinical potential is successfully demonstrated by applying the prototypes of the modular cranial semi-PSI to artificial anonymized skulls produced by additive manufacturing.

Keywords: Cranioplasty; Biomaterials; Additive Manufacturing; Industrial Design; Medical Implants, Concurrent Engineering, Conflict Zone, Low-to-middle-income countries

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1. Introduction

1.1 Context Overview

Five billion people have no access to reliable and affordable surgical care. Low-income and low-to-middle-income countries (LMICs) have the worst access, accounting for 80% of deaths from surgically treated conditions, although they contribute only about 26% of the surgical procedures carried out worldwide (Akenroye et al., 2013). Rural settings have especially limited access to adequate treatment; surgical care is often found only in urban areas, where territory medical centres exist. Nevertheless, the lack of trained physicians and proper equipment often leads to the administration of medical help by poorly trained personnel or even nonmedical workers. For instance, Nigeria's neurosurgeon–population ratio is one per 4 000 000, and the remaining African countries are even worse off because the world's health aid is mainly focused on transmissible diseases whose treatment costs are low (Rabiu & Komolafe, 2016; Meara et al., 2016). Moreover, factors like extreme poverty, politics, environmental degradation, social and economic imbalances, discrimination and other boundaries between countries, groups and people are always at greater risk of forming the core of a conflict. In fact, most LMICs may be considered prone to conflict. Eight out of ten of the world's poorest countries are experiencing or have recently endured large-scale regional conflict and violence (Bonfield et al., 2014; Giannou C & Baldan M, 2020). As an immigrant originating from a developing middle-income country and a member of a global charity organisation Soroptimist International Europe for the last 15 years, I have observed a lot of struggles with financial resources and infrastructure, preventing even primary healthcare in LMICs. In 21st-century, medicine still experiences a paradoxical imbalance between advanced technologies in some fields and complete lack of progress in others. Humanity fosters high-tech robotics and utilisation of modern materials; in contrast, when it comes to the medical treatment of human beings, the methods are sometimes astonishingly primitive, especially in LMICs (Rubiano et al., 2015). Currently, new technologies offer a unique opportunity not only to narrow the

gap between the Western world and developing nations but also to boost growth, as there are real prospects for developing nations to become more self-sufficient. Hence, it is time to act by bringing about life-changing solutions, which are still simple and affordable.

1.2 Objectives

The objectives of this thesis are to formulate a design of a set for the creation of modular cranial semi-patient specific implant (semi-PSI) and demonstrate its clinical potential as an affordable implant solution for on-the-spot cranial reconstructions in LMICs and conflict zones.

1.3 Thesis Structure

This thesis is structured in six chapters. The first chapter is describing the motivation behind this project as well as project objectives. The second chapter is dedicated to the topic overview based on scientific literature and potential development direction of the project. The third chapter is defining methodological approach employed for this thesis. Chapter four is design in practice, where the actual design process is presented. Chapter five discusses the theoretical and practical outcome of the project and its limitations as well as suggestions for further development. Chapter six is dedicated to conclusions. The thesis structure also includes the list of references and the description of figures sources.

2. Background

2.1 Cranioplasty: Review of the History

Cranioplasty is one of the oldest surgical procedures. It is used to reconstruct cranial defects. Cranioplasty aim is to control cerebrospinal fluid alterations, blood flow, and

the metabolic demands of the brain to maintain aesthetics and social performances as well as to relieve psychological drawbacks (Mah & Kass, 2016). Complex anatomy of the bones, vast diversity of the defect shapes and the vicinity of a vital structure present significant challenges in the reconstruction of cranial defects. Typically, cranial defects are due to trauma, tumour resection, infection, or congenital malformations (see *Figure 1*). Brain decompression after infarction or intracranial haemorrhages requires the removal of large skull bone segments.

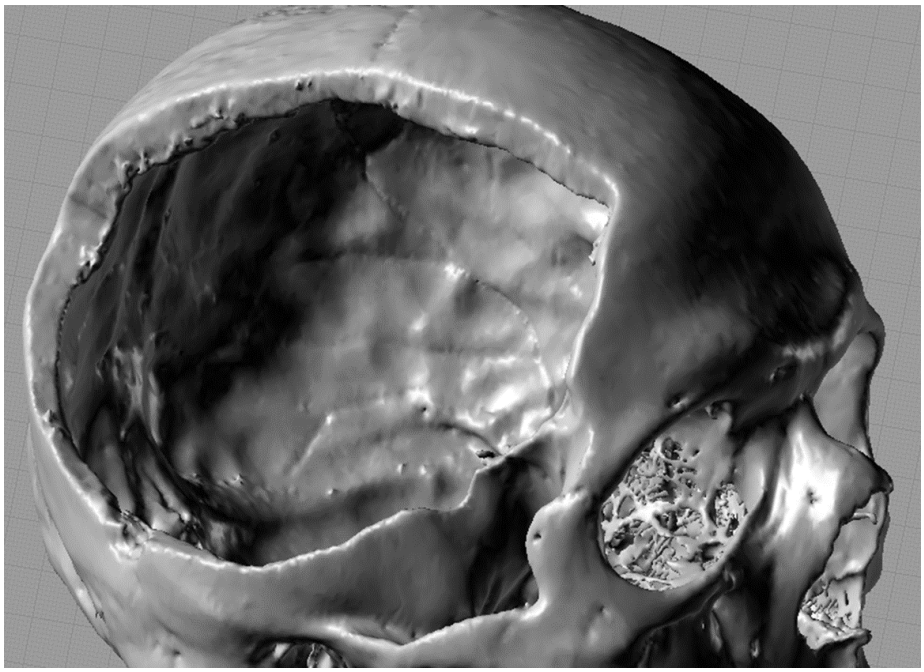

Figure 1. Example of bone defect created during cranioplasty procedure.

The reconstruction of these defects involves consideration of both functional and aesthetic aspects (Aydin et al., 2011; Eghwrudjakpor & Allison, 2010). Cranioplasty is a challenging procedure in terms of brain protection. While a cranial implant is not a load-bearing structure, it must withstand significant pulsation forces, since implant breakage due to impact is a common complication (Jaberi et al., 2013a). The first cranioplasty procedures were performed back to 7000 bc by Incan surgeons using cranial plates made of precious materials (Sanan & Haines, 1997). Despite that, the procedure was first documented by Italian anatomist Fallopius only in the 16th century (A. M. Shah et al., 2014). Later, in 1668, Job van Meekeren, a Dutch surgeon recorded the first bone graft procedure for cranial reconstruction (Sanan & Haines,

1997). This procedure is based on removal of a bone flap (typically from cranium, iliac crest or rib) with its subsequent salvage with the goal to be placed back into the bone defect in a second surgical procedure. However, due to the loss of blood supply in the bone flap, there is a significant risk of bone flap resorption resulting in a need for removal and replacement (see *Figure 2*). Moreover, there is a limited availability of autologous bone and patient exposure to donor-site morbidity involved. Nevertheless, despite the high complication rate, this reconstruction procedure using autologous bone is still common nowadays especially in developing countries.

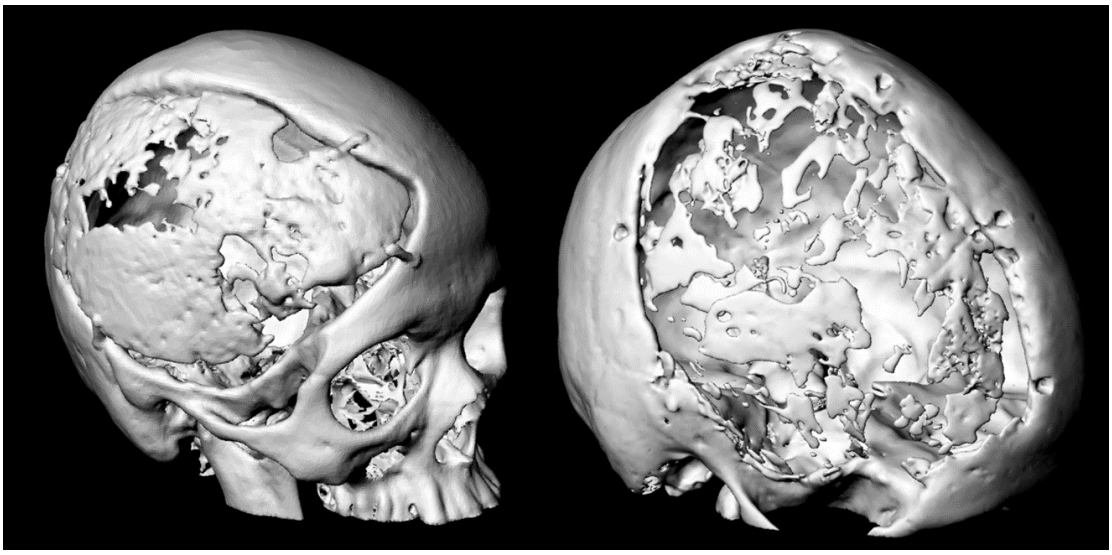

Figure 2. Example of autologous bone flap resorption.

Further, in the 19th century, the experiments with bone grafting continued and culminated in gaining high popularity by early 20th century. The next substantial progress in this area was made during the World War I and II due to the high volume of cranial injuries. At this time, novel plastic biomaterial Polymethylmethacrylate (PMMA), an intraoperatively moulded conventional transparent thermoplastic, was introduced and partially replaced highly prevalent metals. PMMA is still widely used despite the severe obvious drawbacks (Sanan & Haines, 1997) which are described in detail in section *2.3 Low-to-middle-income Countries: Challenges in Cranioplasty* of this thesis.

During the past decades, in Western societies, neurosurgical reconstruction of cranial defects has transformed and undergone a significant change. Based on

the current knowledge, recently it has been suggested that an initial synthetic implant should be considered for cranial reconstructions, especially in younger patients (Iaccarino et al., 2021). The overall workflow during the design stage, implant material choice and fabrication technologies has evolved and became more tailored. Besides standard cranial implants, patient-specific ones are now gradually taking the lead. Personalized medicine intended to cover specific cases where commercially available products or alternative remedies are inadequate for matching the indications and requirements of a particular patient. The increasing demand for cranial patient-specific implants (PSIs) has also advanced due to the reduced surgical time, post-surgical care requirements and smooth rehabilitation process. Currently, cranial PSIs are mostly produced by additive manufacturing (AM) techniques from various biomaterials.

2.2 State-of-the-art. Trends and Future Prospective in Cranioplasty

In the cases involving an implant, an artificial medical device, created by an implant manufacturer is employed. Although there is currently no cranial implant, which satisfies all clinical requirements, developed countries have a wide choice of material and manufacturing techniques to advance this issue through research and innovation.

Cranial implants are either standard or PSIs. Typically, implant manufacturers offer standard implants of pre-defined shapes and sizes, these are viable solutions mainly for smaller defects. However, since defects often have irregular shapes, sometimes with overtly uneven edges, standard implants do not provide sufficient solutions in many clinical cases. In these cases, there is a need for PSIs, unique devices created specifically for each patient. From design perspective, standard implants are always of a "onlay" type, in turn PSIs could be of "inlay" or "onlay" types. The "inlay" types (see *Figure 3B*) fill the defect area with the implant and require high precision in planning. In turn, the "onlay" types (see *Figure 3C*) cover the defect area and the bone adjacent to the defect. As a result, the "onlay" type of implant does not require

as high accuracy in respect to the shape of the defect, as the "inlay" counterparts. The downside is the fact that the "onlay" implants protrude to a certain height above the surface of the bone. However, when the thickness of "onlay" implants over the bone surface is in the range of 1 – 1.5 mm, no significant aesthetical issues typically occur. Consequently, the "onlay" implants provide an attractive route for the optimal solution.

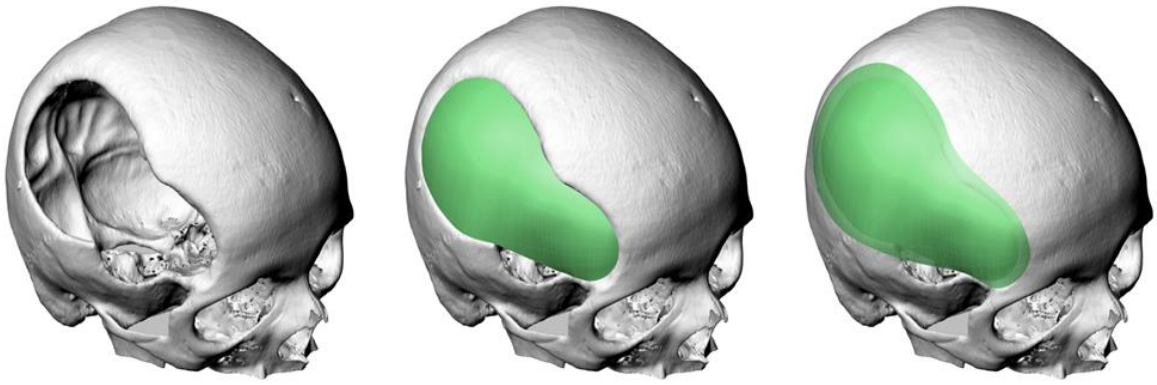

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Figure 3. An example of a typical cranial bone defect: A. Polygonal model of the skull reconstructed from computer tomography images; B. Cranioplasty with an" inlay" type of implant; C. Cranioplasty with an "onlay" type of implant.

There are various synthetic materials used to manufacture cranial implants, such as metals (Titanium alloys), polymers (Poly(methyl methacrylate) (PMMA), Polyether ether ketone (PEEK)), ceramics (Hydroxyapatites and calcium phosphates) as well as composite and hybrid combinations of materials. Despite a long-lasting debate, no agreement has been reported in the literature regarding what cranioplasty implant material is best. In fact, most of the clinically used biomaterials are biologically inert and develop either minimal tissue response or even provoke adverse tissue reactions. For instance, some polymers used for cranial reconstructions leach residual monomers, which are harmful in the human physiologic conditions (Arossi et al., 2010; Tuusa et al., 2005). In addition, all biomaterials to some extend are prone to bacterial colonization. Therefore, typical

complications involve infection, fibrous tissue capsulation and disintegration of the implants (Kurland et al., 2015).

There are several manufacturing technologies of cranial implants: standard ones and PSIs. These include milling, injection moulding and AM. However, according to the report, "Societal transformation 2018–2037 100 anticipated radical technologies, 20 regimes, case Finland" prepared by the Committee for the Future, Parliament of Finland (Linturi R. and Kuusi O., 2019), AM is one of the radical technologies expected to shape our lives in the nearest future. AM has a high potential for fabrication of cranial implants especially it is widely used for fabrication of cranial PSIs, as AM meets the high demands for mechanical and structural stability, biocompatibility, and aesthetics. Moreover, the present industrial centralised manufacturing controlled by large enterprises is changing towards decentralised local manufacturing based on small production volumes and special needs. AM has been well-known already in the 1990s. However, rapid growth started in the 2010s chiefly due to the expiration of the original patents of the anaemic forerunner companies. Regardless of the technological progress, today, the whole chain of cranial PSI creation is rather complicated and time-consuming (see *Figure 4*).

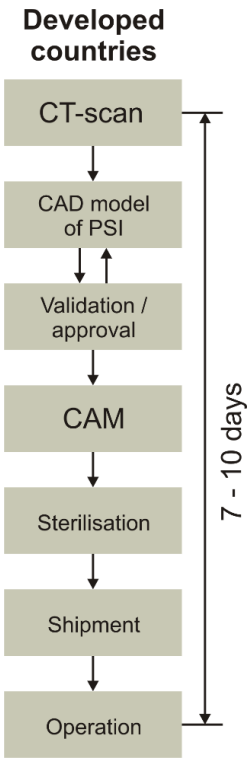

Figure 4. Routes of cranial reconstruction in developed countries.

Engineering solutions, such as computer-aided design (CAD), involve the application of computer systems to analyse, optimise and design implants for the reconstruction of cranial defects. In turn, computer-aided manufacturing (CAM) allows the fabrication of the implants (Edward H. Smith, 1994). In the late 1980s, the combination of CAD/CAM and three-dimensional (3D) imaging data obtained by computed tomography (CT) allowed the fabrication of the medical implants. Consequently, due to excellent representation of complex anatomical features of the human bone, high fitting accuracy of the implants and reduced operation time, the combination of the CAD/CAM and CT technologies became industry standard for the planning and implementation of cranio-maxillofacial reconstructions (Levine et al., 2012). In recent decades, CAM has witnessed the rapid expansion of AM techniques, such as 3D printing in various industrial fields. These developments led to the adaptation of AM for the manufacturing of non-implantable and implantable medical devices. The former includes templates which aid in cutting and drilling during the operation and splints which replicated the postoperative location of the patient structure. PSIs are not just accurate replicas of the anatomical features of a specific patient; they also allow engineered constructs with integrated structural and functional features, which can be directly implanted in the patients (Jacobs & Lin, 2017).

At present, there are several CAD/CAM applications typically used for the design and manufacturing of cranial PSIs (Jacobs & Lin, 2017). In general, a patient's CT scan, presented as a stack of cross-sectional images in digital imaging and communications in medicine (DICOM) format, is transferred to CAD software to create a virtual triangulated surface model of the skull in the preoperative form (Owusu & Boahene, 2015).This virtual skull model, or parts of it, can be printed by a 3D printer and used as a mould or template for the fabrication of implants (Danelson et al., 2009; Daniel et al., 2011). The virtual skull model can be manipulated in CAD software by performing virtual resection and reconstruction to fabricate resection guides or templates for surgery. The virtual skull model can be manipulated in CAD software to reconstruct the skull defect, e.g., by mirroring the unaffected side, and then can be printed and used to fabricate the physical implant. Moreover, the virtual

skull model can be manipulated in CAD, e.g., by mirroring the unaffected side, to design a PSI that precisely fits the bone defect. The PSI implant data are further transferred to CAM to manufacture the implant (Park et al., 2015).

Currently, the PSI fabrication process requires several days to complete outside the hospital. Consequently, despite all the benefits, it is often not suitable for emergency procedures, which require immediate post-traumatic surgery. Moreover, due to the process of PSI design and manufacturing, there is an elevated degree of interaction between the surgeon and the device manufacturer; the surgeon provides feedback on the modelling stage and approves the final implant design before it goes into production. Surgeons have a propensity to use one supplier for most purchased implants and preserve brand loyalty over an extended time. Therefore, device costs are often unnecessarily high and are then pushed by the hospitals into prices charged to insurers (Keith D, 2017; Robinson, 2008).

Remarkably, state-of-the-art solutions for cranial reconstruction vary in different countries. In LMICs, cranial reconstructions are still mostly dependent on either reconstruction with autologous bone or on the manual skills of the surgeon who is hand-crafting the implant using PMMA, an old-fashioned material with low aesthetical features and high complication rates, which is not considered as a first-choice option in developed countries (Adeleye et al., 2012; LEÃO et al., 2018).

2.3 Low-to-middle-income Countries: Challenges in Cranioplasty

Cranial reconstructions even with PSIs are typically offered without any cost to the patient in developed countries, but not in most LMICs. In LMICs, cranial PSIs typically cost 1500–5000 EUR, which is expensive treatment modality. Moreover, most medical personnel in LMICs have limited access to advanced equipment such as computer tomography (CT), nor skills and software for planning cranial PSIs. Similar conditions are seen in war. Military reconstruction of a cranial defect in combat zones presents a major challenge in neurosurgery due to the modern blast explosions, which create severe infected soft-tissue and cranial defects (Jeyaraj, 2020).

Therefore, in LMICs, due to the low cost and availability, autologous bone remains the most common material to fill cranial defects. However, recent studies suggest that complications after cranioplasty with autologous bone are common with the prevalence of bone flap resorption, which results in the structural breakdown of the cranioplasty commonly requiring its replacement (Dünisch et al., 2013; Korhonen et al., 2019). Moreover, donor site morbidity, prolonged operational time and limited availability of bone supply for the reconstruction of large defects are limiting factors for the use of this material. In severe bony comminution, bone graft resorption, bone tumour, infection or limited donor site options, a reconstruction has to be performed with a synthetic material (Iaccarino et al., 2021; Sundstrøm et al., 2020).

A hand-made bone replacement out of PMMA, the most common synthetic material for cranial reconstructions in LMICs, is often the only affordable artificial alternative to expensive PSIs. It can be used as PMMA liquid or as solid PMMA customised implants. Intraoperatively, liquid PMMA takes approximately 20 min to be turned into a mouldable paste, which is then applied directly to the cranial defect (Hsu et al., 2014). However, the use of liquid PMMA in order to obtain the intraoperative symmetric cranioplasty is limited by the manual skills of the surgeon and does not always result in cosmetically satisfactory results (see *Figure 5*). In addition, an exothermic reaction which raises the epidural temperature up to 64 °C during the setting period might lead to severe complications.

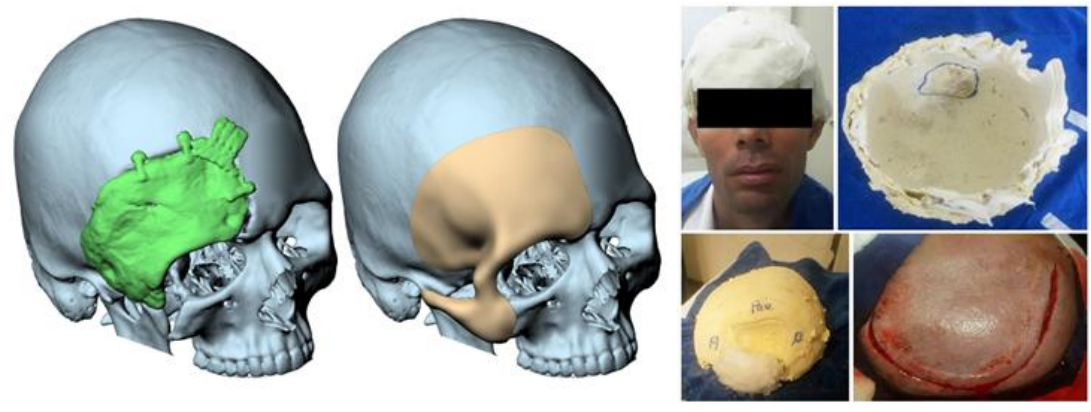

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Figure 5. A. Intraoperative hand-made bone replacement using liquid PMMA widely used in LMICs. Insufficient replication of anatomical features is visible. B. Typical CAD-based PSI widely used in developed countries. C. (DIB et al., 2018) Intraoperative hand-made bone replacement using liquid PMMA widely used in LMICs. Insufficient replication of anatomical features is visible.

Since then, PMMA implants have been intraoperatively moulded or prefabricated into the shape of the cranial defect (Stieglitz et al., 2014). The procedure requires making an impression of the patient's head, creating a mould, creating the implant using this mould, and sterilising (see *Figure 6*).

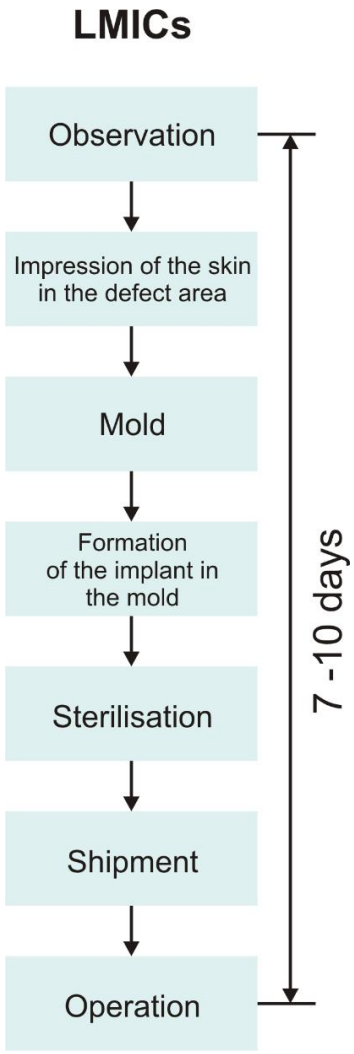


Figure 6. Typical routes of cranial reconstruction in LMICs.

The mechanical properties of PMMA are not ideal, as the implant is typically relatively brittle, and exposure of the implant and breakages due to impact were reported (Jaberi et al., 2013b; López González et al., 2015). This might be explained by the change in mechanical properties of the material during the exothermic reaction. When air bubbles form, they unite and trigger shrinkage, and the strength of the material is affected. The strength of the material also varies depending on the mixture ratio of the polymer and monomer. Moreover, residual monomers leaching from such an *in situ* fabricated implant may provoke adverse tissue reactions and

potentially have a neurotoxic effect (López González et al., 2015; Pikis et al., 2015), leading to scalp erosion and implant loosening. Overall, complications include postoperative haematoma, chronic pain, scalp erosion, migration of the implant, and infection being the most widespread. Attempts were made to improve cosmetic results with PMMA reconstructions.

During the past decade, with advances in CAD and AM techniques, the percent of intraoperative moulding in LMICs has slightly decreased. These technologies allowing manufacturing of patient-specific customised silicone moulds to be filled with liquid PMMA for the creation of prefabricated implants in order to avoid straight contact of liquid PMMA with the patient's tissues (Abdel Hay et al., 2017; Guerrini et al., 2017). The cost of solid, custom-made PMMA implants is still high for most LMICs; regardless, the complication rates with these implants is significantly lower than with liquid PMMA handmade replacements. Nevertheless, in many cases, the preoperative planning of reconstruction and fabrication of the implant are achieved manually, using topographical information, which is lacking accuracy, as advanced CT is unavailable. Though infection remains the most common cause for revision surgery, poor fit of the implant nevertheless represents a crucial area for improvement in LMICs (DIB et al., 2018). Despite all the complications, PMMA is frequently the best available alternative in countries with limited access to modern treatment modalities as it is the only option today for the creation of the patient-specific implant on the spot when infrastructure is poor, and funds are limited.

2.4 Research for Design

2.4.1 Bionic Mindset: An Overview.

In nature, biological systems present diverse solutions to solve complex engineering problems through organisation, optimisation, and adaptation. Various natural structures have a hierarchical organisation with building blocks on different levels, from nano to macro. Radiolarian and diatom shells represent simple, lightweight,

well-organised biological structures which occur naturally in a vast variety of forms and shapes. Consequently, these planktonic organisms can float although their skeletons, formed from a silicon compound, are denser than water. Bone is another example of a hierarchical, structurally, and functionally organised system. Every bone in the musculoskeletal system is optimised to function yet is an integral part of the whole. For body parts, the structures of the cortical and trabecular bones are optimised to maximise performance, while keeping it lightweight. In turn, material-wise, the bones' composite structure provides adequate mechanical properties such as strength and stiffness. Overall, the ideology of bionics is associated with structures and processes mimicking nature's code. Bionic principals suggest using the most efficient way out while utilising minimal resources. The same holistic approach can be employed to artificially created nature-inspired bionic systems.

In science, bionics was first defined as biomimetics. The term biomimetics and a concept of creative biologic engineering were proposed in 1950s by American biophysicist Otto Schmitt (Mehdi Sadri, 2014). During his PhD project, Schmitt was using analogies from nervous system of a squid when invented a Schmitt Trigger for changing a sinusoidal wave into a square wave, clean up noisy signals, and convert slow edges to fast edges. Later, in 1960s, Jack Steele came up with a term bionics, which he defined as "the science of systems which have some function copied from nature"(Vincent, 2009). Bionic principles are commonly utilised in architecture and design (Mehdi Sadri, 2014; Nazareth A, 2018; Sugár et al., 2017). For example, Shiro Studio`s project called "Trabecular Series" is inspired by structural features of porous bone tissue (see *Figure 7*) and culminating in five household objects.

Figure 7. The "Trabecular Series" by Shiro Studio, the household objects inspired by porous bone tissue. http://www.shiro-studio.com/trabeculae.php.

This project is an attempt towards creation of a new architectural language based on biological integrity and natural lightness of bone. Another illustrative case is the project led by Andrea Morgante, the architect who is working with complex shapes, has been impressed by the variety of forms and structural integrity of radiolarian skeletons. Andrea has created the Radiolaria pavilion produced with the aid of AM (see *Figure 8*).

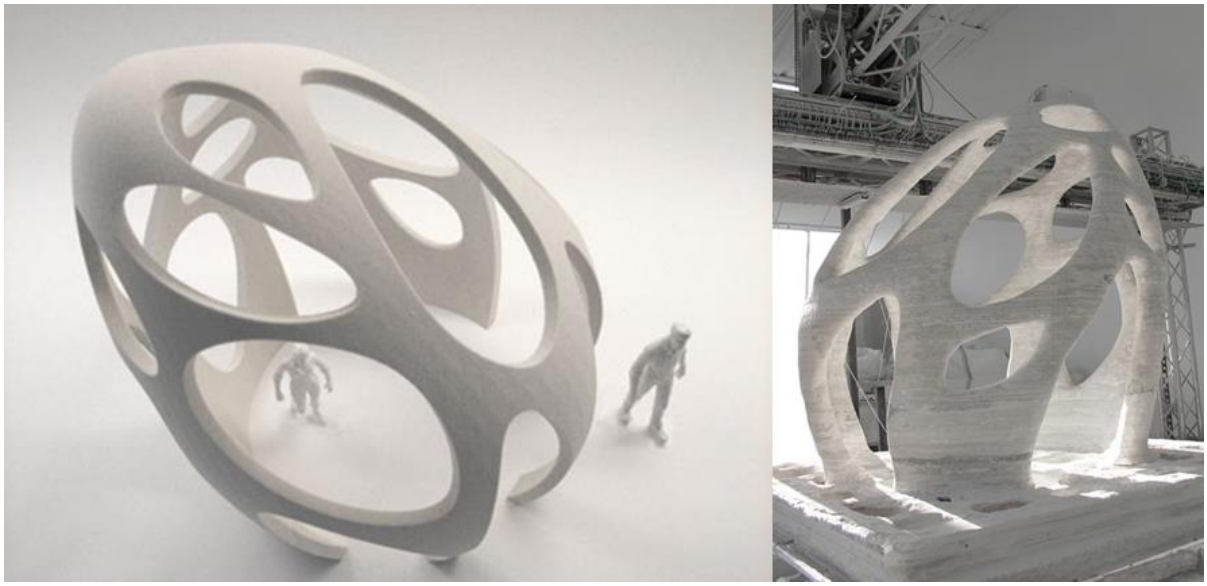


Figure 8. The Radiolaria pavilion by Andrea Morgante, a complex, free-form structure produced by additive manufacturing. https://www.dezeen.com/2009/06/22/radiolaria-pavilion-by-shiro-studio/.

Diplosphaera hexagonalis (see *Figure 9*) is one example of Radiolaria which bony skeleton consists of hexagonal meshes. In fact, despite their unique diversity, radiolarian micro-skeletons are often shaped like simplified hexagonal meshes (Schiftner et al., 2009), since hexagon is considered as one of the most stable structural figures. In early 1950s, Buckminster Fuller, an American architect and designer, invented a geodesic dome, which consists of a symmetric structural mesh of a spherical shape tiled by hexagons or trigons. Fuller was one of the strongest adepts of bionics in architecture. The geodesic dome was a result of Fuller's discovery of nature's constructing principles and was almost a primary attempt to create a complex, self-balancing structural framework based on a network of triangles using minimal materials. Interestingly, the idea was to use such a dome as affordable and efficient housing that could be built quickly from mass-produced parts. The *Figure 10* presents the illustration by Boris Artzybasheff for the cover of

one of a 1960s issue of *Time* magazine portraying the head of R. Buckminster Fuller with simple geometrical shapes resembling his most famous lattice shell structure - geodesic dome. The illustration provided a direction for deeper research on the topic in the framework of this thesis.

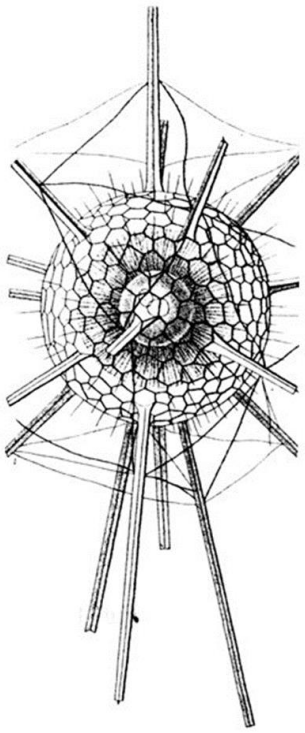


Figure 9. Diplosphaera hexagonalis shorturl.at/ikruB.

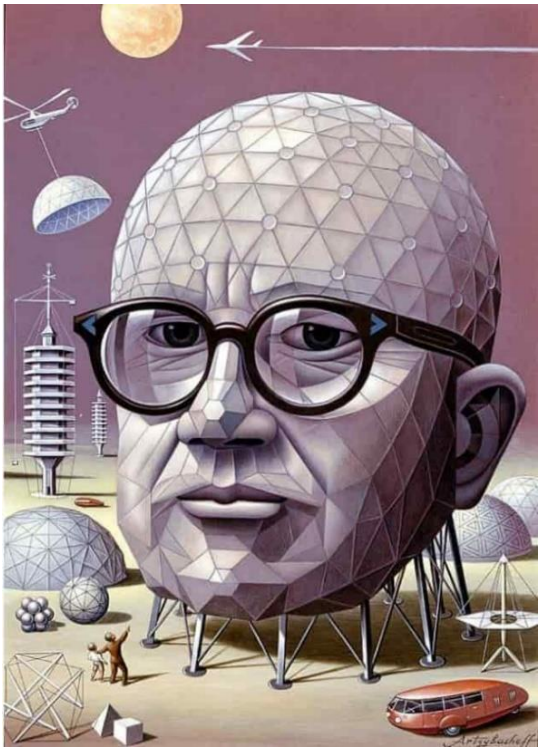


Figure 10. The cover of Times magazine by Boris Artzybasheff. https://www.bidoun.org/articles/buckminster-fuller.

Later, in the 1980s, a postmodern architectural style known as deconstructivism gained widespread attention. Pioneered by Frank Gehry, Rem Koolhaas and Zaha Hadid, the style was characterised by the fragmentation and manipulation of a free-form surface. The objects are usually formed from elements that have been initially disassembled and further reunited in an unconventional way, giving a sense of a chaotic design lacking logic. However, the fundamental problem of large-scale architectural free-form surfaces is still in transforming a geometrically complex design into a practical and affordable production. The solution is "tessellation", which is largely based on panelling or tiling, i.e., segmenting a shape

into simpler surface tiles that can be fabricated at a fair cost with a selected manufacturing process (Pottmann et al., 2010; Schiftner et al., 2009).

Tessellation is largely inspired by various armoured animals and insects (Connors et al., 2019). The armour comprises of bony plates called "scutes" that provide protection from predators. The scutes or osteoderms that form a turtle's shell, a crocodilian's skin, and a bird's feet hint at how different free-form scale shapes are dived simply and are panelled in nature. Interestingly, the armour of these creatures is typically highly flexible. The overlapping scutes attached to the underlying flexible derma to form shell-like exterior, which can protect the vital organs of the animal from a piercing force in the case when attacked (Xu et al., 2021). Armadillo is a good example of such an armoured animal (see *Figure 11*). Its flexible telescopic exterior allows for curving into a shape of a ball by growing on three sections: the scapular shield, the pelvic one and sliding part of the armour in the middle. This natural example of simultaneous flexibility and stiffness could bring in mind the analogy with origami, the Japanese art of paper folding.

Figure 11. Armadillo. https://www.dkfindout.com/uk/animals-and-nature/armadillos/.

Origami is a form of surface two-dimensional tessellation by various figures, which upon unfolding transforms into three-dimensional one. Origami patterns could be frequently found in nature. Leaves and flowers have such foldable ornaments of veins. These ornaments are often served as an inspiration for the creation of new origami patterns such as a pine-cone pattern by N. Maillard and B. Kresling (see *Figure 12)* or intriguingly display resemblances with certain established artificial folding patterns, such as the Miura-ori (Kresling, 2012).

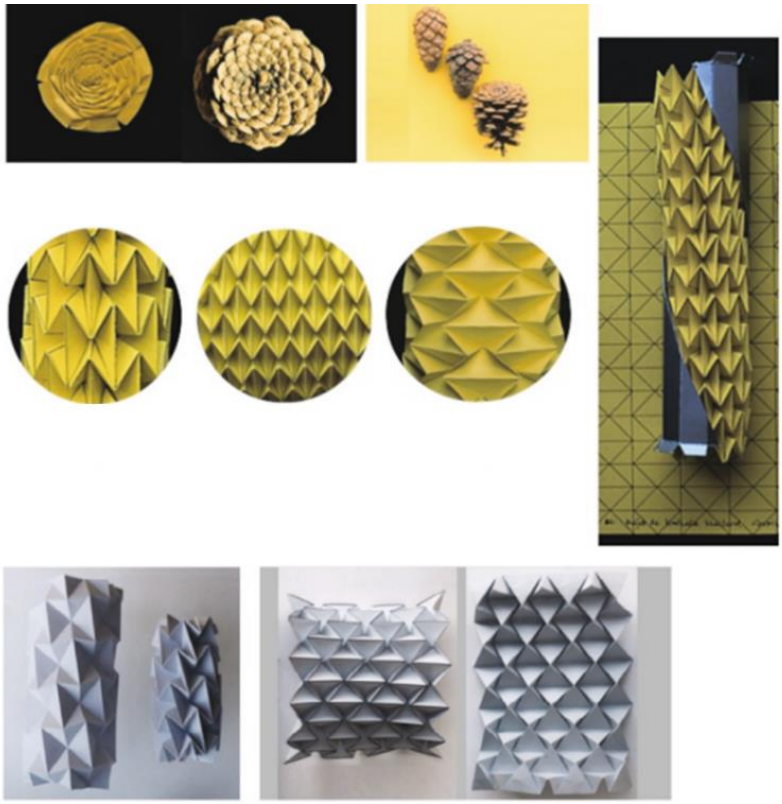


Figure 12. The pine-cone pattern created by N. Maillard and B. Kresling.

Miura-ori or Miura fold was invented by Japanese origamist and astrophysicist Kōryō Miura who created this folding pattern for aerospace and industrial applications (Kresling, 2012). Miura-ori could be described as a rigid origami expressed via parallelograms tessellation, where at each step of continuous motion each parallelogram is entirely flat. This type of pattern is observable in nature, exemplified in poppy flowers, wherein the impulsive in-plane wrinkling of the petals culminates in a natural ornament reminiscent of the Miura-ori (see *Figure 13*).

Miura-ori pattern is used in a wide variety of industries including biomedical. One example is a cover for the extendable arm of an X-Ray medical machine used during surgical manipulations and produced by Brigham Young University in cooperation with GE Healthcare. The cover is made of DuPont synthetic paper. Miura-ori pattern was used in the design of this paper cover to allow for a functional geometrical change of an extendable arm by continuous folding and unfolding movements. Previously, conventional plastic drapes were used for keeping an extendable arm in sterile condition; however, this plastic drape needed manual replacement after each

rotation outside the sterile field. This manipulation was expensive and time-consuming. New origami-based paper cover keeps an extendable arm sterile during the movement and does not require a frequent change (Johnson et al., 2017).

Figure 13. The Miura-ori pattern seen in poppy petals (Kresling, 2012).

In contrast to Miura-ori pattern, a biomimicking pine-cone pattern created by N. Maillard and B. Kresling is more complex and rather a free-form type of origami allowing for various shapes and configurations upon twist-buckling. This specific origami pattern was successfully used for the creation of an origami-based self-assembly Ni-rich titanium/nickel (TiNi) shape memory alloy (SMA) stent graft, a medical device used for the treatment of tracheal diseases or vascular stenosis in minimum invasive surgery (Kuribayashi et al., 2006; Zhao et al., 2022). This device gain advantage from origami`s flexibility and power of dynamic change.

This striking intersection of bionic principles and biomedical technology underscores the potential and value of biomimicry in advancing medical solutions.

The flexible and adaptable nature of these designs signifies a potent driving force for innovation.

In recent times, elements of sustainability have emerged as fundamental underpinnings of bionic design. The harmonious incorporation of these principles into design practices stimulates a wave of mindful innovation, marking a pivotal phase in the trajectory of technological advancement. Presently, bionic design extends beyond the mere adoption of shapes or functions from nature. It now encapsulates a holistic worldview that factors in the ecological, socio-economic, and other implications of such designs. Consequently, nature has evolved from being a mere source of inspiration to a significant force shaping the evolutionary path of new technologies and innovations.

2.4.2 Designing for Medical Device Industry.

A medical device is an instrument, apparatus, implant, *in vitro* reagent, or similar or a related article that is used to diagnose, prevent, or treat diseases or other medical conditions and does not achieve its purposes through chemical actions within or on the body such as drugs (Ciurana, 2014). Medical devices are made of biomaterials. In turn, biomaterials could be defined as materials, which are used in medicine and dentistry and intended to encounter living tissues. All biomaterials could be simply subdivided into three main categories: metals, ceramics and polymers and composites thereof. The main feature of all biomaterials is biocompatibility, which means that they should be safe for the recipient (Pavlovic, 2015). The main purpose of medical device is to enhance the patient's well-being during diagnosis, treatment, and/or medication stage (Ciurana, 2014). Over the last decades, the medical device industry in developed countries became an emerging field with a diverse, innovative, and vibrant spirit. Nevertheless, designing for this industry is drastically different from any other one. It has many nuances and constraints. It is of utmost importance to get understanding of such a complex context already at the design research stage before diving to a real design process. In this section of the thesis, the most vital aspects of the process of designing for the medical device industry will be covered.

These aspects will include regulatory landscape, choice of design approach, overview on medical device design context with a special reference to LMICs and some highlights on the role of Human-Centered Design principles.

2.4.2.1 Regulatory Landscape.

The medical device industry is one of the most regulated. The regulatory system is very complex and somewhat different in various parts of the world. However, all medical device manufacturers should establish and later follow an internal quality management system. The International Organization for Standardization (ISO) sets standards for quality management systems in many industries, including medical devices. The ISO 13485 Quality Management System (QMS) is the standard specifically designed for medical device manufacturers and ensures that medical devices meet the safety, performance, and quality requirements of their intended use. This standard is applicable to any medical device, whether it is a product or a service. It is intended to provide a framework for a set of processes that will ensure the quality of medical devices and their components. The ISO 13485 QMS focuses on processes such as design control, document control, purchasing, production and service control, monitoring and measurement, risk management, and corrective and preventive action. It requires the manufacturer to have procedures in place to ensure that any changes made to the design or manufacture process of a medical device are properly documented, reviewed, and approved. The ISO 13485 QMS also requires that the manufacturer performs regular audits to ensure that the processes are being followed and that the medical device meets the requirements of the standard. The audits should include an assessment of the quality system, the product design, production processes, and document control.

All medical devices are categorized into three main classes (subclasses exist) according to the risk level of burden to patient health. Class III represents the most regulated life-sustaining medical devices, which are typically permanent devices placed in proximity to vital organs such as the brain or heart. Such devices possess a highest risk for patient health. Examples of Class III devices include cranial implants,

implantable pacemakers, vascular stents, breast implants etc. Class II is a medium/high risk device, which comprise around 66% of the market and refer to continuous, partial, or complete invasive contact with patient body. Examples of Class II devices include catheters, syringes, surgical gloves, absorbable sutures, blood pressure cuffs, pregnancy test kits, contact lenses etc. Class I medical devices are typically non-invasive devices which carry a minimal potential risk for patient health. Such devices are usually needed to fulfill only a few regulatory requirements. Examples of Class I medical devices include software, examination gloves, bandages, facemasks etc.

In Europe, the regulation carried out by European Union (EU) Member State level, but the European Medicines Agency (EMA) is involved in the regulatory process. In the EU, all medical devices must be investigated for their compliance with legal requirements to ensure safe and intended performance. This process called a conformity assessment and involves an audit of the producer`s quality system and review of technical documentation regarding safety and efficacy of investigated medical device. After successful conformity assessment, producers can place a Conformité Européenne (CE mark) on a medical device and start marketing and sales activities in EU.

In the United States, medical devices are regulated by the Food and Drug Administration (FDA). The vast majority Class I devices and few Class II devices are exempt from Premarket Notification commonly referred to as a 510(k). Most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval. The 510(k) process was designed as a fast track to the market for those medical devices, which are substantially equivalent to a device that is already on the US market. In turn, Premarket Approval is intended for Class III high risk devices or devices found not substantially equivalent to Class I and II predicate via the 510(k) process. The Premarket Approval process is more complex as well as time-consuming and requires the submission of clinical data to support evidence about device safety and efficacy.

In LMICs, local agencies are responsible for medical devices regulation and certification. Presently, these agencies often but not always aim to adhere to

guidelines similar to those in the US and EU; however, a harmonized certification process remains elusive. While regulations play a crucial role in guaranteeing the safety and efficacy of medical devices, they also create economic challenges for developers, manufacturers, and researchers. This burden is particularly noticeable in LMICs, where weak regulatory enforcement frequently results in the use of substandard or counterfeit devices. Consequently, adhering to regulations can be a substantial barrier for those aiming to manufacture, distribute, or even donate medical devices in these countries. Insufficient regulation not only jeopardizes patient safety but also inhibits investment and innovation within the medical device sector. It is crucial to strike an equilibrium between regulatory compliance and economic sustainability, ensuring that secure and efficient medical devices are available to those who require them most, particularly in LMICs. By enhancing regulatory supervision, streamlining bureaucracy, and fostering transparency, governments can facilitate the growth of a resilient medical device industry that caters to their populations' needs while maintaining patient safety. Ultimately, regulatory reform can pave the way for increased investment, innovation, and access to high-quality medical devices, ultimately resulting in improved health outcomes for everyone (Hubner et al., 2021). Currently, there are several initiatives are taking place to support LMICs in regulatory framework transformation. The World Health Organization (WHO) has developed a framework called the Global Model Regulatory Framework for Medical Devices, which offers guidance for countries looking to strengthen their medical device regulatory systems. Additionally, organizations such as the International Medical Device Regulators Forum (IMDRF) and the Asian Harmonization Working Party (AHWP) work to promote harmonization of medical device regulations and share best practices. Regional collaborations and networks, such as the African Medical Device Forum (AMDF) and the Pan American Health Organization (PAHO), have also been established to support LMICs in developing and implementing effective medical device regulations.

Despite these efforts, challenges remain, and further work is needed to ensure that LMICs have robust regulatory system in place to guarantee the safety and effectiveness of medical devices in their markets.

2.4.2.2 Choosing Design Approach. Mapping the Context with a Special Reference to LMICs.

Already at early stage of designing a medical device, design approach should be balanced between regulatory landscape and user needs in a way that safety requirements do not overshadow innovation, aesthetics and user-driven mindset but nevertheless considered. The design of medical devices should be based on well-established design methods and three baseline components should be taken into account: device end-user, user interface and use environment.

In the medical-device industry, the range of stakeholders can be variable and very comprehensive depending on such factors as e.g., size and format of the practice and a clinical indication of the actual device. In ideal scenario, this chain should include a patient, a doctor and a nurse as major players, and a hospital itself as a full-cycle structure with all personnel responsible for ordering devices, storing them, and utilizing. Moreover, it is important to consider during the design process a choice of materials, manufacturing path, transportation and sustainable utilization process after device is being discarded. With this approach in mind, designer should shift the focus from direct user towards the aspirations and preferences of all stakeholders in the value chain to involve distribution, uptake, and possible impact of a product (Fisher & Johansen, 2020). The utmost goal of good design practice today is not just device safety, effectiveness, or market attractiveness but the creation of strong positive social impact. When designing user interface, one should consider all possible points of interaction and identify design opportunity regions between the product and the user. The user interface should primarily ensure intuitive usability with low physical effort, equitability, and accessibility. In addition, usability information regarding package design, labelling and operating instructions should be timely collected. Use environment puts a lot of pressure on designer and creative process, as environmental conditions vary from highly controlled clinical settings to harsh unpredictable setting in the field. Some devices should have a universal design suitable for any type of environment, which is especially relevant for LMICs.

For general audience, the word design is often associated with fashion and art solely. However, design also implies the creation of something significant and sometimes lifechanging. Designing effective, safe and affordable medical devices for LMICs can improve access to healthcare and living standards. However, at the same time, designing in humanitarian framework might carry a risk of discrepancy with a unique challenge of resource-constrained environment (Rose et al., 2020). For example, the device end-user may have limited access to electricity or other resources. In addition, devices itself may require withstanding the local conditions, including extreme temperatures, humidity, dust and dirt. Designers must also consider the availability of spare parts, maintenance, and servicing. In this case, to build effective design process, one should take a transdisciplinary approach, where engineering, clinical expertise, design practice, and regulatory aspects will be crosslinked.

2.4.2.3 Human-Centered Design as Practical Tool for Medical Device Industry

Human-Centered Design (HCD) is an essential approach that may play a pivotal role in solving today's medical-device industry challenges and elevate the design standards. Common industry practices of human factors engineering, usability engineering, and user experience are encompassed within HCD according to the ISO 9241-210 standard defines as "an approach to systems design and development that aims to make interactive systems more functional by focusing on the use of the system and applying human factors/ergonomics and usability knowledge and techniques." (International Organization for Standardization., 2019). The field of HCD spins around encountering human needs and often hidden desires, to design products or services that fulfill these needs. At present, HCD assumes that the resulting design is supposed to be accessible, clear and functional and brings meaningful and pleasurable user experience. Furthermore, design is no longer valuable as a process to create physical objects only. It is gradually shifting towards a conceptual process that leads to the creation of completely new and often innovative type of intervention, which in turn could be a game-changer by bringing

elevated standards to industry. The importance of HCD has been acknowledged as being vital and influential approach when tackling today's complex healthcare challenges (Erwin & Krishnan, 2016). However, Bazzano et al. 2017 analyzed 21 peer-reviewed publications and found out that none of these publications quantitatively assess the connection between HCD and health outcomes. Most of these studies are focused on clinical decision tools, webpages of global health organizations and various software; however, none on medical devices. This paper also acknowledged a lack of publications focusing on a full project cycle, almost no description of HCD methodologies applied, and absence of pulled stakeholder feedback (Bazzano et al., 2017).

Product design originates from engineering design and is often based on research- and data-driven design approaches (Jack Hugh, 2013). However, at present, there is a paradigm shift in design towards more participatory, inspiration-oriented, and emotion-driven approaches. Despite this trend, the emotional aspect in HCD with respect to the medical-device industry is yet another pit. Interaction with the stakeholders here is a journey full of emotions. Nevertheless, medical-device manufacturers especially in the field of medical implants, often reject the importance of emotional component in design and frequently eliminate patient from stakeholders' chain by focusing solely on surgeon's and hospital`s needs (S. G. S. Shah & Robinson, 2008). In this scenario patients can feel frustrated and even miserable after the intervention. Although patients have various specific needs, they want to be equal members of society, be respected, and heard. Often, they consider surgical intervention or another medical procedure just as one part of their overall life experience. Therefore, gaining understanding on how patients deal with this life experience is of paramount importance for developing a solution that will help them in a significant way (S. G. S. Shah & Robinson, 2007).

2.4.3 Benchmarking

AM has transformed the healthcare segment by bringing new modalities for sustainable and effective manufacturing. Medical devices manufactured by AM

techniques have gained popularity due to the better increased patient compliance, reduced surgical time and complications. All these factors act as a driver of the burgeoning growth of the cranial implants market. In 2021, the global cranial implants market was worth of $0.92 billion. The cranial implants market is expected to reach $1.35 billion in 2025 (Cranial Implants Global Market Report 2022, 2022). The global cranial implants market is typically segmented into four main categories:

1) By implant type: cranial PSIs, standard cranial implants

2) By material: metal, ceramic, polymer, composites

3) By end user: hospital and trauma centres, ambulatory surgical centres, speciality clinics, others

4) By the level of technological advancement: innovative cranial implants, non-innovative cranial implants

This benchmarking overview provides various examples of cranial implants, which are currently keeping the lead due to innovative technological touch offered by small university-research-driven companies or in contrast due to abundant marketing resources of large players pushing their products via opinion-leaders in the field. However, it should be noted that this benchmarking research is focused on the solutions offered in the developed countries and rarely in LMICs. Therefore, this benchmarking is presented as the illustration of good practice in cranial reconstructions which should be closely followed when designing for LMICs, however keeping in mind local socio-economic context. In LMICs, Internet penetration and access to smart devices remains low as well as the access to a modern imaging equipment. In Nigeria, there are only 60 radiologists per 190 million people (Huys et al., 2022). In addition, there is a vague understanding of import regulations; therefore, the accessibility of PSIs from abroad is limited (Huys et al., 2022). The typical cranial reconstruction process in LMICs is described in a Background chapter of this thesis.

In 2021, LMICs included 109 economies and 6.5 billion people (Huys et al., 2022). According to the Lancet Commission on Global Surgery, there are 5 billion

poor people (Meara et al., 2015). Among them, a large part is ostracized and living in rural areas facing incredible challenges in getting even a primary treatment. There are countless rural medical centres and other medical care spots in LMICs surviving on governmental support or private donations, where advanced technologies are just not feasible because even the most basic supplies can sometimes be costly, and the waiting time may be too long. Despite all the boundaries, patients in LMICs should be able to receive the same level of treatment. The WHO confirmed that cost-effective strategies for delivering essential surgical treatment for injuries delivered at primary healthcare facilities should reduce the burden of death and disability (World health Organization, 2006).

Innovative cranial implants

There are just a few players on the market, which bring innovation into their products. Typically, these products are offered by small university-research-driven companies.

OssDesign AB

OssDesign AB is a Swedish innovative cranial implants manufacturer, which was formed as a spin-off of collaborative research activities between the Karolinska University Hospital and Ångström Laboratory at Uppsala University. OssDesign produces only cranial PSIs. The cranial PSIs consist of a 3D-printed titanium (Ti) mesh and decorated by hexagonal tiles of hydroxyapatite (HA) (see *Figure 14*). OssDesign to some extend utilizes tessellation approach in the implant design. However, these tiles are not of the same size and used mainly for aesthetical fixation of HA pieces to the titanium mesh surface of a cranial PSI. HA is a synthetic alloplastic material with structural and chemical composition close to human bone mineral (Jarcho, 1986). The OssDesign cranial PSIs claimed to possess bioactive features and reduced rate of complications (Bloom et al., 2020).

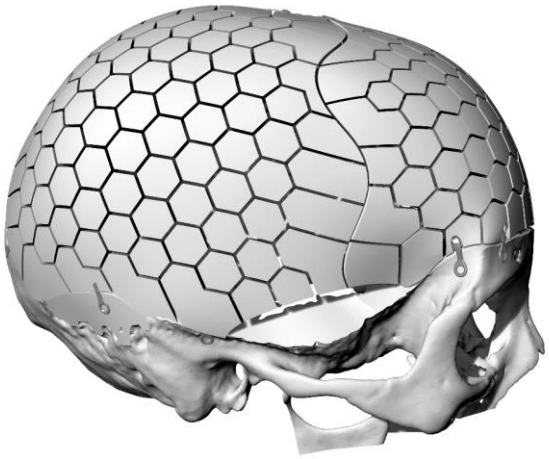


Figure 14. Titanium mesh decorated by hydroxyapatite (OssDesign AB). Image source: https://www.ossdsign.com/us/news/meet-ossdsign.

Skulle Implants Oy

Skulle Implants Oy is a Finnish innovative cranial implants manufacturer, which was formed as a spin-off of research activities at the University of Turku. Skulle Implants produces standard cranial implants as well as cranial PSIs. Skulle Implants composite cranial implants called GLACE™ and based on hand-made fibre-reinforced sandwich structure filled with bioactive glass S53P4 as the main added-value component (see *Figure 15*). The sandwich structure is made of a bisphenol-a-glycidyl methacrylate and triethyleneglycoldi-methacrylate (pBisGMA-pTEGDMA) resin matrix, which is reinforced with silanized E-glass. This resin matrix is commonly used as a matrix for dental fillings and reported to be prone to monomer leaching, which might have a cytotoxic effect (Arossi et al., 2010; Tuusa et al., 2005).

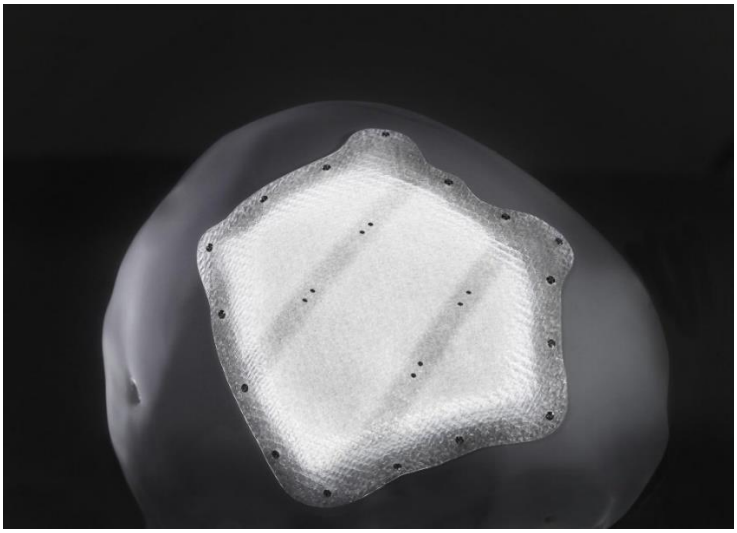


Figure 15. GLACE™ cranial implants (Skulle Implants Oy). Image source: https://skulleimplants.com/.

Bioactive glass S53P4 is a bioactive ceramic material, which has osteostimulative and antibacterial properties (Drago et al., 2018). Despite the clinical advantages, GLACE™ cranial implants are unsustainable due to the high volumes of waste, toxic compounds pollution and energy consumption during the manufacturing process.

Non-innovative cranial implants

The biggest players on the market such as Depuy Synthes, Stryker, KLS Martin Group, Anatomics, Xilloc Medical etc., currently produce standard cranial implants as well as PSIs using AM or other techniques mainly from Ti or PEEK. The main disadvantage of these devices is that they are made of biologically inert materials. Therefore, there is an increased risk of infection and potential for lack of osteointegration. Moreover, from clinical standpoint, all these devices are nearly identical, as they are all made of the same materials and has no extra features such as bioactivity or any other functional cutting-edge advantages.

Xilloc Medical Int.

Xilloc is a cranial implants manufacturer based in Netherlands. Xilloc was the first company to manufacture 3D-printed Ti cranial PSI. Currently, the company produces both, Ti and PEEK cranial PSIs (see *Figure 16*).

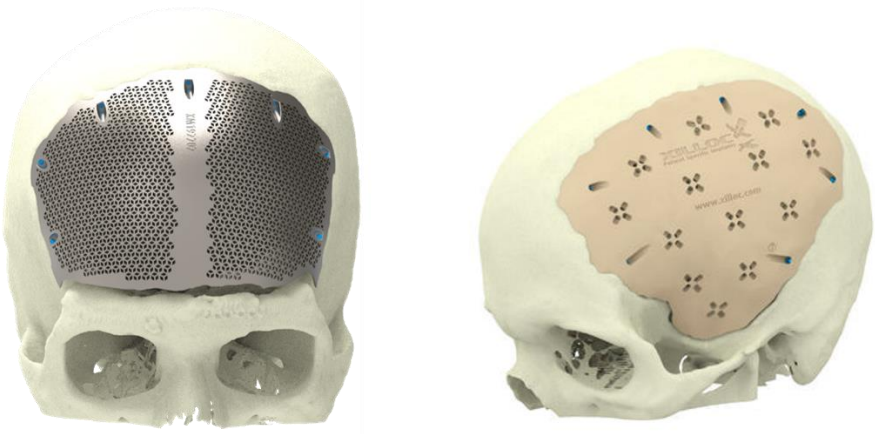


Figure 16. Xilloc cranial Ti and PEEK PSIs. Image source https://www.xilloc.com/products-and-services/.

DePuy Synthes

DePuy Synthes is the orthopaedics division of Johnson & Johnson and one of the leading companies on the market of medical technologies. Their product range is covering joint reconstruction, trauma, craniomaxillofacial, spinal surgery, and sports

medicine. Currently, DePuy Synthes offers simple and robust Ti and PEEK standard and PSI solutions for cranial reconstruction (see *Figure 17*). However, there is no innovation behind these solutions.

Figure 17. DePuy Synthes cranial Ti and PEEK implants. https://www.jnjmedtech.com/en-US/specialty/cmf/cranial-trauma-reconstruction?items_per_page=12.

Stryker

Stryker is one of the world's leading medical technology companies. Stryker manufactures standard cranial implants as well as PSIs from PEEK and porous polyethylene called MEDPOR (see *Figure 18*).

Figure 18. MEDPOR cranial implants by Stryker. https://cmf.stryker.com/products/medpor-customized-implant.

MEDPOR is well-studied polymeric material, which has been in clinical use for various clinical applications since 1985. Stryker MEDPOR cranial implants are cost effective

in comparison with more expensive counterparts; however still not affordable enough to be widely adapted in LMICs.

3. Methodology

3.1 General Approach. Introduction to Concurrent Engineering

The design of a medical device is a comprehensive and complex process, involving multiple steps and requiring the expertise of various professionals from different fields. The main goal is to develop a safe, effective, and biocompatible implant that improves the patient's quality of life. Here are some key general stages in the design and development of a medical device:

Stage 1. Identifying the need: The process begins with identifying a specific medical need that can be addressed with an implant. This involves understanding the problem, determining the target patient population, and assessing the limitations of existing solutions.

Stage 2. Concept development: The initial concept for the device is developed, taking into consideration the desired function, target patient population, and anatomical constraints. Various design options are explored and evaluated based on their feasibility, efficacy, and safety.

Stage 3. Material selection: Choosing the appropriate material for the device is critical for ensuring biocompatibility, durability, and optimal performance. Factors such as the device's mechanical properties, corrosion resistance, and biocompatibility with the human body need to be considered.

Stage 4. Design optimization and prototyping: Based on the selected materials and concept, the device design is optimized through computer simulations, finite element analysis, and other engineering tools. This stage may also involve creating physical prototypes for testing and evaluation.

Stage 5. Preclinical testing: Before a medical device can be used in human patients, it must undergo extensive preclinical testing. This involves conducting *in vitro* (laboratory) and *in vivo* (animal) studies to evaluate its safety, biocompatibility, and efficacy. These tests reveal potential issues, such as adverse tissue reactions, infection risks, and mechanical failure, which need to be addressed before moving to the next stage.

Stage 6. Regulatory approval: Medical devices are subject to strict regulatory standards and must be approved by relevant regulatory agencies, such as the U.S. FDA or the European Medicines Agency (EMA). The approval process involves submitting detailed documentation, including preclinical test results, manufacturing processes, and quality control measures, to demonstrate that the implant is safe and effective for its intended use.

Stage 7. Clinical trials: If the device meets the necessary regulatory requirements, it proceeds to clinical trials, which involve testing the device on human patients. Clinical trials are conducted in multiple phases, each with increasing numbers of participants, to evaluate the implant's safety, efficacy, and long-term performance.

Stage 8. Manufacturing and market launch: Scaling up production and preparing the device for market release.

Stage 9. Post-market surveillance: Once the device has been approved for use and is available on the market, ongoing post-market surveillance is essential. This involves monitoring the implant's performance in real-world settings, collecting data on potential adverse events, and identifying any long-term issues that may arise. This information is used to refine the implant design and improve its safety and effectiveness.

In summary, the development of a new medical device can take from a few years to over a decade, depending on the complexity of the device, the regulatory environment, and the resources available to the development team. Since the design

and development of a medical device is a long and complex process, this thesis is focused on Stage 1 to Stage 4.

Efficient approach towards product development is a critical matter for medical device manufacturing. To ensure rapid regulatory approval and market release, already at the conceptualization and design stages, collaboration between a variety of stakeholders must be facilitated. In this thesis, concurrent engineering (CE) is used as a general approach for initial product development stages. CE is a systematic approach to product design which involves cooperation between cross-functional teams and parallel efforts on all aspects of design to speed up a product development process and avoid costly design changes at later stages of a cycle (Mathelier, 1994). Overall, CE approach allows creation of high-quality products, which are meeting customer expectations. This approach requires careful planning and communication among team members. All team members such as engineering, manufacturing, quality control, clinical and regulatory affairs specialists as well as marketing experts and other relevant professionals must work together to identify potential issues and address them early in design process (Das & Almonor, 2000).
The general key steps of CE in medical device design typically involve the following (Mathelier, 1994):

Step 1: Define product requirements: This includes identifying intended use, target market, and performance criteria for a medical device. Requirements should be clear, concise, and measurable, and should be declared to all team members.

Step 2: Form a cross-functional team: A cross-functional team should consist of experts from relevant fields. The team should work together throughout the product development process, from design to commercialization.

Step 3: Perform risk assessment: Risk assessment is an important part of medical device design. A team should identify potential risks associated with the product performance, handling, registration, marketing etc., and develop strategies to mitigate those risks.

Step 4: Estimate costs for the whole project and every individual step.

Step 5: Plan a regulatory strategy path: Regulatory strategy is necessary to ensure that medical device will meet all applicable regulatory requirements.

Step 6: Create mechanisms to ensure that all necessary information is documented, transmitted, and reviewed as needed. Appoint team members responsible for execution and monitoring.

Step 7: Create design inputs and outputs for each stage of product development. Involve potential customers already at this stage.

Step 8: Visualize and document design to make changes, if necessary, before any physical prototypes are made.

Step 9: Produce a series of physical prototypes: Prototyping is a critical step in the CE process. By creating physical prototypes, a team can evaluate the design, test the product's performance, and identify any potential issues that need to be addressed.

Step 10: Optimize the manufacturing process: The CE team should work together to optimize the manufacturing process, making sure that the product can be manufactured efficiently, and the process comply with regulatory requirements.

Step 11: Continue collaboration after launch: After the product has been launched, the CE team should continue to collaborate to monitor the product's performance, identify potential issues, and make any necessary modifications.

The context of CE assumes that the expectations of customers play a vital role. In the case of medical device industry, customers are not limited to patients but also include healthcare providers and other stakeholders who will use or be impacted by a medical device. Hence, naturally, CE is largely interconnected with HCD. By taking this into account, cross-functional teams can apply HCD principles within CE

approach to improve functionality of a product and allow for its smooth intuitive and enjoyable use. CE in combination with HCD could be implemented via iterative practice, where user participation in product prototyping, testing, and refinement can result in higher product adoption rates and increased customer satisfaction.
In the framework of this thesis, the proposed CE approach is implemented using the tool of Design for Manufacture (DFM).

3.2 Introduction to Design for Manufacture (DFM). Combination of DFM and CE when Designing for LMICs: challenges and opportunities.

The objective of Design for Manufacturing (DFM) is to streamline and refine the design of parts, components, or products for optimization of manufacturing, resulting in a superior product at a reduced cost (Mathelier, 1994). CE could be effectively combined with DFM when designing medical products for LMICs. The combination of CE and DFM in designing medical products for LMICs is particularly important due to the unique challenges faced in these regions, such as:

1. Limited resources: Healthcare facilities in LMICs often have insufficient financial and human resources, which can impact the ability to procure, maintain, and operate medical devices effectively.

2. Infrastructure: LMICs often have underdeveloped infrastructure, including unreliable power supply, poor transportation networks, and inadequate healthcare facilities. These challenges require medical devices to be designed with greater durability, adaptability, and ease of use in mind.

3. Skilled workforce: The availability of a skilled workforce to operate and maintain medical devices can be limited in LMICs. Medical products designed for these regions should be user-friendly, with minimal training requirements and easy-to-follow instructions to ensure proper use and maintenance.

4. Regulatory environment: As previously mentioned, LMICs often have underdeveloped regulatory frameworks for medical devices, leading to challenges in ensuring the safety and efficacy of products in these markets. Designing medical devices that adhere to international standards and best practices can help improve their acceptance in LMICs and promote the development of stronger regulatory systems.

6. Access to technology and maintenance: In LMICs, access to advanced technology and maintenance services are limited. When designing medical devices for these regions, it's important to ensure that the devices are not overly reliant on sophisticated technology and that maintenance can be performed locally using available resources and skills.

7. Supply chain challenges: LMICs often face supply chain challenges due to poor infrastructure, transportation difficulties, and import restrictions. Designing medical devices that use locally available materials and components, or those that can be easily sourced in the region, can help alleviate supply chain issues and ensure the devices' continued availability.

8. Cultural and language barriers: It's essential to consider cultural and language barriers when designing medical devices for LMICs. Devices should be designed to accommodate cultural practices, preferences, and sensitivities, as well as to include instructions and labelling in the local language(s).

By considering these unique challenges and combining DFM and CE in the design process, medical devices can be better tailored to the specific needs and constraints of LMICs. By using CE and DFM together, medical product designers can ensure that the products they create are not only functional and effective but also economically viable and manufacturable with the available resources. In the early stages of product development, CE can help identify the most critical functional requirements of the product and design the manufacturing process in parallel, ensuring that both are optimized for efficient production. DFM can then be applied at the later stages to

refine the product design and make it easier and cheaper to manufacture, ensuring that the product can be produced at scale and at a reasonable cost. Consequently, this approach can lead to more effective, accessible, and sustainable healthcare solutions that improve health outcomes for the populations in these regions.

3.3 Contributors. Methodology and Materials. Ethical Aspects.

3.3.1 Contributors

This thesis reflects a collaborative endeavour, engaging expertise from diverse specialties including biomaterials science, implant technology, and AM technologies. It presents a comprehensive exploration of the entire process chain, from the initial conceptualization of medical implants to their practical implementation, thus paving the way for swift future industrial adoption.

The author of this thesis has been instrumental in guiding this interdisciplinary project towards an innovative solution for cranial reconstructions in LMICs. The author's contributions spanned from the theoretical grounding of the thesis to the design, risk assessment, and practical implementation of the concept. In the early stages, the author meticulously crafted the theoretical framework that underpins this project. Her profound understanding of the subject matter was vital in providing a robust foundation upon which the subsequent practical work was based. In the design phase, the author employed her technical acumen together with a team to develop the innovative concept of modular cranial semi-PSI. In addition, her theoretical insight into the unique challenges faced in LMICs informed the design process, ensuring the implants would be both practical and effective in these contexts. Risk assessment was another critical area where the author's expertise came to the fore. She conducted a rigorous evaluation of potential challenges associated with the implementation of the proposed solution, thereby ensuring the safety and feasibility of the project. Furthermore, the author's leadership facilitated collaboration among the diverse team of specialists, fostering an environment conducive to innovation and problem-solving. Ultimately, during the

implementation phase, the author effectively employed a synthesis of theoretical acumen and hands-on proficiency to illustrate the clinical significance of this design concept.

The complete list of contributors who collaborated with the primary author of this thesis can be found in *Table 1*.

Table 1. List of contributors.

Contributor	*Field of expertise*
Biomedical Engineering Research Group, University of Turku, Finland (UTU)	Biomaterials science, materials science, implant technology, biomechanics, finite element modelling, *in vitro* and *in vivo* testing of biomaterials and implants.
Janek Frantzen, MD, PhD (JF)	Assistant Professor in Neurosurgery at the Department of Clinical Medicine at the University of Turku.
Kalle Aitasalo, DDS, MD, PhD (KA)	Head and Neck Surgeon, Maxillo-Facial Surgeon, Emeritus Professor.
Willy Serlo, MD, PhD (WS)	Professor and Chief of paediatric surgery at Oulu University Hospital, Department of Paediatrics and Adolescence.
Ambrocio Oy, a spin-off of the University of Turku, Finland (A)	Design of patient-specific cranial composite implants for human patients.
Covartim, Belgium (C)	Assessment of regulatory strategy.
Apium Additive Manufacturing, Germany (Apium)	Additive manufacturing technologies, equipment and materials.

3.3.2 Methodology and Materials

The integration of the CE approach and the DFM methodology is commonly used to enhance product development efficiency while reducing costs. The HCD principles are employed to guarantee that the final product is designed with the end-

user in mind. In this context, the author of this thesis and other team members are collaborating closely with leading Finnish neurosurgeons. By applying HCD principles to this project, the implant produced is not only technically efficient but also meets the requirements of patients and medical professionals who will interact with it. The methodology used in the study, related work packages (WPs) and partners involved are described in *Table 2*.

Table 2. Methodology.

WP1: Modular cranial semi-PSI design development
Contributors Involved: UTU, A, JF, KA, WS, C
Review, refinement of modular cranial semi-PSI design and fabrication of prototypes
Task 1.1 Modular cranial semi-PSI design inputs and outputs are defined including the overall product requirements and specifications. Consideration of theoretical aspects.
Task 1.2 Evaluation of the risk factors, safety and efficacy issues.
Task 1.3 Conceptualization of a design of the modular cranial semi-PSI
WP2: In vitro validation of the modular cranial semi-PSI
Contributors Involved: UTU, Apium, A
The objective is to address risk factors identified in WP1.
Task 2.1 Manufacturing of prototype implants for *in vitro* testing.
Task 2.2 Mechanical testing of the prototype implants.
WP3: Visualization of the modular cranial semi-PSI
Contributors Involved: JF, UTU, A, KA, WS, A
The objective is to develop modular cranial semi-PSI for LMICs and demonstrate the design in a clinically relevant artificial skull models.
Task 3.1 Fabricate the final demonstrative prototypes of the modular cranial semi-PSI utilizing AM, PEEK as the material of choice. Subsequently, assess the efficacy of these prototypes in addressing cranial defects by applying them to artificial anonymized skulls produced by AM.

The list of materials and equipment used, and devices produced within this thesis project is presented in *Table 3*.

Table 3. Materials, technologies, equipment, and devices are used within the thesis project.

AM materials	*AM Technologies and equipment*	*AM-manufactured medical devices*
1. PLA-filament, Clas Ohlson, Clas, Ohlson, Finland 2. VESTAKEEP® Fusion PEEK filament, Evonik, Germany	1. Original Prusa i3 MK3S+, Prusa Research, Czech Republic 2. Apium P220, Apium Additive Manufacturing, Germany	1. Modular cranial semi-patient specific implant.

The preliminary prototypes of the joints and elements, as well as crude prototypes of the modular cranial semi-PSI are produced by AM using Fused deposition modeling (FDM) process out of technical poly (lactic acid) (PLA) filament (PLA-filament, Clas Ohlson, Finland). The final prototypes of the modular cranial semi-PSI are produced by FDM (Apium P220, Apium Additive Manufacturing, Germany) out of PEEK (VESTAKEEP® Fusion PEEK filament, Evonik, Germany) medical grade filament - clinically relevant material.

3.3.3 Statistical Analysis

Statistical analysis of the mechanical data is executed with a commercial computer software (SPSS Inc., Chicago, Illinois, USA). Normality of the data is tested with Kolmogorov-Smirnov test. For normally distributed data with equal variances, the paired *t*-test is applied while comparing the measurements. The considered level of statistical significance is 0.05 level ($p \leq 0.05$), meaning that if a *p*-value is less than 0.05, the null hypothesis is rejected in favour of the alternative hypothesis. The null hypothesis typically posits that there is no effect or no difference between groups, so rejecting it suggests that there is an effect or a difference.

3.3.4 Ethical Aspects

As no interventions with real patients is performed, there are no major ethical issues in conducting the study. Therefore, as per regulations, no approval from the ethical committee is needed.

The present study employs patient-based imaging data, specifically thin-layer computed head tomography scans obtained from patients who underwent decompressive hemicraniectomy at Turku University Hospital. The utilization of clinical data in a retrospective manner eliminates the need for informed consent and personal contact with the participants. To ensure anonymity, DICOM identifiers are removed from the 3D imaging data prior to processing. The primary purpose of this data is to collect impersonal information regarding defects and skull anatomy. Additionally, a series of artificial anonymized skulls produced by AM and generously provided by Dr. Kalle Aitasalo is used to analyze the modular cranial semi-PSI. The author considers both PEEK as material and PSI as a means of personalized cranial reconstruction method ethically sound and clinically feasible.

4. Process in Practice

Due to the complexity and intricacies involved in the development of medical devices, it is infeasible to accomplish a comprehensive design within a limited time frame of the thesis project. Consequently, the scope of this work is restricted to the conceptualization and visualization of the implant design as well as testing of some functional features. This approach will allow for the exploration of key design elements and the establishment of a foundation for further development, while acknowledging the time constraints and the numerous factors that must be considered in the creation of a fully functional implant.

4.1 WP1: Implant technology and design development

4.1.1 Implants design inputs and outputs. Consideration of theoretical and practical aspects.

Designing cranial implant necessitates a thorough understanding of both the inputs and outputs to ensure optimal patient outcomes. Design inputs encompass the overall product requirements and specifications, which guide the development process, while the design outputs define the resulting implant characteristics and performance criteria.

Design Inputs

Design inputs are the initial requirements, specifications, and criteria that guide the development of a medical device. These inputs are based on the intended use, user needs, and regulatory requirements. In the framework of this thesis project the design inputs include the following:

Patient Anatomy

The geometric approximations provide a simplified way to understand the shape of the skull. The human skull can be described in terms of simple geometric forms, such as two blended spheres. The skull is composed of the cranium and the facial bones.

The cranium is the upper part of the human skull that surrounds and protects the brain, is made up of several fused bones with various openings for nerves, blood vessels, and structures, and houses and protects the organs of the inner ear. In simple terms, the cranium is the protective bony structure that encases and supports the brain. The bones containing the cranium are the nasal, frontal, parietal, sphenoid, temporal, occipital and mastoid bones, which are fused together to form a protective and structurally sound enclosure for the brain. In addition to the cranial bones, the human skull also includes bones of the face such as the nasal bones, zygomatic bones (cheekbones), maxilla (upper jawbone), and mandible (lower jawbone). These bones work together to support and protect the facial structures, including the nasal cavity, mouth, and teeth.

The cranium can be approximated by a rounded sphere. The facial bones, which include the eye sockets and the nose, can be approximated by a smaller

sphere that blends into the cranium. These two spheres are blended in a way that forms the basic shape of the skull. Alternatively, the skull can be approximated as a rectangular prism with rounded corners. The top of the rectangle represents the cranium, while the lower part represents the facial bones. Another way to approximate the skull is as a cone with a rectangular base. The tip of the cone represents the top of the skull, while the rectangular base represents the facial bones. In addition, the skull can also be approximated by a series of interconnected triangles. This method highlights the various planes and angles of the skull and can be used to accurately depict the complex shape of the human skull. Skulls from different individuals can vary significantly in their size, shape, and overall morphology. These differences are largely due to genetic variation, as well as environmental factors such as nutrition, disease, and trauma (Bakken et al., 2011). On the other hand, there are many landmarks on the skull that can be used to differentiate between individuals. Moreover, cranial implant design requires careful consideration of these anatomical landmarks to ensure a proper fit and adequate functionality of the device.

Craniometry is the study and measurement of the human skull, including its size, shape, and proportions, which can be used to investigate patterns of human variation and evolution. Craniometry takes into account specific craniometric points, landmarks, found on the entire skull, not just the cranium, such as the zygomatic bones, nasal bones, and mandible. The landmarks are used in anthropometry to measure and study human variation and can provide important information about ancestry, identity, and disease. Craniometric points are typically located along the midline and sides of the skull, and they are mirrored along the midline of the skull. This is important in anthropometry because it allows for accurate and consistent measurements of the skull and its landmarks.

Some of the most relevant for cranial implant design landmarks include the following craniometric points (see *Figure 19*) (Vigo et al., 2020):

The craniometric points located along the midline of the skull, starting from front to back:

Nasion (NAS): Located at the intersection of the frontal and nasal bones.

Glabella (GLA): The midpoint between the eyebrows, above the nasal root.

Metopion (MET): Maximal protuberance of the frontal bone between Gambela and Bregma.

Bregma (BRM): The junction of the coronal and sagittal sutures.

Vertex (VTX): The highest point of the skull and the cranium, located along the sagittal suture.

Lambda (LAM): The junction of the sagittal and lambdoid sutures.

Obelion (OBN): The midpoint between Vertex and Lambda.

Opisthocranion (OPI): The most prominent posterior point of the occipital bone.

Inion (INI): The most prominent point of the external occipital protuberance.

Basion (BAS): The front of the foramen magnum, a large opening at the bottom of the skull where the spinal cord connects to the brainstem. The distance between Basion and Bregma is considered as the height of the skull, the distance between Glabella and Opisthocranion is considered as the length of the cranium and the skull.

The temporal line or the linea temporalis superior is a bony ridge on the external surface of the temporal bone. It serves as an attachment site for the temporalis muscle, which is one of the major muscles involved in chewing. In addition to its functional role in muscle attachment, the temporal line is also a morphometric landmark. It virtually separates the curved top section of the skull (also known as the vault or calvaria) from the flatter sides of the skull (also known as the basicranium).

The craniometric points located along the sides of the skull, starting from front to back:

Pterion (PTR): The junction of the frontal, parietal, sphenoid, and temporal bones.

Stephanion (STP): The most lateral point on the frontozygomatic suture, which is the joint between the frontal bone and the zygomatic bone. It is a point located on the

temporal bone of the skull, specifically at the intersection of the coronal suture and the frontal end of the temporal line.

Zygion (ZYG): The most lateral point of the zygomatic arch.

Gonion (GON): The outermost point of the mandibular angle.

The Euryon (EUR): The most lateral point on the skull, and it is commonly used to measure the maximum cranial breadth, which is the widest point of the skull.

Asterion (AST): The junction of the parietal, temporal, and occipital bones.

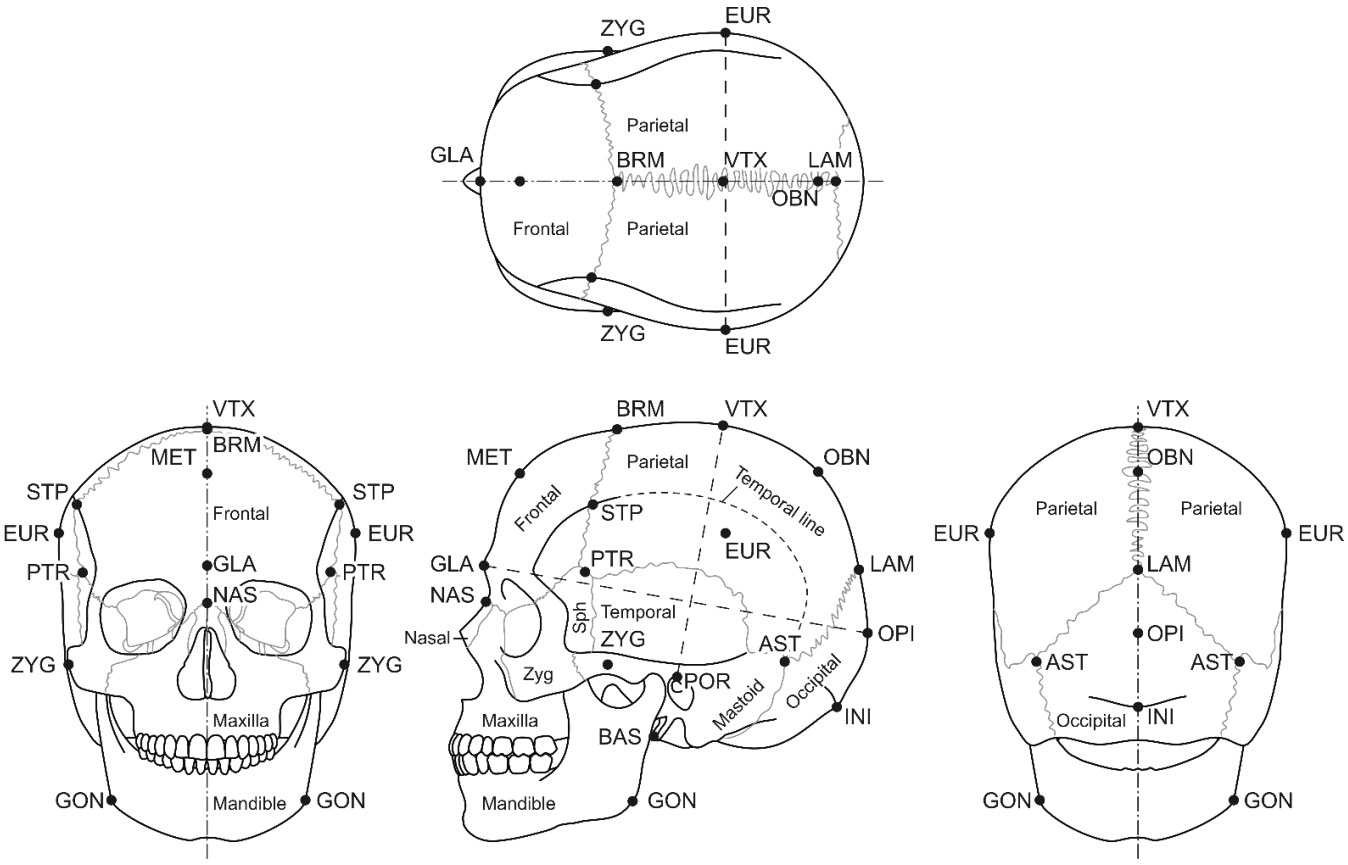


Figure 19. The most relevant for cranial implant design anatomical landmarks.

A thorough understanding of these landmarks is essential for designing cranial implants that maintain structural integrity and restore the patient's cranial contour. Advanced imaging techniques like CT scans can provide detailed information on these landmarks. However, it should be noted that in the context of craniometric

points and cranial implant design, there is not a single "zero point" that serves as an origin or baseline for all measurements. Instead, the measurements are made relative to the specific anatomical landmarks of the craniometric points themselves. In some cases, a common reference point may be used as a baseline for measurements, but this depends on the specific procedure, implant design, or research question being addressed.

Cranial Defect Anatomy

Cranial defects encompass abnormalities or absences within the skull structure, resulting from a variety of causes such as congenital malformations, traumatic injury, surgical intervention, or pathological processes. Thorough comprehension of the anatomy of cranial defects is crucial for accurate diagnosis and reconstruction.

Defects can occur in diverse regions of the skull, including the frontal, parietal, temporal, or occipital bones. The location significantly influences surgical approaches, potential complications, and cosmetic outcomes. Furthermore, cranial defects can display considerable variation in size and shape, which dictates the complexity of the reconstruction process and selection of repair techniques. It is also essential to consider the proximity of critical neurovascular structures, such as the dura mater, major blood vessels, or cranial nerves, when planning surgical intervention. The presence of these structures can affect the choice of implant material and surgical approach, as well as the risk of complications. The involvement of overlying soft tissues, including the scalp, muscles, and connective tissues, may also complicate the reconstruction process due to potential damage, scarring, or adhesion to the underlying bone or dura mater. Lastly, understanding the aetiology of the cranial defect is vital for determining surgical management, prognosis, and potential for recurrence (Principles of Neurological Surgery, 2012).

In cases of trauma, cranial defects are typically caused by a direct impact to the head, which can result in fractures or depressions in the skull. The location and size of these defects can vary depending on the force and direction of the impact, as well as the thickness and strength of the skull at that particular location. Trauma-

induced cranial defects can occur anywhere on the skull, including the front, top, back, and sides (Principles of Neurological Surgery, 2012).

In cases of craniotomy, which is a surgical procedure where a portion of the skull is removed to access the brain, cranial defects are typically created intentionally. The size and location of the defect depend on the specific location of the brain that needs to be accessed, as well as the extent of the surgery required. Common locations for craniotomy defects include the front, back, and sides of the skull, depending on the location of the pathology (Principles of Neurological Surgery, 2012).

In cases of tumours, cranial defects can also be created intentionally to remove the tumour or to access the brain for radiation therapy. The location and size of the defect depend on the location and size of the tumour, as well as the extent of the surgery required to remove it. In general, cranial defects created for surgical purposes are typically circular or oval-shaped and range in size from a few centimetres to the entire thickness of the skull. The location of the defect depends on the specific location of the pathology and the surgical approach used to access it. The size and location of the cranial defect are important considerations in the surgical planning and can have important implications for the patient's recovery and long-term outcomes (Principles of Neurological Surgery, 2012).

Biocompatibility

Biocompatibility refers to the ability of a material to interact with living tissues or biological systems without causing adverse reactions. In the context of medical implants, biocompatibility is a critical property, as it ensures that the materials used for implant manufacturing do not elicit negative immune responses, cause inflammation, or lead to toxic reactions when in contact with the body (Marin et al., 2020). There are various tests and standards to evaluate the biocompatibility of materials, such as ISO 10993 (Biological Evaluation of Medical Devices) and ASTM F748 (Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices). These tests assess aspects like cytotoxicity, sensitization, irritation, and systemic toxicity to ensure the material's safety for its intended use. A biocompatible

material should not only be well accepted by host tissues but also have suitable mechanical properties, chemical stability, and resistance to wear and degradation in the physiological environment.

Mechanical Properties

Mechanical properties of the implant such as strength, stiffness, and durability should be considered to ensure it can withstand physiological loads or impact and maintain its structural integrity over time. The choice of material and manufacturing method can significantly influence the mechanical properties of an implant.

Aesthetics and Function

Cranial implant aesthetics play a critical role in patient satisfaction and quality of life after reconstructive surgery, as the reconstructed area's appearance has a significant impact on the individual's well-being (Worm et al., 2019). To achieve a natural, symmetric outcome that closely resembles the patient's original anatomy, several factors must be considered in the design process. Employing patient-specific or semi-patient specific cranial implant design, which takes into account significant anatomical reference points and landmarks, ensures a clinically adequate alignment of the implant with the affected region.

Surgical Ergonomics

When designing a medical implant, proper ergonomic considerations can reduce physical and cognitive strain on surgeons, minimize the risk of errors, and enhance overall surgical outcomes. The design of an implant should consider ease of surgical placement and ensuring a secure fit. In the case of the modular cranial semi-PSI, it is crucial to design the stackable elements of appropriate size, shape, and texture to ensure comfortable and precise handling. This includes providing a comfortable grip and minimizing the risk of slipping as a major factor. In addition, the design of stackable element connector should be precisely planned to guarantee safe joint between the parts of the modular cranial semi-PSI and intuitive assembling of the implant by the surgeon.

The suitable size of details that are comfortable to hold in hands and assemble can vary depending on the specific object and its intended use. However, as a general ergonomics guideline, the object should be designed to fit comfortably in the hand and minimize strain during use. Ideally, the dimensions should fall within the range of 30mm to 100mm in width or diameter. Smaller objects can be difficult to grasp and manipulate, while larger objects may be cumbersome and difficult to hold. The object's shape should allow for a secure and comfortable grip. Curved or contoured surfaces can provide better grip and reduce the likelihood of slipping during handling and assembly. When the object is intended to be assembled, the parts should be easily aligned and connected without requiring excessive force. The surface texture of the object can influence how comfortable it is to hold. A smooth surface can be comfortable but may be slippery when wet. A textured surface can provide a better grip and reduce slipping.

Overall, prioritizing ergonomic considerations in implant design may lead to improved patient outcomes and enhance the overall effectiveness of implantation procedures. By creating user-friendly, intuitive, and comfortable implant components, the risk of unfavourable events during surgery is decreased, leading to shorter operation times. Furthermore, ergonomic implant design fosters a greater level of precision, resulting in better implant fit and functionality.

Regulatory Compliance

Regulatory landscape in LMICs is very versatile but an essential factor to consider. Frequently, LMICs tend to adopt or adapt European and American standards for medical devices. This is mainly due to the fact that the European Union and the United States have well-established regulatory frameworks, such as the European CE marking requirements and the U.S. FDA regulations, which are considered to be rigorous and comprehensive. Nevertheless, some LMICs has their own set of regulatory requirements for medical devices, which may slightly vary from those in high-income countries in terms e.g., user manuals, labelling and risk management requirements etc. Ensuring that the implant meets the relevant regulatory standards is crucial for obtaining approval, market access, and ensuring the safety and efficacy of the implant for patients in LMICs.

Design Outputs

Design outputs are the tangible results or deliverables produced during the development process that meet the design input requirements. They include detailed drawings, specifications, test results, and other relevant data that describes a medical device's design and demonstrates how it meets the design input criteria. General design inputs for medical devices typically include implant geometry, materials selection and manufacturing methods, safety requirements and risk management, sterilization methods, packaging and labelling, quality control, clinical evaluation, and post-marketing follow-up.

In the framework of this thesis project the design inputs are limited towards conceptual once and include the following:

Implant Geometry

Accuracy and precision of the implant

The final implant design should adequately match the patient's cranial defect for optimal functional and aesthetic outcome.

Accuracy and precision are fundamental measures of observational error in the context of manufacturing cranial PSI. Accuracy refers to the conformity of a measurement, calculation, or specification to the correct value or standard, whereas precision denotes the closeness of measurements to each other. When manufacturing cranial PSIs, the input required is the patient's skull anatomy and the cranial defect's morphology. However, direct access to these inputs is not possible as the human skull is covered with muscles and skin. Therefore, indirect imaging methods such as CT scans are employed to obtain the required data. CT scans enable obtaining the skull's anatomical characteristics and the morphology of the defect but introduce potential errors due to the imaging detector resolution and X-ray data conversion into slices. Additionally, the CT data need to be binarized and segmented into "bone" and "not bone" categories, but inaccuracies may arise due to the threshold greyscale values used, potentially leading to discrepancies in the spatial position of the skull surface.

Next, the binarized data is converted into a polygonal mesh, typically composed of small triangles of varying sizes. The conversion process approximates the binarized volumetric data, which can result in a "smooth" mesh with fewer triangles or a more detailed, "heavy" mesh that may be more challenging for further processing. The polygonal skull model obtained at this stage serves as the foundation for subsequent steps, although it is important to recognize that this model is an approximation of the skull, not an exact replica. It should also be noted that the patient's skull is often imaged at a certain time point, but the decision to create an implant may be made after a follow-up period. Since bone is a living tissue undergoing constant remodelling, the geometry of the defect will change slightly over time, and the edges of the defect will become more rounded. Consequently, the polygonal skull model may be less representative than anticipated.

Furthermore, the polygonal skull model is employed to create a CAD model of the implant by extrapolating the defect anatomy using existing data or an "educated guess" if the data is missing. The CAD model, typically constructed of non-uniform rational b-splines (NURBs), serves as another approximation of the polygonal model. The CAD model is subsequently transferred to the manufacturing process, which introduces additional geometrical inconsistencies.

The typical size of a cranial defect is the size of a palm of hand. Cases involving extremely large defects, e.g., over a half of the skull missing, are very rare. Thus, unlike the development of protective helmets, it is not necessary to consider the geometry of the whole skull, rather just a fraction of it, which can be approximated by a sphere. Since the clinically relevant tolerances for cranial implants are in the range of +/- 1mm, the development of pre-shaped implants with a mean curvature (R1) of human skulls can be advantageous (see *Figure 20*).

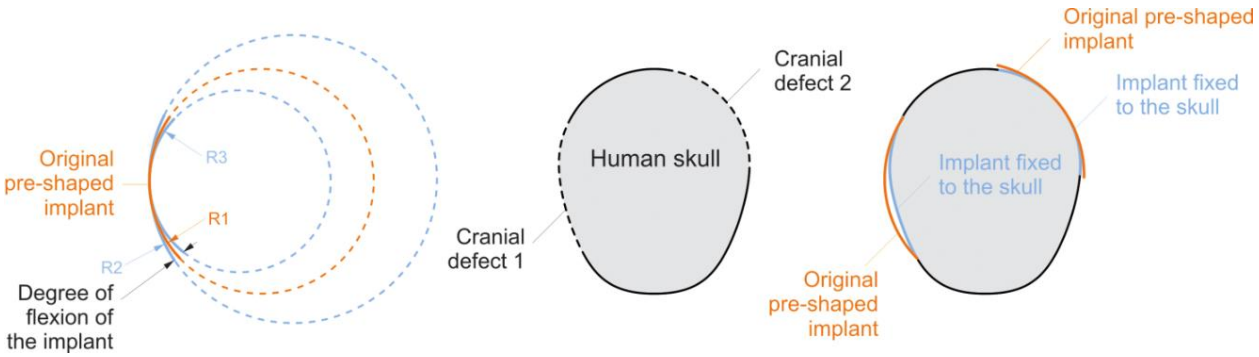


Figure 20. Schematic illustration of approximations used for designing cranial PSIs.

By integrating a certain degree of flexibility into the implant design, either through material properties or implant structure, it is possible to fit these pre-curved implants to a vast majority of cases. Slight flexural deviations at the implant's periphery led to large deviations in the implant's radius (R2 – R3), allowing for a more adaptable fit.

In summary, since the patient's skull anatomy and the cranial defect's morphology are not directly accessible for physical examination, estimating accuracy can be challenging. Furthermore, determining precision is also difficult since it is not possible to create multiple PSIs independently and test their fit to the bone defect during surgery. However, by leveraging pre-curved implants and incorporating flexibility into the design, it is possible to achieve clinically acceptable tolerances in the range of +/- 1mm.

In the case of the modular cranial semi-PSI, by using pre-curved elements, different geometrical shapes, and material properties, most of the anatomical locations can be surgically addressed. The optimal curvature is determined through the acquisition of measurements from five randomly selected artificial anonymized skulls produced by AM. These measurements were obtained using the craniometric points described in “Patient Anatomy” section of this thesis. Although this method may not provide the optimal locations for measuring the human skull shape, it offers a standardized and repeatable measurement approach.

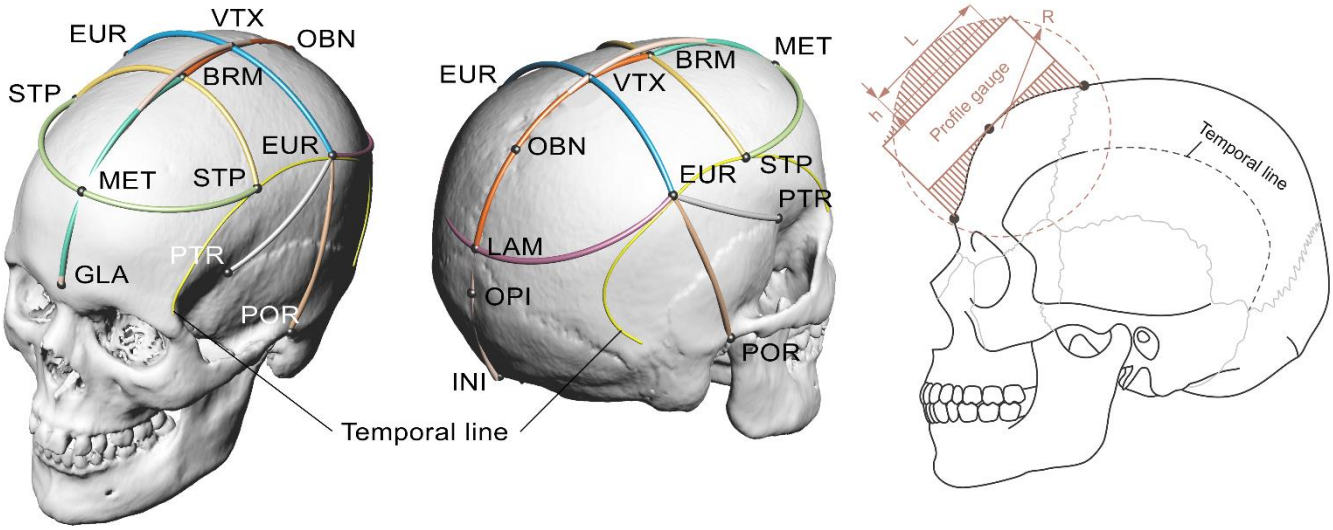


Figure 21. Schematic illustration of the measurement of optimal curvature.

To evaluate the curvature of the cranial surfaces, a profile gauge is employed, as depicted in *Figure 21*. This tool, commonly utilized by carpenters to duplicate and transfer intricate or irregular shapes from one surface to another, is repurposed to obtain the radius of the curvature of the skull. The procedure involves recording measurements from the profile gauge, including the length (L) and height (h) of the profile, and subsequently calculating the desired radius (R) using the formula $R = h/2 + (L^2/(8*h))$.

To assess accuracy, the author and the team members employed a semi-spherical standard object, as a true value, with a standard radius of 85.3 mm, measured using a caliper. The percent error is calculated by comparing the average of 12 measurements obtained with the profile gauge to the known radius of a semi-spherical standard object. The formula utilized is % error = ((|measured value - true value|) / true value) x 100%. Meanwhile, the method's precision is evaluated by calculating the standard deviation of the 12 measurements. The mean value of the measurements is 81.5 mm, the % error is 4.4%, and the standard deviation is 6.4 mm. The normality of the measurement data is assessed using the Kolmogorov-Smirnov test, which allows for the calculation of mean values and standard deviations. However, the presented analysis pertains to the accuracy and precision of the measurement technique.

In turn, measuring the curvature of skulls poses a greater challenge due to the non-circular shape of the skulls and the fact that craniometric points are still rather an approximation. To assess the precision of the measurement method applied to the skulls, 12 measurements are taken at multiple anatomic locations on the artificial anonymized skulls produced by AM. The mean value and standard deviation are calculated for each location to determine the precision of the measurements (see *Table 4.*). The normality of the measurement data is assessed using the Kolmogorov-Smirnov test. As for accuracy, comparing the curvatures measured from a virtual 3D model to those measured from the artificial anonymized skulls is biased due to the deviations in the 3D printing processes. However, the use of a profile gauge to measure curvatures from loosely defined landmarks is expected to yield results that overshadow the differences between the virtual and physical 3D model. The %error is ranged from 3 to 26% depending on the anatomic location (see *Table 4.*). A paired t-test is used to assess the differences between the curvatures measured from a virtual 3D model and the mean values of those measured from the artificial anonymized skulls produced by AM, and the differences are not statistically significant at the level of p-value = 0.05 (see *Table 4.*). These findings confirm the relevance of the selected measurement model for clinical settings.

In summary, the mean value of all curvature measurements for the five skulls was 87.4 mm, which provides a good estimate for the curvature of each individual pre-curved element of the modular cranial semi-PSI. However, the mean value of all measurements of curvatures above the temporal line is 76.5 mm, while below the temporal line, the mean value of all measurements is 125.4 mm, indicating a significant change in curvature along this region. This presents a challenge in the construction of the modular cranial semi-PSI, as the selection and orientation of implant elements need to take this sharp change in curvature into account. For temporal defects, it may be necessary to use a different set of pre-curved elements with curvatures closer to 125.4 mm or even flat elements. Thus, acknowledging this variation in curvature is crucial in achieving optimal implant fit and function.

Table 4. Results of the craniometrics measurements.

Anatomic location	Skull A*	Skull A** mean ± std.dev.	Accuracy (% error)	Skull B**	Skull C**	Skull D**	Skull E**	All skulls** mean ± std.dev.
STP-BRM	65.3	67.9 ± 6.0	*4.0*	61.6	66.3	72,7	75.0	68.7 ± 5.3
EUR_VTX	78.1	86.3 ± 3.9	*10.5*	77.0	78.3	71,6	87.3	80.1 ± 6.6
STP-MET	57.6	72.4 ± 6.2	*25.6*	61.7	58.7	64,1	64.7	64.3 ± 5.1
EUR-LAM	65.3	77.8 ± 2.8	*19.1*	67.5	82.8	81,5	70.9	76.1 ± 6.7
GLA-BRM	77.2	66.7 ± 2.6	*13.6*	68.8	96.3	76,0	76.5	76.9 ± 11.7
BRM-LAM	85.8	83.3 ± 5.0	*2.9*	84.7	86.3	73,1	79.1	81.3 ± 5.3
GLA-INI	96.2	90.5 ± 5.0	*5.8*	84.2	98.0	78,7	90.7	88.4 ± 7.3
PTR-EUR	113.0	134.5 ± 21.12	*19.1*	96.3	136.3	124,7	154.5	129.3 ± 21.3
POR-EUR	140.3	155.6 ± 45.0	*10.9*	98.9	105.2	118,2	130.0	121.6 ± 22.5

* 3D-model, ** artificial anonymized skulls produced by AM

Segmentation of the modular implant: Consideration of theoretical and practical aspects.

The goal of the design process within this thesis project is to create adaptable, customizable cranial implant that can conform to various defect shapes and sizes with clinically acceptable tolerances as described above. In the framework of this project, origami, the art of paper folding, provided valuable insights during conceptualization stage of the design process.

In general, origami principles can be applied to implant`s design, enabling the creation of complex, adjustable structures through strategic folding patterns. By introducing origami mindset into the design process, it is possible to create cranial implants with greater flexibility and adaptability, facilitating a better fit to various skull and defect anatomies. This mindset is rooted in the concepts of geometry, topology, and spatial transformation. Origami designs are based on crease patterns, which are the arrangements of folds on a flat surface. These patterns are often symmetrical and can be represented using mathematical concepts such as tessellations. In origami, tessellations can be used to describe the repetitive arrangement of folds, such as those found in Miura-ori or other origami tessellation designs. Tessellations can help

to understand the underlying geometric structure of the crease pattern and can be used to create complex origami designs with a higher level of symmetry and intricacy.

Tessellation and origami share a connection through their geometric foundations, as both involve the arrangement of repeated shapes in particular patterns. Tessellation refers to the arrangement of a single shape or combination of shapes on a flat surface, such that they cover the entire surface without any gaps or overlaps. A connection between tessellation and origami can be also found in Truchet patterns, an intriguing link between the two fields. Truchet pattern can be applied to the design of origami-like structures by using the tiles as a guide for folding patterns, or by considering the folds and creases in origami as analogous to the edges and vertices of tiles in a tessellation.

Truchet tiles are a type of polygonal tiles that are decorated with non-rotationally symmetric patterns. They can be created in the shape of any polygon but are typically square or hexagonal. The tiles can be coloured in a checkered pattern so that the corners alternate in colour. When arranged in a tiling, they create complex and beautiful patterns. Truchet tiles were first described in a 1704 memoir by Sébastien Truchet and were popularized in 1987 by Cyril Stanley Smith(Smith & Boucher, 1987). The original Truchet tile is a square tile with a diagonal line that separates it into two equal regions that can be coloured (see Figure 22A). Multiple tiles can be combined to create various patterns. Another common form of Truchet tile is decorated with two quarter-circles that connect the midpoints of adjacent sides. This separates the tile into three regions: two quarter circles and a leftover region after subtracting the two quarter circles from the square. These regions can be coloured (see *Figure 22B*). Alternating vertices of a hexagon can be decorated by 120-degree sectors of a sphere (see *Figure 22C*), and the hexagonal tiles can be arranged in different ways to create patterns (see *Figure 22D*). Hexagons have a mathematical advantage, as they can be described in terms of identical, equilateral triangles. Each vertex of such a triangle can be decorated by 60-degree sectors of a sphere (see *Figure 22E*). By colouring the regions of the triangles formed by the sectors with, one can create a versatile system that includes all the patterns provided

by hexagonal Truchet tiles, as well as other systems such as the "bubblewrap" system seen in the tiling of the Birmingham Selfridges building and "Apilakivi" + circle system, such as Aamos Rex tiles, and (see *Figure 22F*).

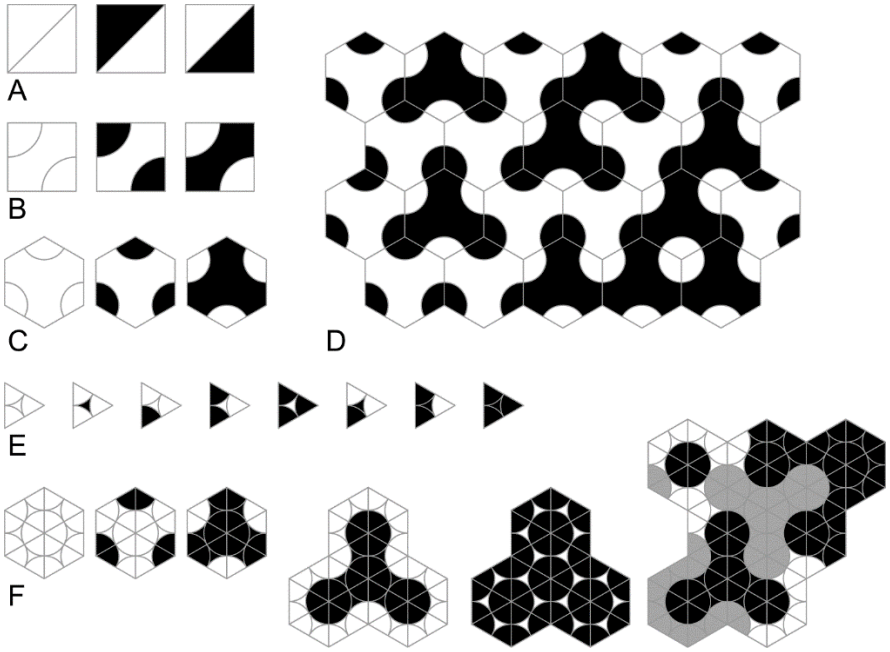


Figure 22. A) The original square Truchet tiles; B) square Truchet tiles decorated with quarter-circles according to Smith and Boucher; C) hexagonal Truchet tiles; D) tiling with the hexagonal Truchet tiles; E) tiles made of triangle can be decorated by 60-degree sectors of a sphere; F) Different patterns created by the triangular tiling.

Considering the pattern's-colored areas as separate objects can result in irregularly shaped pieces like a jigsaw puzzle that can be securely attached to each other due to their concave and convex nature.

Amos Rex Apilakivi is a paving stone designed in collaboration with architect Asmo Jaaksi. Apilakivi, also known as "Apila Stone" or "Clover Stone," was created to bring a playful, undulating appearance to the Lasipalatsi Square, where the Amos Rex art museum is in Helsinki, Finland. The stone has a unique pattern that resembles a clover leaf, making it visually interesting and aesthetically pleasing. This particular shape presents an appealing functional and aesthetical foundation for the development of modular cranial semi-PSI, representing a specialized instance of the overarching concept described above.

Material Selection and Manufacturing Method

Selecting an appropriate material is crucial for ensuring that the implant is biocompatible and can withstand physiological loads and maintain its structural integrity over time. PEEK is a high-performance thermoplastic material that has become increasingly popular for cranial reconstruction due to its biocompatibility, mechanical properties, and stability. In the framework of this thesis project, PEEK in the form of a filament (VESTAKEEP® Fusion PEEK filament, Evonik, Germany) for AM is used for manufacturing of the final demonstrational prototypes of the modular cranial semi-PSI. PEEK is biocompatible material with modulus of elasticity close to human bone, which allows for better stress distribution in the case of an impact. In addition, it prevents aberrant motion or distortion of the implant, while simultaneously offering the capacity for contouring and polishing to achieve a refined surface finish. These characteristics contribute to the overall effectiveness and aesthetic appeal of the cranial reconstruction. This material is radiolucent and does not interfere with diagnostic imaging. In addition, PEEK is highly resistant to chemical degradation and maintains its mechanical properties over time. This ensures that the implant remains stable and functional throughout its lifetime (Garcia-Gonzalez et al., 2017; Ng & Nawaz, 2014).

Manufacturing methods also play a critical role in determining the properties of an implant. Traditional manufacturing techniques, such as casting, forging, or machining, can offer precise control over the implant's geometry and material properties. However, these methods are not always optimal especially in LMICs due to high costs and lack of process flexibility. AM has emerged as a promising technology with the potential to revolutionize healthcare provision in LMICs. AM enables the cost-effective and rapid production of implants with complex geometries on the spot. AM equipment can be easily set up in local hospitals in LMICs, reducing the need for expensive imports and enabling faster access to PSIs. In addition, AM can process various biocompatible materials, including polymers, metals, and ceramics, providing the opportunity to select the most appropriate material for the patient and the specific clinical situation.

In this thesis, FDM process using PEEK printer Apium P220, Apium Additive Manufacturing, Germany is employed for manufacturing the final demonstrational prototypes of the modular cranial semi-PSI. FDM is an AM technique that constructs three-dimensional objects by depositing successive layers of material. The FDM process begins with a digital model of the object to be created. This model is then converted into a series of thin layers using specialized slicing software. During the printing process, a thermoplastic filament is fed into the FDM printer's extruder, which heats the material to its melting point. The molten plastic is then extruded through a nozzle and deposited onto the build platform, tracing the shape of the object's first layer. As the material cools and solidifies, it bonds to the previous layer, forming a solid structure. The build platform lowers, and the next layer is deposited on top of the previous one. This process is repeated until the entire object is complete. In the context of LMICs, in particular FDM process can significantly contribute to addressing challenges related to accessibility, affordability, and quality of healthcare services. However, it should be noted that design of the modular cranial semi-PSI, which is described in this thesis is not restricted to AM or any specific material and could be adapted to other economically relevant for LMICs materials and technologies such as e.g., injection moulding using PMMA, porous polyethylene etc.

Regulatory Compliance

In this thesis project, it is infeasible to ascertain all potential regulatory constraints that may arise in a specific LMIC. Therefore, the modular cranial semi-PSI is designed according to European standards for safety and efficacy of Class III medical devices.

Evaluation of Functionality

Prior to market entry and obtaining regulatory approval, comprehensive preclinical and clinical evaluations should be conducted to establish the safety, efficacy, and performance of the implant. These assessments are crucial in ensuring patient safety and implant functionality. However, in this thesis project, due to the time constrains, only preliminary mechanical testing is performed. A detailed description of these tests can be found in WP 2.

4.1.2 Evaluation of the risk factors, safety, and efficacy issues.

When designing a cranial implant, it is essential to carefully assess risk factors, safety, and efficacy to ensure the implant is both reliable and effective in addressing the patient's needs. General safety considerations for any cranial implant involve ensuring biocompatibility and non-toxicity of the materials used, as well as the manufacturing techniques employed. In turn, modular design of the cranial implant possesses specific challenges compared to traditional cranial PSIs, requiring additional consideration during the development process.

In the author`s opinion, the main risk factors associated with the modular cranial semi-PSI may include the potential for mechanical failure at the interconnecting elements, inadequate fit due to limited module options, and the complexity of the assembly process. To minimize these risks, it is important to develop robust connections between elements, create a comprehensive range of element shapes and sizes, and simplify the assembly process to reduce the possibility of errors during implantation. In the future, quality control measures should be implemented throughout the production process, and the modular design should account for the possibility of contamination or element breakage during assembly when assembled in the operation theatre. Therefore, the implant should be thoroughly tested to ensure the connections between elements maintain structural integrity and mechanical stability under physiological loading conditions.

Efficacy is a critical aspect in the development of modular cranial implant. The design should provide sufficient flexibility to adapt to a wide range of cranial defects, while maintaining a high level of anatomical accuracy and biomechanical performance. Moreover, a successful cranial modular implant should offer streamlined intraoperative assembly and adjustment capabilities, reducing surgical time and associated risks.

4.1.3 *Conceptualization of a design of the modular cranial semi-PSI*

The conceptualization of the modular cranial semi-PSI design is inspired by Amos Rex Apilakivi clover-like pattern and presents a set of stackable pre-curved elements (See *Figure 23*). The design features two main elements: a central load-bearing element and terminal elements that provide both load-bearing function and smooth contouring of the final implant. Additionally, there are two assistive elements which function as structural components for filling cranial defects and connecting the central element with the terminal elements in a robust and secure manner. The assistive elements are specifically designed to ensure compatibility with the other elements of the implant and to enable straightforward and efficient assembly by surgeons.

The development team, including the author of this thesis, advocates for a minimalist approach to the design, with the belief that minimizing the number of stackable elements will enable a straightforward, fast, and simple assembly process for surgeons. The design's modularity facilitates customization to patient-specific anatomical variations, while also simplifying the implant assembly process.

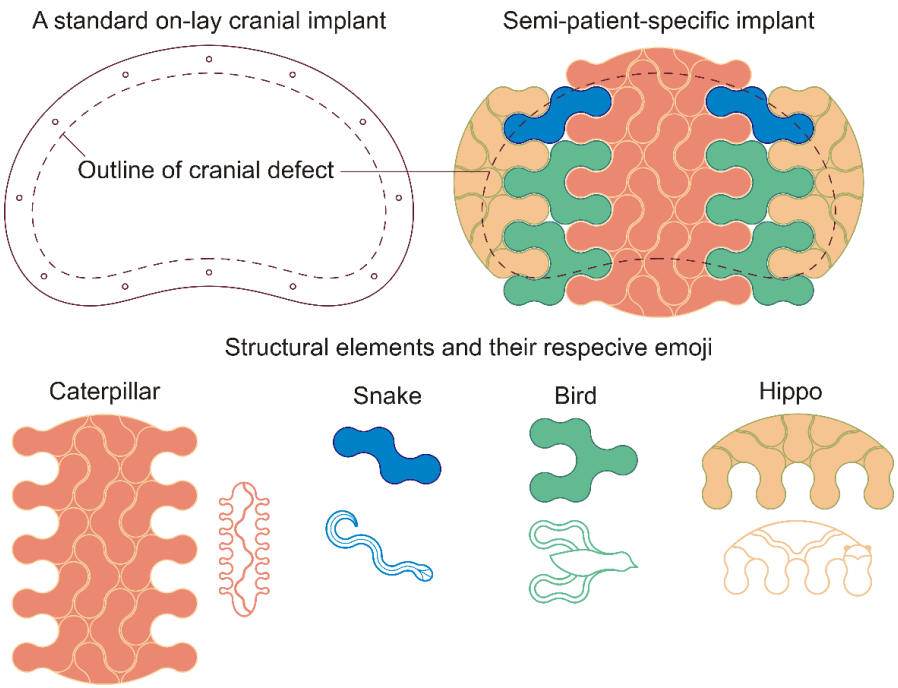


Figure 23. Conceptualization of a design of the modular cranial semi-PSI.

The assembly of stackable pre-curved elements for constructing a modular cranial semi-PSI is referred to as the "Armadillo" set. The development team believes that when assembled, the collective appearance of these elements resembles the shell of an armadillo. To facilitate intuitive usage, each type of stackable, pre-curved element is designated by a nature-inspired creature that is associated with the geometry of the respective element. The central element is named "Caterpillar," the terminal element is called "Hippo," and the two assistive elements are denoted as "Bird" and "Snake." Emojis are employed for visual representation.

The snap-fit joints are a common in modular objects that need to be assembled and disassembled easily and produced by AM. In the context of Armadillo set, snap-fit joints can be used to connect individual stackable pre-curved elements together, allowing for a secure and stable connection, while maintaining the ability to disassemble and reconfigure the modular cranial semi-PSI if needed. Therefore, in the framework of this thesis, for conceptualization and demonstration purposes, snap-fit of an annular type (see *Figure 24*) is used. The annular snap-fit design is well-suited for applications, where connection needs to be strong and stable but also allow for some degree of movement.

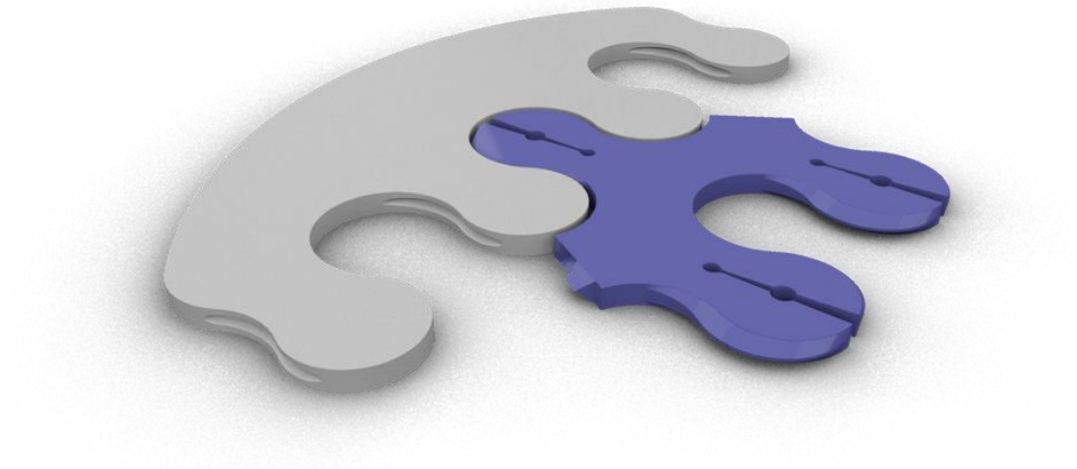


Figure 24. Snap-fit joint used in this thesis project.

Annular snap-fit connectors permit a limited degree of rotational movement, which can be advantageous in cranial implants where slight adjustments may be necessary

to achieve a precise fit on the patient's skull. This movement can help accommodate variations in skull shapes and allow for easier assembly and alignment during implantation. This type of connector can be designed to facilitate easy assembly and disassembly of the stackable pre-curved elements. In turn, this can facilitate potential replacements of specific components if needed during the assembly or even in revision surgeries. For example, as a child grows, the skull undergoes significant changes in shape and size. A modular cranial semi-PSI with annular snap-fit connectors can accommodate these changes by allowing for easy revisions or replacements of specific components. In such cases, a modular cranial semi-PSI can be designed with adjustable or replaceable components, ensuring a proper fit as the child's skull develops.

The design of the Armadillo set is created using Rhinoceros 7 (Robert McNeel & Associates, USA). The geometry (NURBs) is converted into a polygonal mesh and exported as an STL file. Thereafter, the STL file is imported into PrusaSlicer (Prusa Research, Czech Republic) and the output G-codes are generated. The layer thickness was 0.1 mm. The stackable pre-curved elements of Armadillo set are initially printed flat (2D without curvature) using FDM 3D-printer Original Prusa i3 MK3S+ (Prusa Research, Czech Republic). PLA-filaments (Clas Ohlson, Finland) of different colours are used for visualisation purpose. Thereafter, the elements are post-treated by heating up to 80°C and forming into a curved shape using a mould made of stainless steel and then assembled into the final shape (see *Figure 25*).

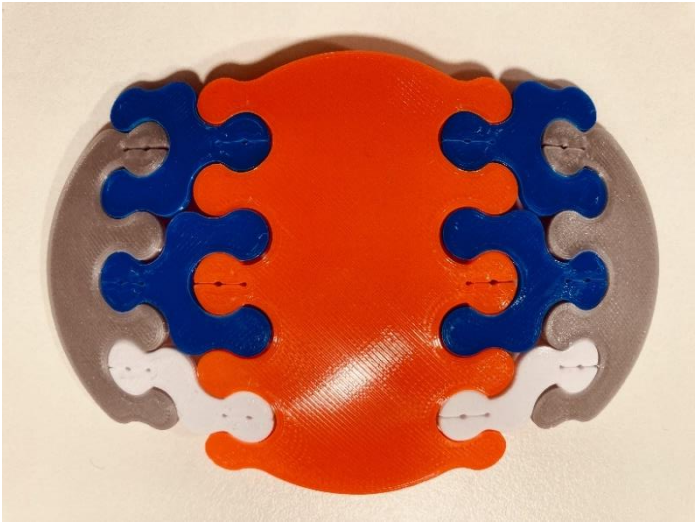


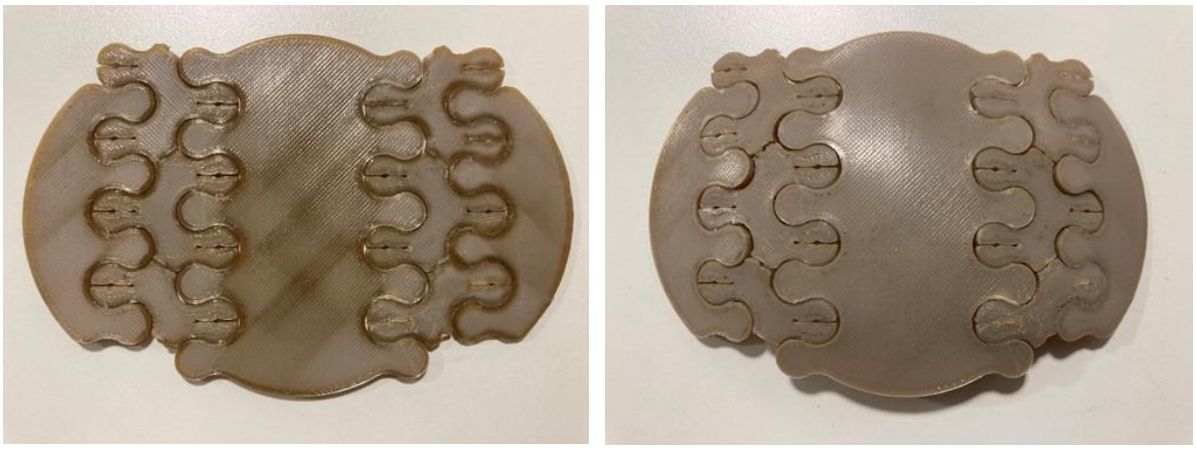
Figure 25. The PLA Armadillo set assembled into the PLA prototype of the modular cranial semi-PSI.

Conceptualisation of design is performed in iterative manner together with contributors of WP1 which are listed in *Table 2*.

4.2 WP2: In vitro validation of implants

4.2.1 Manufacturing of prototype implants for in vitro testing.

The design of the Armadillo set is created using Rhinoceros 7 (Robert McNeel & Associates, USA). The geometry (NURBs) is converted into a polygonal mesh and exported as an STL file. Thereafter, the STL file is imported into PrusaSlicer (Prusa Research, Czech Republic) and the output G-codes are generated. The layer thickness was 0.1 mm. The stackable pre-curved elements of Armadillo set are initially printed flat (2D without curvature) using Apium P220 3D-printer (Apium Additive Technologies GmbH, Germany). PEEK filament (Apium PEEK 4000 Natural, Product Code A130231, Apium Additive Technologies GmbH, Germany) was used. During the printing process, the filament was kept at 120°C in a filament dryer (F300, Apium Additive Technologies GmbH, Germany). Thereafter, the elements are post-treated by heating up to 150°C and forming into a curved shape using a mould made of stainless steel and then assembled into the final shape (see *Figure 26 A and B*).



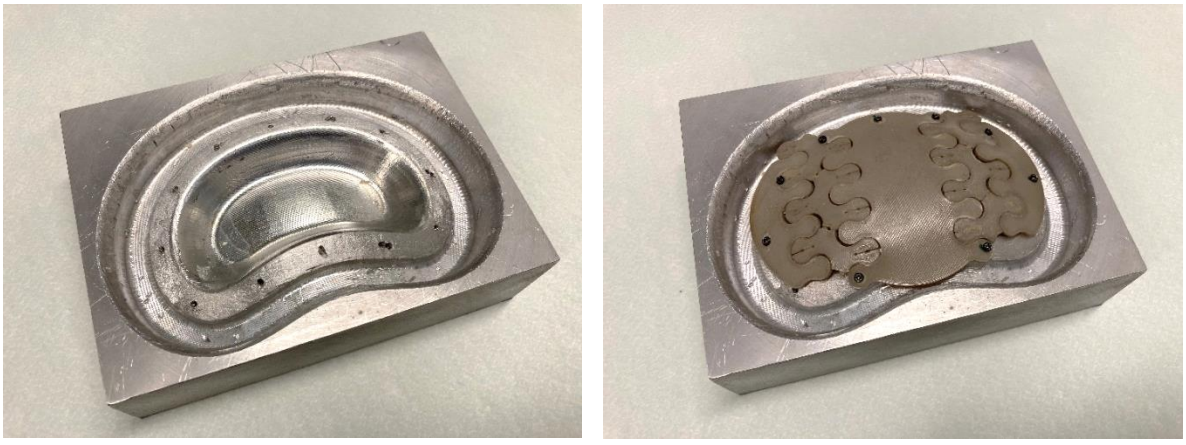
A *B*

Figure 26. The 3D printed PEEK Armadillo set flat (A) and after post-processing and final assembly (B) into the PEEK prototype of the modular cranial semi-PSI.

4.2.2 Mechanical testing of the prototype implants.

Experimental Set-Up

The mechanical testing is performed in compression according to the methodology described by Piitulainen et al., 2017. In total, five PEEK prototypes of the modular cranial semi-PSI were tested. In brief, the PEEK prototype of the modular cranial semi-PSI is attached to a purpose-built supporting jig with nine 2mm thick generic screws (see *Figure 27A*). The supporting jig is designed according to the geometry of a standard cranial implant (Piitulainen et al., 2017) and milled from a solid block of aluminium under computer control. The supporting jig has a central cavity offset 8 mm from the outer edge of the implant to simulate a cranial defect. The cavity allows the plunger to compress the central part of the implant. The jig, shown in *Figure 27A*, was previously used in paper Piitulainen et al., 2017. It is a challenge to attach the implant to the jig as the existing screw holes should have been matched by drilling the holes in the implant.

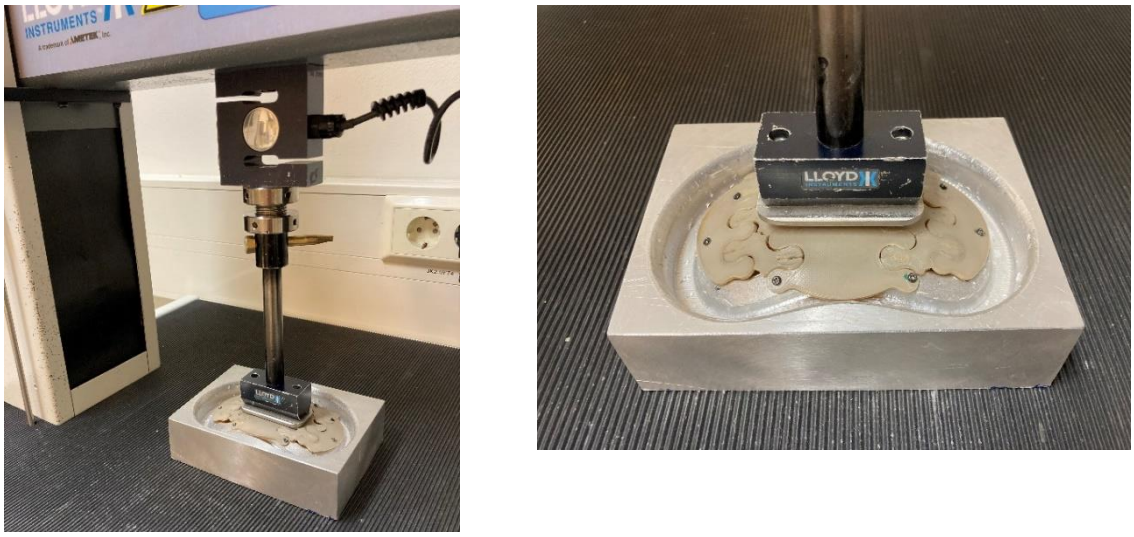


A *B*

Figure 27. Jig for mechanical testing (A). The PEEK prototype of the modular cranial semi-PSI attached to the jig with nine screws.

The PEEK prototype of the modular cranial semi-PSI is loaded at a constant speed of 1 mm/min in compression. The load was applied to the central area of the implant using a plunger. The plunger was rectangular in shape (60 x 30 mm) with rounded corners. A universal mechanical testing machine (LR30K, Lloyd Instruments Ltd, UK) was employed. The compressive force was recorded using Nexygen Plus software

(Lloyd Instruments Ltd). The prototype is tested up to 10-mm displacement of the plunger from the original implant surface. The set-up for the compression test is shown in *Figure 28*.



A *B*

Figure 28. The set-up for the compression test (A). The PEEK prototype of the modular cranial semi-PSI prior to the test.

Compressive force values are derived from the raw data acquired in the testing. Absorbed energy is measured from the raw as the areas under the force-displacement curves. The measurements are performed in Origin 2016 (OriginLab Corp. USA).

Results

In compressive mechanical testing, all five PEEK prototypes of the modular cranial semi-PSI kept their original shape up to the displacement of 6 mm (see *Figure 29A*). Thereafter, the connecters between the stackable pre-curved elements started to open, as seen in *Figure 29B* at the displacement of 8 mm. Nevertheless, the PEEK prototypes of the modular cranial semi-PSI did not fail catastrophically and stayed in one piece even after the displacement of 10 mm (see *Figure 29C* and *D*). Moreover, all the segments remained partially attached to each-other until the end of the test and none of the two "Bird" segments kept in place only by the snap-fit joints did disengage from the prototype. One of the PEEK prototypes of the modular cranial

semi-PSI is shown after the test in *Figure 29C and D*. No major delamination of the sections is observed. The quantitative results of the mechanical testing are presented in as means in *Figure 30A* (Compressive force) and *Figure 30B* (Absorbed energy).

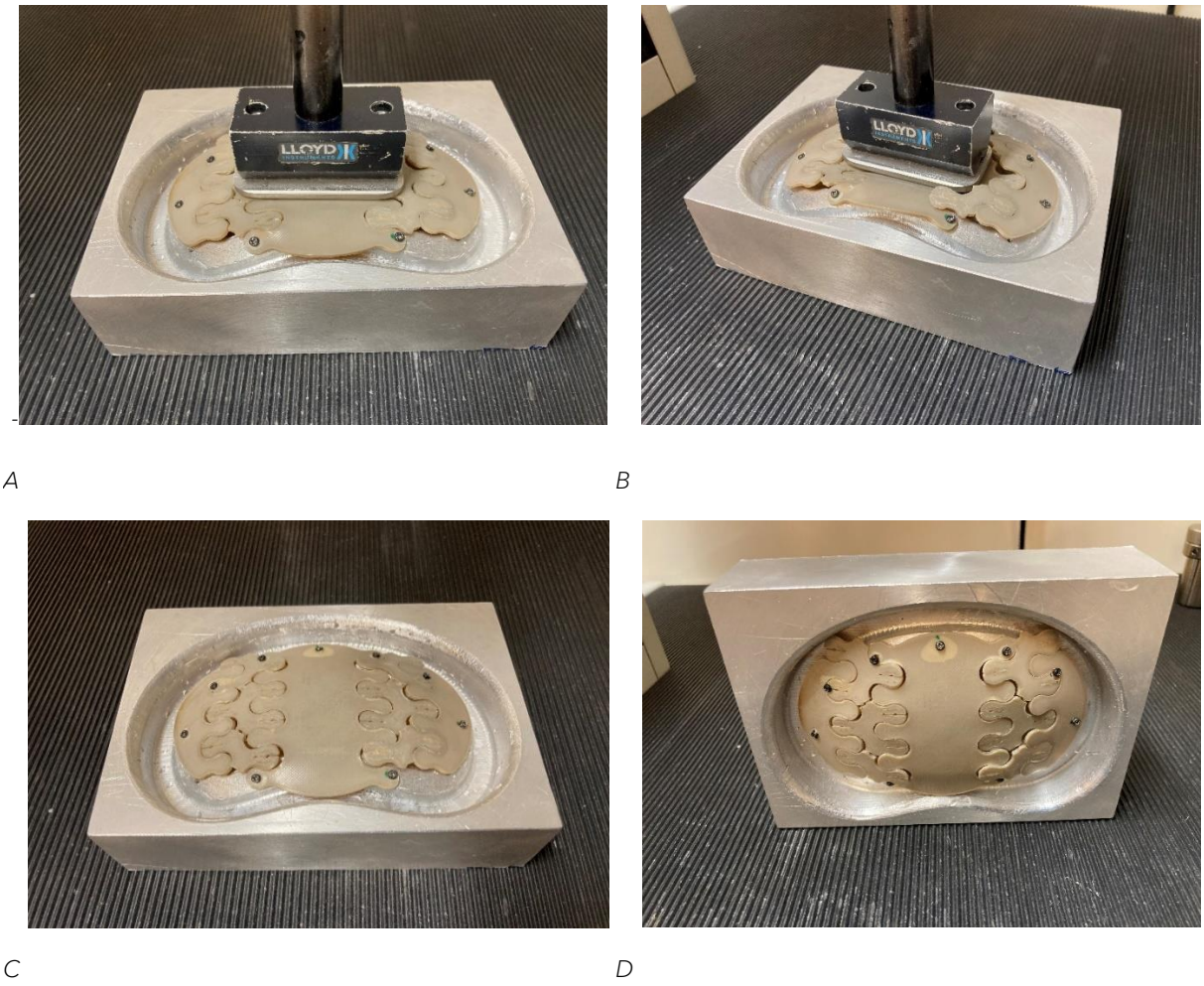


Figure 29. Mechanical testing at the displacement of 6 mm (A). Mechanical testing at the displacement of 8 mm (B). The PEEK prototype of the modular cranial semi-PSI after the test (C) and (D).

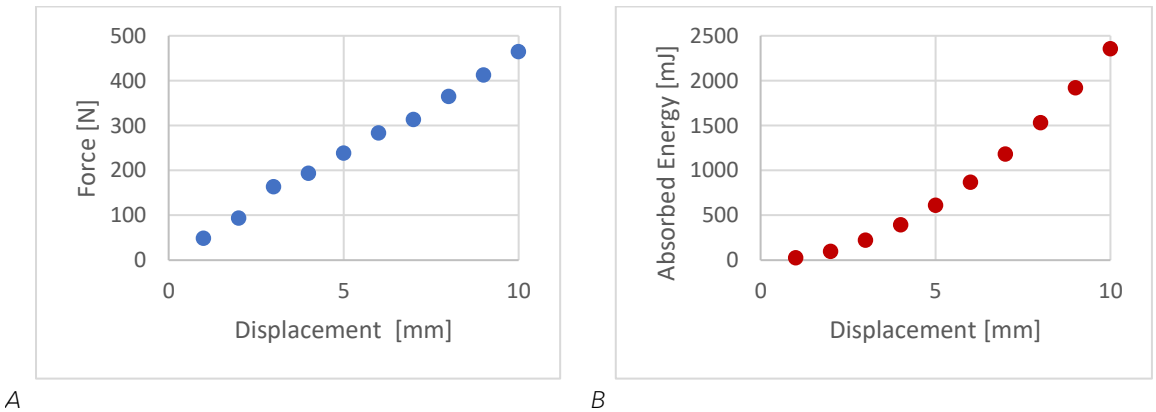


Figure 30. Compressive force (A) and Absorbed energy presented at 1 mm displacement step.

4.2 WP3: Visualization of the modular cranial semi-PSI

The objective of this part of the thesis project is to demonstrate the initial clinical relevance of the concept. For that purpose, a few Armadillo sets are produced by FDM (Apium P220, Apium Additive Manufacturing, Germany) out of PEEK (VESTAKEEP® Fusion PEEK filament, Evonik, Germany) medical grade filament. Following this, three modular cranial semi-PSIs are assembled, each tailored to correspond to an anonymized artificial skull produced by AM (see *Figure 31*). This figure demonstrates that the cranial defects of different sizes and geometries are successfully repaired by modular cranial semi-PSIs assembled from various parts of the Armadillo system. However, the annular snap-fit connectors should be improved in the future to provide extra flexibility and at the same time stability of the construct.

Figure 31. Three modular cranial semi-PSIs are assembled, each tailored to correspond to an anonymized artificial skull produced by AM.

5. Discussion

The objectives of this thesis are to formulate a design of a set for the creation of modular cranial semi-PSI and demonstrate its clinical potential as an affordable implant solution for on-the-spot cranial reconstructions in LMICs and conflict zones.

This thesis represents a multidisciplinary endeavour, integrating bionic, architectural, mathematical, and bioengineering perspectives. The proposed implant concept features a modular design, assembled from an assortment of geometric elements with a selection of pre-defined curvatures. A primary advantage of this concept is its immediate availability in sterile form, making it particularly appropriate for emergency situations frequently occurring in LMICs, rural areas and conflict zones as the modular cranial semi-PSI can be assembled on-site out of Armadillo set. The initial practical and theoretical efforts have been undertaken within the scope of this thesis. The constituent elements are derived from thorough analysis and optimization, ensuring pre-curvature tailored to the skull's shape and compatibility with the reconstruction of diverse cranial defect geometries and dimensions. Nevertheless, further work is required to yield optimal results.

The team has access to the CT data of approximately 500 patients. The systematic analysis of this extensive dataset outside the scope of this thesis will

enable us to further refine the Armadillo set design including finding an optimal curvature, tailoring it to a broader range of defect geometries and sizes. This comprehensive approach will enhance the precision and adaptability of the product, facilitating more accurate, patient-specific reconstruction procedures. The research involves analysing and categorising the CT data based on defect geometry, location, and size. Subsequently, we aim to virtually cover the defects using the designed set of elements to assess the fit and estimate the percentage of cases that could be addressed with this product, as well as identifying the anatomical locations where the set exhibits the most optimal fit. Furthermore, by identifying trends and patterns within the dataset, we can optimize the implant design to better address the unique challenges presented by different anatomical locations.

Various challenges associated with different anatomical locations can influence the design and optimization of cranial implants. One example of these challenges includes complex curvature, where some regions of the skull exhibit more intricate curvatures than others, making it difficult to create a custom-fit implant that accurately conforms to the patient's cranial geometry. Another challenge is the proximity to critical structures, such as blood vessels, nerves, and brain tissue, which may necessitate more cautious and precise implant design and placement to avoid potential complications or damage during surgery. The aesthetic considerations are also important, especially in visible areas of the skull, where the implant should seamlessly blend with the surrounding bone structure to achieve a natural appearance and minimize any psychological impact on the patient. To address this challenge, variations in bone thickness and strength across different skull regions should be taken into account.

This consideration could influence the selection of materials, design specifications, and attachment strategies for the implant, thereby guaranteeing sufficient support and stability, whilst reducing the likelihood of potential complications or patient discomfort. In addition, the intricate curvatures of the skull, the proximity to critical structures, and the variations in bone thickness and strength across different regions necessitate a design that can adequately withstand various forces while maintaining its form and function. This outlines the importance of

thorough mechanical testing in verifying that the implant can provide an adequate support, adapting to the individual cranial geometry of each patient, and enduring the physiological strains it would be subjected. In addition, mechanical testing is mandatory for the certification of the implants, e.g., by the 510(k) route with the FDA in the USA. What are the requirements for mechanical testing and the results obtained? The OSSDSIGN cranial PSI, which has been approved by the FDA in the United States under the designation K161090, serves as a pertinent example of the importance of such testing in ensuring the safety and efficacy of medical devices (Birgersson Ulrik & Weissburg David, 2021).

- Dynamical Load Test: To verify that the cranial PSI supports the forces exerted onto the implant from sleeping during the device lifetime. Requirement: no deformation. Method: orbital shaker, 125 rpm, 60 hours. Relevance: test simulates changed head position every 20 minutes for 8 hours sleep for 50 years. Both the subject device and predicate passed the test.

- Max Force [N]: To establish the maximum force that can be applied to the device before failure. Requirement: >100 N. Method: Universal testing machine at 1 mm/min Relevance: protection from falling objects and blunt trauma. Both the subject device and predicate passed the test. The subject device provided moderately better performance than the predicate.

- Energy absorption [mJ]: To establish the maximum energy the device can absorb before failure. Requirement: >1000 mJ. Method: Universal testing machine at 1 mm/min Relevance: protection from falling objects and blunt trauma. Both the subject device and predicate passed the test.

- Resistance to Deformation [mm]: To establish device resistance to deformation before device failure. Requirement: <6 mm. Method: Universal testing machine at 1 mm/min to 100 N applied force. Relevance: Both the subject device and predicate passed the test.

The methodology and experimental configuration employed in the static compressive testing of the five PEEK prototypes for the modular cranial semi-PSI adhere to the specifications outlined in the mechanical testing section of the 510(k)

Premarket Notification submitted by OssDsign AB. (Birgersson Ulrik & Weissburg David, 2021). The results of the compressive testing indicate that at displacement of 2.1 mm the PEEK prototypes for the modular cranial semi-PSI can tolerate compressive forces more than 100 N and at displacement of 4.2 mm compressive forces in excess of 200 N respectively. The prototypes did not fail catastrophically under the displacement of 6 mm and even at the displacement of 10 mm. The results of the compressive testing indicate that at displacement of 6.4 mm the PEEK prototypes for the modular cranial semi-PSI can absorb energy of 1000 mJ. Which is close to the requirements set by FDA. All values presented in this section are mean values of five samples.

The mechanical testing demonstrated the importance of the central element ("Caterpillar") to be firmly attached to the jig by screws. The designated element, according to the design concept, primarily ensures the implant's integrity as it possesses the capacity to withstand forces associated with protection from falling objects and blunt trauma. Overall, the performance of the PEEK prototypes for the modular cranial semi-PSI exceeded the original expectations. The implants did not disintegrate and were capable of mechanical performance in line with the FDA requirements. It should be noted that this were the crude prototypes used for conceptualization. Interestingly, the PEEK prototypes for the modular cranial semi-PSI, in relation to the test results, demonstrated superior performance compared to a commercially available, clinically employed, and CE-marked cranial implant manufactured by Skulle Implants Oy when compared with the mechanical performance data described by Piitulainen et al. (Piitulainen et al., 2017). Based on that, it is obvious that by improvement of the joints between the elements, it would be possible to improve the integrity of the implant to a clinically relevant level.

While this thesis has laid the foundation for the early stages of product development, several additional research endeavours are necessary to transform the prototype of the Armadillo set into a feasible medical solution. Manufacturing optimization is a vital area for future research. This step should include the exploration of different materials and manufacturing techniques to provide affordability and safety of this solution. Additional mechanical testing should be

conducted. It's essential to evaluate the mechanical stability and durability of the implant under varying physical stress conditions, replicating different conditions the implant may encounter within the human body. Further, the proposed solution should undergo testing in both preclinical models and clinical trials to confirm its safety and efficacy. This process involves not only surgical implementation but also long-term monitoring for potential complications. Finally, an extensive market analysis and health economics assessment is necessary.

CE approach, which is employed as the main design methodology in this thesis is particularly suited to address the above-mentioned challenges. CE, also known as Simultaneous Engineering, entails the integration and simultaneous consideration of product and process design activities. This approach aims to reduce the product development cycle time and improve overall product quality and performance. In the case of the Armadillo set design, CE enables simultaneous consideration of whole complexion of factors such as material selection, manufacturing processes, anatomical fit, functional performance, regulatory constraints and other risk factors partially covered by this thesis and leading to a potentially superior and more efficient design process. One can speculate that the approach applied in this thesis project could also be seen as a Product-Service System (PSS) approach. Vandermerwe and Rada's 1988 work pioneered the concept of servitization (Vandermerwe & Rada, 1988). Later, this laid the groundwork for the advent of PSS. Servitization refers to the shift that manufacturing companies make from simply selling products to selling integrated product-service systems that deliver value over time. This often results in a more customer-focused approach, with organizations aiming to provide solutions to customer needs rather than simply selling physical products. CE and PSS are both centred on fulfilling user needs. In general, CE achieves this by integrating various aspects of product development, thereby providing effective solutions. On the other hand, PSS emphasizes a shift from product-oriented value to user-oriented value, focusing on user experiences and outcomes (Ceschin & Gaziulusoy, 2016). In the context of this project focused on healthcare challenges in LMICs, both CE and PSS have significant potential to contribute to social sustainability. In these settings, CE can promote the

development of medical devices and technologies that are better tailored to the unique needs and constraints of LMICs, including affordability, ease of use, and adaptability to local conditions. Moreover, the inclusive and participatory nature of CE can help to ensure that the perspectives of local healthcare providers, patients, and communities are taken into account in the design and development process, thereby promoting social equity and inclusivity. The PSS, meanwhile, can offer a transformative approach to healthcare delivery in LMICs. By integrating products (i.e., medical devices) with services (e.g., education of medical personnel, ongoing technical support, practical instruments to assist in surgery implementation), PSS can help to improve access to essential healthcare services and enhance the quality of care. This is particularly critical in LMICs, where health systems often face significant resource constraints and health inequities are pronounced. As a continuation of this thesis project, the team is willing to integrate software and hardware assistive tools for effective use of Armadillo set and surgery planning. For example, in instances where CT imaging is either unattainable or impractical, a simple hardware tool such as a simplified set of elastic caps could be employed as an assembly guide to facilitate the implant assembly process. When the edges of the defect are visible and/or can be palpated through the skin, elastic cap can be directly placed on the patient's head, allowing for the estimation of the modular cranial semi-PSI configuration based on the marked elements that serve as a guide. Nevertheless, this may not always be feasible, for example, when substantial swelling is present at the defect site. In such cases, elastic cap can be utilized in conjunction with the surgical procedure to aid in the assembly and estimation process. The concept of elastic cap requires verification, which can be achieved virtually by selecting eligible patient cases and using the CT data to reconstruct the skulls and skin of the patients. Overall, the elastic cap concept could substantially contribute to further development of Armadillo set by offering an accessible, cost-effective, and user-friendly tool for on-the-spot cranial implant planning and assembly in LMICs.

This project embodies a synthesis of modern technologies such as AM, bionic design principles, and a comprehensive understanding of developing nations within a global context. The transition from primitive practices of our forebears to the

modern applications of bionic design is not as abrupt as it may seem. Indeed, the ancient creation of tools, such as the notched animal bone harpoons resembling animal teeth, can be seen as an early form of bionic design, a testament to humanity's consistent tendency to seek inspiration from nature and innovative resourcefulness. Today, according to Anthropocene Working Group we live in Anthropocene, when a shift of the Earth to a new geological epoch of human domination of the planetary system has happen (Malhi, 2017) . The key element of Anthropocene is a pervasive change in functioning of the whole globe, which related not just to simply a climate change provoked by industrial revolution but to a whole complexity of political, socio-economic, and ecological factors. Humanity realized that the planet is a holistic system and the industrialisation often influence nature in an offensive way. This recognition underscores the importance of seeking harmony between human-made technologies and the natural world. It represents a response to the unique challenges of the Anthropocene epoch, demonstrating how human ingenuity can work in harmony with nature to find solutions that are both practical and respectful of our holistic planetary system.

6. Conclusions

The study concludes that the proposed design concept of Armadillo set for the creation of modular cranial semi-PSI presents a promising, cost-effective solution for cranial reconstruction in LMICs and conflict zones. The modular approach allows for customization to accommodate diverse cranial defects, potentially reducing complication rates associated with current reconstruction methods. Further research is needed to validate the effectiveness and safety of this innovative approach. The implications of this work could extend to improving the standard of care for cranial reconstructions in areas where access to advanced healthcare is limited.

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Figures

Tables