GRIFFITH COLLEGE DUBLIN

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Dedication

This work is dedicated to my sister Catherine.

Catherine passed away due to a ruptured cerebral aneurism on the 15th of May 2023. She encouraged me during the whole course of this research and all the way through life.

She was one of life's natural cheerleaders.

Table of Contents

Table of Figures

Abstract

An Evaluation Of The Use Of 3D Technologies In Developing Patient Specific Medical Devices For Interventional Radiology, And Its Potential Use For Producing A Personalised Embolic Coil for Peripheral Vasculature Embolization

Joseph O' Donovan

In this study it was shown that patient specific embolic coils for peripheral intervention can be produced utilising 3D patient scans and current materials and industry standard processes.

The use of patient specific medical devices is growing since the invention of 3D technologies. This study investigated using this same technology to design a patient specific embolic coil. A key objective of the research was to establish if a patient specific coil could address complications and issues that are encountered with Off The Shelf (OTS) embolic coils.

Literature on patient specific medical devices, 3D imaging, and embolization were reviewed to map the current landscape of embolic coiling, patient specific medical devices, costs, and regulatory considerations. There was a gap in the literature regarding patient specific embolic coils. Primary Research was conducted via individual interviews with 13 subject matter experts (SMEs) from the fields of Interventional Radiology, Research & Development, Marketing, 3D Design and Process Development Engineering.

The research found that there was no barrier to rendering a 3D anatomical scan into a patient specific embolic coil. Opinion of the SMEs was that current materials and standard manufacturing processes can be used to fabricate the same. The necessity for secondary devices, such as stents, can be overcome by producing a coil tailored to the patient's anatomy. Prolonged procedure time can be reduced by delivering coils with a patient specific length. A wide range of OTS coils and liquid embolics exist, which provide the Interventional radiologist with a level of customization for each patient. It was found that a patient specific coil could be produced but that there may be only niche use for peripheral vascular treatment. The emergent nature of peripheral embolization procedures was deemed incompatible with the planning, design and manufacture required to produce a patient specific device. It was recommended the study be carried out in the field of Neuro Interventional Radiology as the level of planning, risk-reward and the specificity of tools required were greater than in Peripheral Vascular field. Also, it was recommended that research be conducted into the development of resorbable coils for Musculoskeletal (MSK) conditions.

Chapter 1: Introduction

Three-Dimensional Printing (3DP) has enabled rapid prototyping for the manufacturing and design industries. The development of 3D printer technology and advances in materials science has opened the door for ever more exciting uses, especially in the field of medicine (Jamróz *et al.*, 2018). Also, as medical *imaging* techniques and Digital Imaging and Communications in Medicine (DICOM) viewers have become more advanced, they have afforded the translation of 2D scans into digital 3D models (Popescu *et al.*, 2021). These two areas have been brought into symbiosis in recent years: key uses in medicine are the creation of patient specific models for surgical procedure planning and surgical training, and the fabrication of patient specific medical devices (Squelch, 2018). The author works in the medical device industry, specifically in embolic coil development and manufacture. This research asks if a patient specific embolic would be of benefit to the interventional radiology field and suggests a potential workflow for manufacturing the same from a 3D anatomical model using industry standard processes and materials. Why patient specific coils have not yet been developed will be investigated and evaluated. Material considerations and constraints, technology availability, provision of 3D printing trained technical staff, regulatory aspects and complications in clinical procedures will be probed. The author conjectures that an embolic coil can be shaped in a custom manner to occlude a specific and complicated anatomical feature where 'off the shelf' coils would require addition of another device such as a balloon or stent (Lazareska *et al.*, 2018).

Aims & Objectives of this research:

Assess if 3D Imaging and printing technologies are effective in producing customised medical devices.

Explore current practices and identify issues with embolic coiling.

Investigate why patient specific embolic coils have not yet been developed

Propose how a custom embolic coil could address embolic coiling complications.

Propose a workflow for using 3D models to produce custom embolic coils - with existing manufacturing methods and materials

1.1 3-D Printing

Charles Hull invented the 3D Printer in 1984 (Hull, 2015). Both the printer technology and the materials that can be printed have undergone extensive development (Karakurt and Lin, 2020) to the point that 3D printing is now the preferred method for rapid prototyping and is firmly established in the manufacturing sector for mass customization (Shahrubudin *et al.*, 2019). This affords the medical device industry and physicians with the ability to create and fabricate custom devices and anatomical models quicky and cheaply, without the geometrical limitations inherent in traditional fabrication processes - otherwise the fabrication of the items would be non-feasible (Javaid and Haleem, 2019).

Note: the terms 'Custom', 'Patient Specific' and 'Patient Matching' are used interchangeably to describe a device or model that is bespoke to an individual patient's anatomy.

1.2 3D Printer Technology

3D printers' basic function is taking a material and building successive layers on top of one another until the item to be fabricated is complete. There are numerous mechanisms of 3D Printing, Shahrubudin et al (ibid) detail that the American Society for Testing and Materials (ASTM) categorize 3D print technologies into seven distinct categories based on the mechanism used to build up material layers. Each printer category has its own application. Following is some of the printer technologies that are used in the field of medicine and in medical device manufacture with examples of specific applications:

1.2.1 Powder Bed Fusion

Powder Bed Fusion (PBF) uses a laser beam to fuse powdered particles into the desired form (including powdered metals), allowing the manufacture of extremely intricate parts. This is achieved through sintering with lasers or electron beams and is the preferred method of 3D printing *tibial* base plates for knee replacement surgery. This due to PBFs ability to manufacture a fine porous surface (Nelson, 2021). A porous surface enables ingrowth of bone tissue, which provides the implant with a *biological* fixation versus having to use a fixing cement (*Stryker 3D Printing for Artificial Joints; From R&D to Production*, 2019).

1.2.2 Material Jetting

Material Jetting, here a UV curable photopolymer is placed on a base and the 3D form built up in layers, resulting in a very accurate and smooth model, which per Pietrabissa et al is the most reliable method for 3D printing anatomical structures (Pietrabissa *et al.*, 2020). One company, *Stratasys*, even produce material jetting printers *branded* as 'anatomical printers', the same are installed in numerous hospitals for the purpose of surgical planning and training (Carlota, 2020).

1.2.3 Binder Jetting

Binder Jetting adds a liquid binder to a powder base to form successive layers of material, any material that can form a droplet with a suitable liquid binder can be used. This method of printing can produce a wide range of colors and materials for use in anatomical modelling but is reliant on secondary processes, such as heat treating, to dictate material hardness and finish (Garcia *et al.*, 2017). 3D printing functionality means that scans/medical imaging of complex anatomy can be translated into solid 3D structures. Section 1.3 below details the imaging and rendering of the scans to 3D printable models.

1.3 Medical Imaging and DICOM

Various methods of imaging the internal human anatomy and structures are available to the medical practitioner. Digital Imaging and Communications in Medicine (DICOM) is the global standard for medical imaging data (DICOM, 2022). The term 'DICOM' as a noun, as used in the reviewed literature, encompasses imagining techniques such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT), X-Ray, Ultrasound and numerous other technologies which are employed to create an image of a patient's internal anatomy (Zhou et al., 2021). CT and MRI are the most common forms of visualization mentioned in the literature. Each has its uses depending on the condition being assessed; CT being identified as the method with the most wide-ranging and appropriate applications for musculoskeletal application (Blum *et al.*, 2020) and MRI for injury to tissues, and tissue discrimination (Fayad, 2022). MRI and CT scan images are made up of multiple 2D slices (aka 'voxels') which require an additional step to render them into a 3D format (Plavitu *et al.*, 2018).

1.4 Conversion of Medical Scans to 3D Models

Post processing of scan/DICOM files entails the conversion of the 2D slices into a 3D digital model using 3rd party software (Punyaratabandhu *et al.*, 2018). Wang et al lay out a detailed post processing workflow (Wang *et al.*, 2021), see basic overview graphic in *Figure 1* generated by the author.

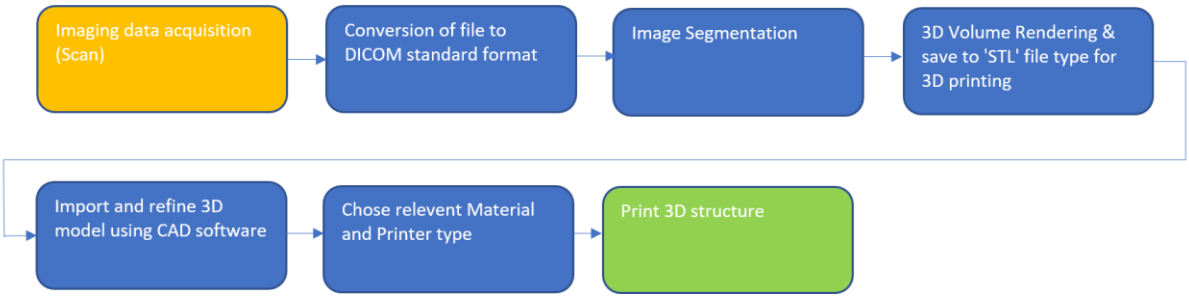

Figure 1: Workflow for generating a 3D model from patient scan data files. Workflow data is from Wang et al., 2021. The workflow begins with the patient scan and ends with a printed model (or medical device), everything in between is known as 'post processing'.

- Once the scan has been completed the scan image files are saved in a DICOM compatible format (e.g., cross platform industry standard format).
- Image 'segmentation' is a crucial next step: segmentation requires the physician to define the regions of interest, delineating the boundaries of the 2D slices they want to model (Blum *et al.*, 2020).
- The slices are folded into a 3D structure during Volume Rendering (AlZu'bi *et al.*, 2018), at that point the image is saved as a 3D Standard Tessellation Language (.STL) file, which is the standard file type for 3D printers (Library Of Congress, 2019).
- Computer Aided Design (CAD) software is used to further refine the model's characteristics, such as hollow sectors, surface roughness and section colouring (Wang *et al.*, 2021).
- Material selection is based on the final use of the printed model as well as the anatomy it is representing and how realistic the model is to feel. A key consideration for material selection is the print accuracy and resolution required as well as the capability of the *printer* technology (e.g., Binder Jetting) to work with specific materials (Mitsouras *et al.*, 2015). Ultimately the *end application*, whether it be a model for clinical training, surgical planning, or a custom medical device, will dictate printer and material choice (Hong *et al.*, 2019).
- Another consideration is the cost (and availability) of specially trained staff to run the software required for rendering the scans to a 3D segmented image. Additionally, personnel would have to be competent and available to oversee the model fabrication process, such as loading and running the printer and be required to perform any post processing that may be needed (Javaid and Haleem, 2018)

Chapter 2 - Literature Review

2.1 Patient Specific Medical Devices

3D Printing has enabled the fabrication of patient matching medical devices such as artificial corneas, heart pumps (Shahrubudin et al., 2019), cranial implants (Schön *et al.*, 2021) and custom tip (shape) catheters for endovascular coil embolization procedures (Ishibashi *et al.*, 2016). Custom devices offer advantages over 'one size fits all' solutions and reduce potential for complication during medical procedures (Mitsouras *et al.*, 2015). Yang et al state that the customizability of the devices produced has led to 3D printing being widely used in fields such as orthopaedics and plastic surgery, however it has not been easily adopted for use in patient specific cardiovascular applications (Yang et al., 2021). Per Wallace et als paper on spinal implants, 3D print technology has been very effective in surgery, where the customization element lends itself to the complex anatomy of the spine. Implants such as rods, plates and cages have been effectively manufactured and complications such as pseudarthrosis (failure of bones to fuse), loosening or migration were not observed in 17 cases reviewed (Wallace *et al.*, 2020). Use in facial prosthesis has also been recorded, where the advantage of a patient specific device is obvious (Sherwood *et al.*, 2020).

2.1.1. 3D Printed Medical Device Market Growth

Information on usage can be established by looking at the market for 3D printed medical devices. The market for 3D printed medical devices shows a 16% Compound Annual Growth Rate (CAGR) in Asia Pacific region from the period 2018 out to 2028, with the largest market being in North America (Mordor, 2023). Value wise, the market for 3D printed medical devices is set to grow from $2.07 billion in 2020 to $7.92 billion in 2029 (Exactitude Consultancy, 2022). Articles on 3D models and the adoption of additive manufacturing for making medical devices for the orthopaedic market are well represented (Wixted *et al.*, 2021). Likewise, the use of 3D *model* 'phantoms' (practicing a procedure on a model prior to the real surgery) for embolization procedures has been widely published, yet the manufacture of patient specific medical devices from 3D models is not as prolific. Martelli et als 2016 study showed the use of 3D printing technology for custom *implant manufacture* was significantly lower than its use in preoperative models and aids (Martelli *et al.*, 2016). A PubMed search performed by the author of this dissertation, compared 3D technology utilization in orthopaedics versus embolization use, with the results being 809 articles for 3D printing in Orthopaedics and only 22 related to embolization use published in 2022-2023. The same search terms were used with only the term 'orthopaedics' and 'embolization interchanged.

2.1.2. Clinical Outcomes & Advantages due to Patient Specific Medical Devices

The literature also holds that patient specific devices, not only lead to better clinical outcomes but also reduce lead time in device design and manufacture (Haleem and Javaid, 2019). Clinical conditions that *could not be* treated, those that had *ineffective* treatments or were extremely challenging e.g., tumour site reconstruction, are now possible to treat due to the progression of 3D print and imaging technology in the area of patient specific medical device fabrication (Willemsen *et al.*, 2019).

2.2. Current Practices and Issues Embolization

Embolization is a treatment that occludes blood vessels, stopping blood flow; this can be desired for a number of reasons such as treating acute bleeds, aneurisms, malformations and cutting blood supply to tumours (Hu *et al.*, 2019). Embolization techniques vary depending on the vessel to be embolized and the anatomy and geometry of the same. Occlusion Coils, Flow Diverters,

vascular plugs and Comaneci devices among other mechanical means are used to achieve occlusion (Munich *et al.*, 2019). Coils are however the most versatile and prolific device, used in embolization procedures of the spleen, liver, renal artery, pelvic trauma and lower gastrointestinal bleeding, bronchial artery hypertrophy and aneurismal sac packing (Ierardi *et al.*, 2020). Embolization is by enlarge performed with an endovascular approach; this facilitates the use of non-mechanical means of embolization such embolic beads, liquid embolics and PVA embolization particles, all of which can be used in tandem with coiling (Venturini *et al.*, 2022). Each has its own advantages and disadvantages, uses and constraints: for instance, gel and liquid embolic agents suffer from issues with controlled release, meaning they may leak out of the target vessel and embolise healthy vasculature (known as 'extravasation'). The same are costly and require specific catheters, whereas coils are very precise, and many are marketed for multicatheter use (Ierardi *et al.*, 2020).

2.2.1 3D Printing and Medical Devices for Embolization

3D printing of aneurism models has been extensively recorded in the literature, examples of the same are Frölich's paper on Three-Dimensional printing of intercranial aneurisms (Frölich et al., 2016). Printing of custom devices for embolization focuses mainly on the *catheter* used to introduce an embolic device, such as printing patient-specific catheter tip shapes for occlusion procedures from CT-3D models (Xu et al., 2020). Of all the methods of embolization, coiling is by far the most widely used (You *et al.*, 2017). Embolization coils have been 3D printed in *research settings* to match patient vasculature but were not fabricated using standard manufacturing techniques or materials (Lin *et al.*, 2022). One reason may be the material required: the platinum 'primary wind' material used in embolic coils has explicit properties that affect the device performance, such as the softness of the coil, which dictates the packing capability and ultimately the ease of placement in the aneurism (White *et al.*, 2008). There are instances in the literature of 3D printing platinum for battery cells (Wong and Hernandez, 2012), rocket thrusters, via laser sintering (ESA, 2015) and jewellery, however precious metal powders are costly and are difficult to fully melt using current laser sintering technology (AMFG, 2018). No literature could be found that detailed printing platinum *primary wind coil*. Some sources mention the use of *stainless-steel* embolization coils (Flanagan *et al.*, 2016), stainless steel coils gave way to platinum due to platinum's superior radiopacity and softness, therefore 3D printing primary wind from stainless steel, albeit cheaper, would not be as malleable or surgically visible a material as platinum (Cowley and Woodward, 2011).

One paper recorded the use of DICOM and 3D technology to aid the fabrication of a patient specific, novel, occlusion device (for which there was no predicate). The device itself was not manufactured on a 3D printer, but using standard methods and materials (i.e., nitinol), due to its patient matching characteristic the device was a perfect fit for a unique use and prevented the need for a risky open-heart surgery (Sodian *et al.*, 2009)**.**

2.2.2 Embolization Complications

The reviewed literature records a number of complications specific to embolization procedures. Those detailed below were very common and represented complications typically experienced in the field of endovascular medicine.

2.2.2.1 Recanalization

Recanalization (where blood flow begins to be restored to the embolized vessel after a period of time) is the main risk factor to successful embolization procedures (Wiśniewski et al., 2019).

Fuga et als study showed that the key coil characteristic leading to recanalization was coil compaction- also known as 'coil prolapse' (Fuga et al., 2022). The literature called out the presence or absence of recanalization as the main indicator of the *success* of the embolization procedure, examples are Flanagan and Golzarian's 2022 review of coil shapes and sizes (Flanagan and Golzarian, 2022) and Nishihara et als paper on successful bronchial embolization (Nishihara *et al.*, 2022). Yasumotos et als conclusion regarding the long-term outcomes for patients is that recanalization results from insufficient embolization and low packing density (Yasumoto *et al.*, 2013). Coil compaction, which leads to recanalization (Ishii *et al.*, 2021) is discussed in 2.2.2.2

2.2.2.2 Coil Compaction

Coil compaction (aka prolapse), where the coil mesh/basket collapses into the interspaces in the same, is an issue that is directly related to the *packing density* of the coils (Sluzewski *et al.*, 2004). The more coils packed into an aneurismal sac, the lower the chances of recanalization with a packing density of >24% being key to reducing instance of recanalization (Grandhi *et al.*, 2021). Compaction may lead to coil migration, where the coil dislodges and moves out of the aneurism or into non-target vasculature (Shah *et al.*, 2007). Not having enough coils packed into the aneurism means that the 'water-hammer effect', a result of normal pulsate blood flow, can compact the coil into the interspaces between the coil mesh (Sluzewski *et al.*, 2004). Coil compaction and migration are not only complications in of themselves but are directly linked to recanalization, which can lead a rupture (Yasumoto *et al.*, 2013). Fuga (ibid), Wisniewski (ibid), and Lee (Lee *et al.*, 2020) as well as numerous other sources, show that aneurism shape is also a key factor **-** specifically *wide neck aneurisms* are identified at greatest risk for coil migration as the coil can protrude at the aneurism *neck*, or migrate through the same **(**Hargis et al., 2022). Lazareska et al point out that wide neck aneurisms are particularly difficult to treat and embolize (Lazareska *et al.*, 2018).

2.2.2.3 Scaffolding Coils

Opening up of the aneurism, allowing a high number of coils to be packed into the same, is achieved using scaffolding/framing techniques (Hargis et al., 2022). This scaffolding creates an endoskeleton inside the aneurism; 'stiffer' coils are employed to create the scaffold, which are approx. 2mm larger in diameter than the vessel itself (White, 2007) - the purpose to open out the space in the 'aneurismal sac'. A number of commercially available coils are on the market with this function in mind, such as Boston Scientific Interlock-35 Cube™ (Boston Scientific, 2022), Stryker Target 360™ (Stryker, 2022), Terumo Azur™ (Terumo, 2022) and Medtronic's Axium Prime Frame™ (Medtronic, 2022) to name a few.

2.2.2.4 Issues Due to Inadequate Scaffolding

The issue of not having a robust scaffold at the neck of wide-neck aneurisms has been detailed in numerous sources, including in Lee et al, where the scaffolding coil had to be removed and replaced with a stent at the aneurism neck (Lee et al., 2005). Current off-the-shelf scaffolding coil inadequacy has surgeons rely on secondary devices to scaffold complicated cases, such as Comaneci devices (Hargis *et al.*, 2022) and clips (Fukuda *et al.*, 2019). Scaffolding coils are off-the-shelf shapes/sizes, offered in a catalogue fashion and therefore are not made to be patient specific (MedicalMaterials, 2022).

2.2.2.5 Medical Device Alternatives for Treating Wide Neck Aneurisms

In order to overcome issues with wide neck morphology, multiple techniques have been employed to bolster coiling, such as balloon assisted and stent assisted coiling (D'Urso *et al.*, 2012). In recent years a device known as a Flow Diverter (FD) has been developed specifically to

address wide neck aneurisms (Lazareska *et al.*, 2018). They are made from very fine mesh and are deployed (similar to a stent), across the aneurism dome and divert blood flow away from the aneurism opening (Munich *et al.*, 2019). However, Flow Diverters are not suitable for use where the aneurism has already ruptured, or on bifurcation aneurisms, furthermore, occlusion is not achieved until months later, over which period of time dual antiplatelet therapy has to administered to prevent thromboembolism (travelling clots). Additionally, FDs are also not *economically* feasible in aneurisms less than 11mm diameter (Briganti *et al.*, 2015).
There are a number of flow diverter type devices available, such as the Woven EndoBridge (WEB) developed as an 'intrasaccular' device (placed inside the aneurism), it's mechanism of flow diversion is similar to a flow diverter (Ding *et al.*, 2011). Due to the WEB being inserted into the aneurism (versus the parent vessel) it provides an immediate reduction in blood flow, therefore it can be used where the aneurism has been ruptured (Monteiro *et al.*, 2022). It doesn't require antiplatelet treatment as it is nitinol, however WEB has a significant rate of recanalization, which requires a follow up procedure, the majority (59%) of which are performed with coils (Peterson and Cord, 2021). WEB is also strictly for neurovascular use, which means WEB does not meet the challenges relating to wide neck aneurisms in the peripheral vasculature and is limited to delivery with the manufacturer's catheters (Microvention, 2023).

The invention of devices targeted at wide neck aneurisms does go some way to addressing complications due to complex vessel morphology, however they are not patient specific and have limitations as described above.

Coils on the other hand do not specifically require antiplatelet therapy, though some studies found that the complication rate was marginally lower when medication was used (Yamada *et al.*, 2007). Another study showed that continued administration of antiplatelet drugs after coiling was not necessary, except in cases where the aneurism was unstable and/or where ischemic complications were already evident (Goto *et al.*, 2022).

2.3 Current Embolic Coil Shaping and Manufacture

Following is the conventional method used to produce embolic coil 'primary wind' (the wire that embolic coils are formed from)

- Platinum wire is the material of choice for coil manufacture (Hui et al., 2013). This Platinum alloy is wound around a shaping mandrel to make 'primary wind' (Grandhi et al., 2021).
- The primary wind is then wound around a secondary mandrel, this secondary mandrel gives its shape to the coil (White et al., 2008) via an annealing process (stress relieving the wire).

Patent information, in the public domain, lays out this process, such as US patent US20050021074A1 (Fay, 2005) and US8043321B2 (Elliot, 2011).

2.4 Viability of a Personalized Embolic Coil?

3D printing has been utilized in the creation of phantoms for preoperative planning for endovascular procedures, but little has been published regarding clinical use of 3D printed

custom embolization devices (see section 2.2.1), and specifically no information on a patient matching embolic coil could be found.

The author proposes that a personalized embolic coil can be manufactured to overcome coiling complications when embolizing difficult anatomy. This coil would be a custom scaffold for embolization procedures, better fitting wide neck aneurisms, preventing coil protrusion and enhancing vessel expansion for packing. The need for stent or balloon assistance may be negated, speeding up procedure times and removing the risk of complications, e.g., balloons are not effective for side-wall aneurisms (Vignesh *et al.*, 2022) and can only be used for a limited time due to ischemia risks, therefore a balloon assisted procedure may require multiple balloon deflations, which prolongs the operation (Meritt, 2021). The author's research will gather expert opinion regarding the potential benefit of a patient specific scaffolding coil and its potential to reduce coiling complications.
Also, expert opinion will be sought on the development of a framework for producing a custom coil from a 3D anatomical model using current embolic coil manufacturing processes and materials.

2.4.1 Challenges In Developing A Patient Specific Coil

Developing a patient specific coil is virgin territory and there is little secondary research material available to guide development. However, other embolization devices have been designed using a similar framework, such as the aforementioned novel occluder (Sodian *et al.*, 2009). This serves as an example of using a scan to ultimately inform the shape of a patient specific embolization device. However, though this gives great optimism regarding the *framework* for producing a patient matching coil, there are other challenges outside of the framework that have to be considered.

2.4.2 Regulation

3D technology is rapidly advancing in the fields of pharmaceutical and biomedical applications; with rapid prototyping opening the way to novel treatments tailored to patient anatomy (Jamróz *et al.*, 2018). The approval process, be it in the USA, China or the EU is not in tandem with the advances in technology or treatment (e.g., advent of patient specific treatments), leading physicians to choose surgical options that are conventional rather than the most technologically advanced (Willemsen *et al.*, 2019).

2.4.3 FDA Regulatory Routes - Custom & Patient Specific Devices

In the United States, the FDA has released guidelines on the technical considerations for additive manufacturing of medical devices (FDA, 2017), the route for approval of a patient specific (meaning made for a single patient), yet *non-emergency* use device is still ambiguous and is need of clear regulation (Willemsen *et al.*, 2019). Di Primas' article explains that the FDA actively seek to remove ambiguity around approval of 'patient matching' devices. The paper also lays out the confusion over approval of materials for 3D printing versus the use of *new* materials to make predicate devices; material approval is no different in either case than the *conventional* route for material approval (Di Prima *et al.*, 2016). These of course are considerations when approaching making a *custom* embolic coil device from *existing* (and already tested) materials. The burden is on the device manufacturer to prove the material is safe or as safe as the predicate (Di Prima et al ibid). The FDA do have guidance on the same, known as Expanded Access (EA) approval routes (FDA, 2019). These routes have strict criteria: approval under EA can be sought only when no adequate or effective therapy alternatives are available or immediate use is required in "life threatening or serious conditions," (FDA, 2022b).

In this circumstance, the treating physician is not obligated to get prior approval from the FDA or have an *Investigation Device Exemption* (IDE) in place, they need only report the use to the FDA within five working days. If there *is* an IDE application in progress, the trial Sponsor must report the emergency use within five working days (FDA, 2022a). A *Custom Device Exemption* (CDE) approval route is available where the device is used on only one patient and where the clinical needs cannot be met by a currently marketed device. For example, in spinal reconstruction surgery, where anatomical abnormalities exist, fitting an *Off-The-Shelf* (OTS) solution may increase patient trauma, blood loss and procedure time. In this scenario a custom printed spinal implant is superior (Burnard *et al.*, 2019). Van Norman's article on the FDAs *Expanded Access* (EA) approval routes (Van Norman, 2018) gives guidance on the debate over what route to use for a custom-made device. *Custom Device Exemption* approval is restricted to five units (meaning five new patients treated) per year and requires a 510k for approval based on a predicate (FDA, 2014).

2.4.4 Europe and the International Medical Device Regulators Forum (IMDF)

In the EU, a 'custom device' is defined under a number of criteria, with a key characteristic being that it is made to meet the *individual* needs of a *sole* patient (EMA, 2017). The same excludes devices that are fabricated to a *prescription* by a medical practitioner but are mass produced using industrial manufacturing processes. Devices defined as 'patient matched devices' in the EU are

- made to match a specific patient by scaling the device based on anatomical references or patient scans/medical imaging.
- are "typically" produced in a batch under a repeatable/validated process.
- The design and fabrication of the device is the responsibility of the manufacturer, under the guidance of a medical practitioner,

See the International Medical Device Regulators Forum document (IMDRF, 2018).

The definition of a *batch* is defined in the same document as devices being made of the same raw material and with the same manufacturing process – NB not the same dimensions etc.

All of the above guidance is relevant to a custom embolic coil if that device met FDA criteria under any of the three Emergency Access routes or Custom Device Exemption route. However, there is no clear regulation for a repeat manufacture (patient after patient), of a custom *individual patient matching* device in the US. The EMA guidance for patient matching devices defines what *is and is not a custom device* but does not clearly state requirements for a patient matched device. The IMDRF guidance is far clearer and would allow DICOM medical imaging to be used as the basis for a patient specific device and also permit a validated and repeatable industrial process to mass produce those devices. In short, the IMDRF guidance allows mass production of devices matched to specific patients based on their unique anatomical scans. This would facilitate the production of patient specific embolic coils, using existing manufacturing methods and materials.

2.4.5 Ethical Considerations

Patients need to be informed that they are using a *first in use* device, this facilitates informed consent, a key tenet of which is *patient information disclosure* (O'Neill, 2021). Obviously, it is ethical that patient is fully informed that the device they are being treated with has not been evaluated previously (i.e., at least in its patient specific form, but notwithstanding a predicate device with similar function). Another ethical problem is linked with the issue of abusing 'Emergency Use' under the FDA Expanded Access program as Van Norman lays out: some physicians have conducted unauthorized human experimentation, using custom or customized devices, citing Emergency Use criteria. He further points out, that as 3D printers and devices can be accessed by any physician,

custom device abuse is a very pertinent area for discussion (Van Norman, 2018). Regarding testing of custom devices that by their patient specific nature mean that each unique device cannot be trialled (such as a patient specific embolic coil), the route exists for *computer modelling* to be used to test the device (in silico) where animal or human testing is not possible (FDA, 2020). This may go some way to answering the question of testing, further assessment of device performance can be based on predicates - embolic coils have been well used for many years. As O'Neill points out, the patient must be made aware of alternative therapies and medical devices (O'Neill, 2021), which may pose a challenge when trying to convince a patient to use a custom coil. In the US, the 510k route would cover a custom embolic coil, made from current coil materials and processes, as the device would meet a number of requirements as laid out by the FDA: the coil would have the same intended use and the same technological characteristics as an approved device. The safety profile can also be backed up by *non-clinical* bench data (e.g.in silico testing) and key to its approval is that the new device does not have to be *identical* to the predicate (FDA, 2022c). Additionally, as the material (platinum wind) would be the same as already used for marketed coils, the biocompatibility data from the predicate can be leveraged (FDA, 2022d).

Overall, though regulations are ambiguous relating to the approval of a patient matching device of the type the author proposes, there are regulatory pathways to allow approval of a patient specific coil, designed from DICOM information and made using current industry standard methods and materials.

2.4.6 Cost

Differing views of the expense of 3D printing anatomical models appeared in the literature. Some practitioners, like Sun and Liu, argued that phantoms/models could be produced relatively cheaply (Sun and Liu, 2018). However, the cost of 3D printed medical devices is not cast in the same light - some analysts of the 3D printed medical device market state that the high cost of 3D printed devices limits their availability in emerging nations (Fortune Business Insights, 2023). Although the device the author proposes, is not itself 3D printed, it depends upon the same workflow as a 3D Printed device to generate the 3D image, and so may incur similar cost. Martelli et al state that the additional cost per procedure when comparing a 3D printed versus conventional device was €100 to €700. The increase is due to a number of factors, for example the need for a 3D printer(s), imaging and modelling equipment, associated Computer Aided Design (CAD) software and fabrication materials (Martelli *et al.*, 2016). Conversely, as custom devices reduce surgery time (Tack *et al.*, 2016), the overall cost of a *surgery* was lower when using a 3D patient matching device (or phantom) as one study found, with the price of the 3D print being more than compensated for by the cost saving in surgery time (Lethaus *et al.*, 2012) - this is backed up also by Andres-Cano et al (Andrés-Cano *et al.*, 2021).

For a personalised embolic coil, the material cost would be commensurate with off the shelf (OTS) devices (as the material is identical). The cost of manufacture from the point in the workflow that the coil hits the factory floor (i.e., is processed and fabricated per OTS coils) would also be in line with OTS devices. However, the stages prior to this would not be standard and would incur a higher price than OTS coils. On the other hand, the benefit of not having to perform balloon assisted or stent assisted coiling reduces surgery time and the need to purchase those additional devices. Where the proposed device reduced complications or follow up procedures (see section 2.2.2) the cost of the personalised coil would balance itself out per Martelli (ibid) and Lethaus's (ibid) findings.

2.4.7 Staffing for 3D Imaging and Processing

3D printing, post processing and CAD activities require trained staff. One study found that out of 20 clinics using 3D printing, a percentage had medical staff trained in the use of 3D print technology, others had non-medical staff working as technicians while one clinic hired an outside firm to handle the technical aspects (Zeller *et al.*, 2022). The translation of a DICOM format file to a 3D digital model is a time consuming and an involved process, where high technical skill is required to render and segment the image (see section 1.4). Newer software solutions based on machine learning and automation, taking some of the technical burden away from the user, are currently being evaluated (Virzì *et al.*, 2020). The level of technical acumen required to make an accurate rendering is very high: one paper reviewed the rendering of CT images of cadaver anatomy performed by a clinical doctor versus that of a commercial technology company. Both were compared to a gold standard *laser scan* of the anatomy in question, each deviating from the laser model (the doctor's model deviating more significantly), showing that technician skill is a significant factor in producing an accurate model (Fourie *et al.*, 2012). Operation of the 3D printer and post processing also require technically trained staff (Javaid and Haleem, 2018), which also is a factor in the overall cost (see section 2.4.4). Andres-Cano et al also holds this view and includes ancillary staff in the list of required personnel, such as radio-diagnostic technicians and bioengineers (Andrés-Cano *et al.*, 2021). For the coil proposed by the author, the fact that manufacturing would be carried out using existing techniques in an industrial facility allows a leveraging of skills already in house such as 3D design and CAD, tool making and manufacture, 3D printer availability and proficiency, *experienced* technical staff and proven proficiency of the same. These can overcome the barriers that a clinical site may experience if introducing a 3D printing element to their capabilities, making it feasible to produce a custom embolic coil from DICOM images in an already technology savvy manufacturing environment.

2.5 Proposed Framework

A framework for producing a patient specific coil from current manufacturing materials and production processes has a number of elements to it, which can be broadly broken into three workstreams:

1. Obtaining and rendering of DICOM format files into a 3D digital model of the anatomy.
2. The design and manufacture of a tool (a winding mandrel), based on the 3D model, which will be used to form the embolic coil into its final shape.
3. The manufacturing process of the embolic coil from the point that the mandrel is made.

2.5.1 Production of a 3D Digital Model of Patient Anatomy

This workstream is detailed in section 1.4 of this dissertation. The primary research will inform the workstream in the context of producing a patient specific embolic coil.

2.5.2 Design of a Winding Mandrel

Embolic coil manufacturers have adopted annealing as their method for forming coils into their 'secondary shape'/structure, for this we will need to design a tool called a winding mandrel (White *et al.*, 2008) from the 3D anatomical model.

2.5.3 Manufacture of the Embolic Coil

Coil manufacture will follow a well characterized process, with platinum primary wind tightly conformed to a secondary mandrel and stress relived in an annealing oven to permanently give the coil it's shape (Elliot, 2011)

2.6 Summary of Literary Review

Review of the available literature on 3D printing, and modelling from DICOM imaging, has revealed that the technology has been used prolifically in the field of orthopaedics (Crawford, 2017) and has a strong track record for patient specific applications (Wong, 2016). The medical device industry is moving into this area, with major companies, such as Stryker Medical, investing heavily in additive manufacturing for the production of hip, knee and spinal implants (Epperson, 2021). Such is the confidence in this new technology that analysts predict the market for 3D printed medical devices will triple in size from $2B to approximately $8B by 2029 (Exactitude Consultancy, 2022). Literature has shown that 3D imaging and printer technology has advanced to the point that very accurate patient specific anatomical models (aka phantoms) can be produced (Hong *et al.*, 2019), and without a massive financial burden (Bangeas *et al.*, 2019). Phantoms are used across a wide range of medical disciplines for procedure planning, medical research and surgical training (Squelch, 2018). There is a good body of information in relation to use of the technology in the endovascular field for manufacturing custom medical devices, such as patient specific catheter tip shaping (Komada *et al.*, 2022) and the fabrication of patient specific surgical aids (Pugliese *et al.*, 2018). However, there remains a gap in the literature in the area of *patient specific embolic coils,* which is the focus of this dissertation.

2.6.1 Embolic Coiling

Embolic coiling is the preferred method of embolization and is arguably the most important due to its usability, superior radiopacity and availability (Xiao and Lewandowski, 2022). Coiling complications such as migration (Sutanto *et al.*, 2022) and coil compaction lead to a risk of recanalization (Wiśniewski *et al.*, 2021).

2.6.2 Potential Barriers to the Development of a Patient Specific Embolic Coil

2.6.2.1 Cost

The literature discusses cost re 3D printing and imaging technology, opinion is that 3D phantoms are produced relatively cheaply (Frizziero *et al.*, 2019). Expense is relative to the cost-benefit of reducing theatre time, i.e., use of a more expensive custom device may be more cost effective overall than using a cheaper OTS device if procedure time can be reduced by use of the same (Lethaus *et al.*, 2012).

2.6.2.2 Staffing

Specially trained staff need to be employed across a wide range of roles to run the equipment, software and 3D imaging technology and associated processes (Andrés-Cano *et al.*, 2021).

2.6.2.3 Regulatory Landscape

The regulatory landscape for patient specific medical devices, particularly where they are not made for an emergency situation, is nebulous and as such the regulation has not kept in pace with the technological advances in this area and is a barrier to superior, patient specific treatments (Willemsen *et al.*, 2019).

2.6.2.4 Overview of Challenges and Path to Progression

Primary research with experts in the relevant fields will explore if these or other challenges represent significant impediments to developing a framework for manufacture of a patient specific embolic coil.

This dissertation explores the possibility of using a patient specific embolic coil, manufactured using 3D imaging with conventional manufacturing techniques, to remove (a) the need to use secondary devices when embolizing wide neck aneurisms and (b) reduce the incidence of complications due to

coil compaction and migration and (c) ascertain why this approach may not have already been investigated**.**

Chapter 3: Research Paradigm

3.1 Research Strategy

The research is in the interpretivist paradigm as qualitative data will be gathered (Halfpenny, 1979). However, the field of investigation is in science and engineering, where the results are ontologically positivist and the data quantitative, which is a key benefit of qualitative research in that the methods and methodologies can be tailored to fit a particular study (Douglas, 2017). Therefore, it can be stated:

1. That the experts consulted will base their opinion on experience with the methods, technologies, and processes relevant to this research (deductive approach from empirical evidence). (Newman, 2000)
2. The author will use the expert opinion and take an inductive approach to build the hypothesis. (Newman, 2000)

3.2 Methodology

The above approach fits Pandey's description of qualitative methodology, whereby we derive knowledge from information which has been itself informed by *data* (Pandey, 2019). In this case the data is from the experts' prior experiences, experiments and studies in their fields.

3.2.1 Method

From a Methodological Level, the approach is Naturalistic, as the data is gathered by interacting with participants in the form of an interview (the chosen method) (Erlandson *et al.*, 1993). *Interview* has unique facets that make it a superior method for qualitative research (Adhabi and Blash Anozie, 2017). The participants (qualified in fields relevant to this study) are essentially co-researchers as their knowledge is key to answering the research question (Collis and Hussey, 2021).

3.2.1.1 Rationale for Method

Rationale for choosing the participants and the information from data gathered is below:

- 3D modelling and printing Subject Matter Experts (SMEs) in industry can answer questions relating to technical aspects of tooling design, 3D modelling, and the feasibility of designing a tool which is based on a 3D anatomical model.
- Embolic coil SMEs, such as R&D Engineers and Process Development Engineers can provide expert opinion on embolic coil manufacturing processes, device design and material technologies.
- Clinical experts in the field of Radiology can give expert guidance on procedure complications and the potential for meeting these challenges with patient specific embolic coils.

This group of SMEs will assess the benefits and usability of custom embolic coils. All the above can inform the research, with a specific focus on the feasibility of producing patient specific embolic coils from standard coil material including a framework for manufacture. This constitutes what Patton calls 'purposeful sampling', where the interviewees chosen are 'information rich' and offer data appropriate and relevant to the purpose of the research/evaluation (Patton, 2003).

3.3 Philosophical Approach – Blended Model

A mixed approach qualitative and quantitative, is not uncommon and is logical, especially where both help to build knowledge in a field of study (Newman, 2000).

As mentioned above, the use of a qualitative methodology means the research will derive knowledge from information which has been itself informed by *data* (Pandey, 2019). The data *informing* the *information* for this research has come from the experts consulted and the literature review.

The quantitative analysis of material properties, 3D design approach, personalized medical device usage, segmentation of images, validation of manufacturing processes etc is based on primary and secondary sources, where a *hypothesis was tested* - be it that a particular material, method, or design approach could yield a desired result e.g. a better fitting cranial implant (Schön *et al.*, 2021). This research has a Qualitative approach informed by quantitative methods (Liamputtong, 2009).

3.3.1 Hypothesis

The primary research will use the experts combined experience to put forward a hypothesis based on already quantitatively tested *hypotheses*.

Hypothesis: The author proposes that a personalized embolic coil can be manufactured using DICOM/3D imaging techniques and current coil manufacturing processes. The resultant coil can lead to a reduction in coiling complications when embolizing difficult anatomy, in the peripheral vasculature.

3.4 Validity

Validity is recognized as trustworthiness for qualitative research (Golafshani, 2015). The validity of a qualitative approach is recognized as being high by Collis and Hussey (Collis and Hussey, 2021) and therefore, though no product is going to be manufactured as part of this study, the findings can still be deemed valid. Validity is underpinned by the accurate and clear representation of participants perspectives as key to qualitative data gathering (Noble and Smith, 2015), so interview of experts is an ample method in performing valid research (Adhabi and Blash Anozie, 2017).

3.5 Reliability

Bashir et al point to Patton's 2001 study as a framework for what is classed as '*reliability'* in a qualitative study (Bashir *et al.*, 2008), these are listed below in italics with the answers corresponding to this research.

- *What techniques and methods were used to ensure the integrity, validity, and accuracy of the findings?*
  -Expert opinion was consulted using interview as the method of information collection. This opinion was based on experience, which was gained from the quantitative data that the experts were required to gather in their respective fields in order to reach the level of competency required for their roles. This will be used as accurate and valid information to inform the research.
- *What does the researcher bring to the study in terms of experience and qualification?*
  -The researcher brings 19 years of medical device engineering experience, with 14 of those years working with embolic coils. The researcher has participated and led projects that entailed embolic coil design, process development, new product initiatives, process improvement and related intellectual property (the author has a number of embolic coil patent applications submitted).
- *What assumptions undergird the study?*
  -The study is undergirded by the assumption that (a) 3D technologies have already been used to make custom implants, (b) a personalized embolic coil can overcome performance issues in medical procedures (which currently use OTS coils) and (c) that standard methods

and materials can be combined with 3D technologies to make a patient specific medical device - leveraging existing processes, skills and modern 3D/DICOM imaging.

The above establishes that though the method is *qualitative* and the paradigm *interpretive*, the research may be deemed *reliable*.

3.5.1 Triangulation and Overall Credibility of the Research

The following items from the framework of Nobels and Smiths, for ensuring valid and reliable qualitative data is conducted, will be used for this research (Noble and Smith, 2015):

Triangulation, one element of which is using different perspectives across a number of fields of expertise (using interview as the method) has been used as part of the research to ensure the credibility of the qualitative research, which is prescribed.

Respondent validation of the research, where the respondents are invited to make a commentary on the interview transcript to ensure that the themes and concepts identified accurately reflect the phenomena being investigated.

Establishing a comparison, by identifying similarities and differences in responses, to ensure that different perspectives are represented in the research.

Acknowledging biases and criticizing methods, to ensure data is relevant and sufficiently deep to credibly answer the research question.

3.5 Generalization

Generalization is the extension of findings from other samples and cases to this research (Collis and Hussey, 2021). The literature review regarding the DICOM/3D element of the research will be generalized to apply the learnings found concerning the imaging of patient anatomy, and translation into patient specific medical devices, to personalized embolic coils. The expert opinion in the field of embolic coil design and manufacture will be generalized to cover manufacturing and designing a patient specific embolic coil. What was true in one place and time regarding the elements used for the production of patient specific medical devices and in OTS coil design/manufacture, can be said to be true in another place and time (Payne and Williams, 2005) - in this case that is the production of a patient specific coil.

Conclusion to Chapter 3

The research will be in the interpretivist paradigm, using qualitative data. The positivist and interpretivist paradigm will be blended to a degree however, as the experience of the experts consulted will be ontologically positivist, in that it is based on quantitative data they have gathered in their roles.

The research method chosen is *interview*, which is naturalistic and qualitative in nature and maintains contextual validity (Hameed, 2020). The methodology seeks to use expert opinion based on their knowledge, incorporating their past experience with quantitative methods in their fields, to be generalized regarding the research question. This is an inductive approach (Imenda, 2014). Reliability and Validity will be established through the qualifications of the witnesses, with comparison of different perspectives sough to ensure the data is credible. Triangulation and a number of different tools shall be incorporated into the research to ensure it is as reliable, valid and non-biased, in so far as qualitative research can be - what constitutes validity and reliability in

qualitative research is a debate within the academic/research community (Noble and Smith, 2015) & (Rolfe, 2006).

The above is a fitting research approach as expert opinion will be gathered from fields that are in the positivist realm of science and engineering, yet no experiment will be carried out to prove the concept can be realized i.e., the actual fabrication of a personalized embolic coil will not be attempted as part of the research.

The interviews conducted as Primary research for this dissertation will explore the potential for 3D imaging and standard manufacturing techniques to be used in producing a patient specific embolic coil. The interviews will gather expert knowledge on the same and investigate if in their opinion a custom coil would be of benefit to (a) remove the necessity to employ a secondary device(s) when embolizing wide neck aneurisms, and (b) reduce the incidence of complications due to coil compaction and migration.

Also, the interviews will probe why the above approach has not already been adopted.

Chapter 4 Findings and Analysis

4.1 Introduction

This chapter will analyse the information and opinions of the Subject Matter Experts consulted during the Primary Research phase. Key Assumptions made will be set out and the Research Plan detailed, showing the context used to direct the primary research and the method for data analysis and collection. A *semi-structured interview* was the mode of gathering data, which allowed the author to follow a set of pre-determined questions *and* pose supplementary questions when the subject matter was deemed to enhance the research (Adhabi and Blash Anozie, 2017).The analysis and findings draw on the interview material, where the information is presented after undergoing Coding, Theming and Data Synthesis - a recognised method of data collection and analysis in qualitative research, as laid out by Austin et al (Sutton and Austin, 2015).

4.1.1 Key Assumptions

Key Assumptions below were the basis for the hypothesis and the catalyst for the research.:

1. 3D imaging/DICOM has already been employed in making patient specific medical devices and therefore can be used in the same manner for peripheral embolization procedures.
2. Performance issues with Off the Shelf (OTS) coils can be overcome with a personalized embolic coil.
3. Existing manufacturing methods, materials and skills can be combined with 3D imaging technology to produce a patient matching coil.

4.1.2 Research Plan

In order to gather expert opinion on the areas identified in the key assumptions three groups were consulted via semi structured online interviews (as listed below in 4.1.2.1). During the course of the interviews, it was highly recommended by one of the R&D engineers that the author interview marketing personnel (which was not in the original research strategy). When reaching out to an Oncology UK Business Unit Manager (with Boston Scientific) in order to get an interview with an Interventional Radiologist, the same *also* suggested the author speak to the marketing group. This group described how they interfaced with R&D engineers and Interventional Radiologists on their needs and practices. These marketing SMEs provided the author with a rich consultation resource; a *single* data source that had networked with multiple customers and developers. These interactions provided them with a holistic knowledge of embolization - from product design and innovation to the end user requirements and user habits. The same have been categorized below as *Interventional Oncology/Radiology Marketing SMEs.*

Interviews with all the SME groups were conducted online as one-to-one engagements. The interview *form* was *semi-structured*. This afforded a level of flexibility to the questioning. Where a reply or subject branched off into an appropriate topic, that was deemed relevant and informative for the research, an improvised question was asked of the SME on the same. In instances, the improvised topic was added to the bank of questions used in the interviews with other SMEs. An example is the topic of physician product loyalty/rigidity, one that had been brought up by the SME consulted in the initial research interview and then incorporated into the bank of questions for subsequent interviews.

SMEs employed by Boston Scientific were featured heavily as Boston Scientific is a major company in the embolic coil/product market and produces a wide range of pushable, fibered, and non-fibre detachable coils.

4.1.2.1 SME Listing

3D modelling and printing Subject Matter Experts (SMEs) background on 3D imaging/modelling and tooling design from the same:

1. Paul Cullen: An Equipment Engineer with Boston Scientific, working in the medical devices industry for 3 years, with an additional 15 years in Automation & Instrumentation and 10 years 3D printing and design experience.
2. Darren Carroll: Process Development Design Engineer with Boston Scientific. Experience in Computer Numerical Control (CNC) processes, Aerospace design, and 3D modelling on various platforms.

Embolic coil SMEs

R&D Engineers

1. Grigory Severyukhin: Senior R&D Engineer in Peripheral Vascular Coils at Boston Scientific, with 10 years' experience in the role.

3. Marie Claire Anderson: Senior R&D Engineer in Peripheral Vascular Coils with Boston Scientific, with 8.5 years' experience in the same.

Process Development (PD) Engineers:

1. Shane O' Driscoll: Process Development Engineer, with 7 years' experience on next generation coils for Boston Scientific, with extensive experience in coil primary material manufacture, coil winding and annealing (aka front-end manufacture).
2. Conor O' Sullivan: Innovation Lead and PD Engineer for Boston Scientific with 21 years' experience. Experience in design of Neurovascular & Peripheral Vascular coils as well as developing manufacturing methodologies for the same.

The above provide expert opinion on embolic coil design, manufacturing processes, material technologies, tooling design and user needs.

Clinical experts in the field of Radiology

1. Dr Kunal Khanna: Consultant Interventional Radiologist, Wexham Park Hospital, Slough, Berkshire, UK. 10 years' experience. Specializing in Radiology (interventional, diagnostic and Uroradiology), vascular and gastrointestinal imaging, vascular access, fibroid and varicocele embolization.
2. Professor Mark Little: Consultant Interventional Radiologist, Royal Berkshire NHS Foundation Trust UK. Extensive experience of embolization and endotherapy within Interventional Radiology.
3. Dr Sachin Modi: Consultant Interventional Radiologist/Oncologist, University Hospital Southampton, UK. Specialties include gynaecological and urological embolization.

This group offer expert opinion on physician practice, procedure complications, and the potential for meeting these challenges with patient specific embolic coils.

Interventional Oncology/Radiology Marketing SMEs:

1. Emma Brown: UK & Ireland Product Manager for Interventional Oncology with Boston Scientific and previously direct sales (Interventional Oncology products)
2. Ms. Duygu Besler: currently the EMEA product manager for embolization products with Boston Scientific and was a Product Manager in Interventional Radiology prior to this. Total of 15 years' experience in Interventional Radiology.
3. Andrew Sorensen: Upstream Product manager in the Interventional Oncology and Embolization Division of Boston Scientific, with a focus on coil embolization. Previously worked as a Downstream Product Manager for embolic coils.
4. Michael Mohs: Product Manager Interventional Oncology Marketing with Boston Scientific. Several years in embolization marketing (both upstream and downstream), with experience in embolization coil platforms and liquid embolics.

Note: *upstream* marketing is everything from idea creation for a new product all the to commercialization. User needs are identified and inform product design. *Downstream marketing* is everything from commercialization to product 'end of life' (obsolescence). Potential users are shown capability and utility of the new product. (Paraphrased from Interview with Michael Mohs).

4.2 Overview Of Current Position Of Use Of Patient Specific Embolic Coils

The following section will focus on areas discussed in the interviews around the current practices in embolic coiling. Themes identified will be explored through the eyes of the interviewees.

4.2.1 Current Practices & Issues with Embolic Coiling

4.2.1.1 Off the Shelf Coils

The interviews showed that Off-the-Shelf (OTS) coils are manufactured by various companies and come in many different sizes (length and outer diameter), shapes and levels of stiffness/softness. 'Liquid embolics' such as gels and glues are also used in interventional radiology, often in combination with coils where clinically required. One issue highlighted was the need to place multiple coils into a vessel to pack it out due to the limitation of coil length. Per the interviews, in this scenario the Interventional Radiologist (IR) is faced with a number of challenges:

1. Prolonged procedure – use of multiple coils increases the time taken to deliver the coils to the target.
2. Risk of catheter position loss – the catheter is advanced to the vessel and held in place and may move while introducing multiple coils.
3. Large volumes of coils (shapes, sizes, softness) are required on the hospital shelves.

The large volume of coils on shelves reflects the vast choices that a clinician has when conducting an embolization procedure. This point was brought out very clearly in the interviews by six of the SMEs consulted. Not that alone, but multiple SMEs pointed out that Interventional Radiologists (IRs) as a discipline are innovative in how they approach a procedure. For instance, the marketing and R&D groups consulted (who have extensive interactions with physicians), pointed out that IRs will adopt tools from other specialities to 'get the job done'. One example given by Marie-Claire Anderson of how this plays out in the operating theatre (OR) is the use of catheter *guidewires* (used to navigate through the vasculature to the target vessel) as *coil plungers* (devices used to advance pushable coils out of the introducer sheath into the catheter). So, while IRs may be comfortable to innovate and adapt to use the tools they have to hand, the sheers choice of OTS coils can lead to administration and stocking issues for staff (Cath-Lab Technicians was one group identified here by Duygu Besler).

With a wide range of OTS coils comes different modes of use, for example with detachable coils the *method of detachment* varies by manufacturer and model. This variation/range can cause problems, per Dr Kunal Khanna's interview, this is especially the case where the device comes with the need to remember multiple steps, is a bit awkward or "weird and wonderful." The same commented that if your delivery system is easy to use and works - people will use it. A clinician may have to turn the delivery wire 8x times to detach one model and may have to press a button on another, (a detachment tool handpiece for instance). Detachment tools vary also, again depending on the product being used. See *Figure 1* below for an example of some of the various detachment devices/systems marketed with coils.

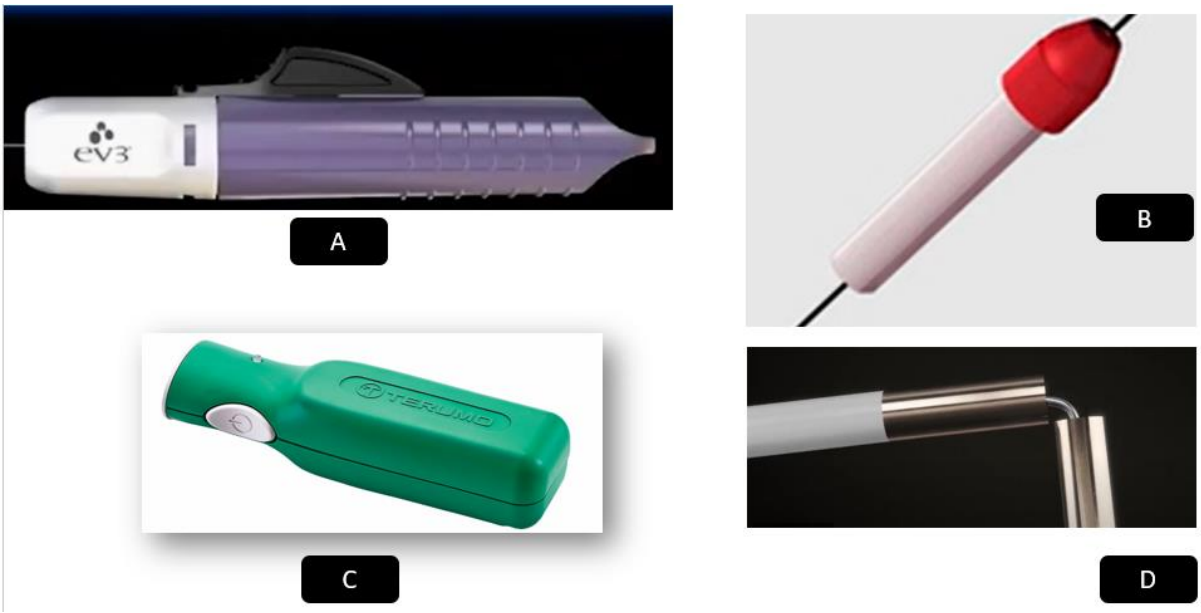

Figure 2. Example of detachment devices that accompany embolic coils. Each have a different method of detachment: (A) Medtronic Concerto Detachable Coil (Medtronic). (B) Cook Retracta® Detachable Embolization Coil, (C) Terumo AZUR™ CX Peripheral Coil System, (D) Boston Scientific Embold Detachable Coil. (CITATIONS TO BE ADDED). Example of detachment devices that accompany embolic coils. Each has a different method of detachment: (A) Medtronic Concerto Detachable Coil (Medtronic, 2022). (B) Cook Retracta® Detachable Embolization Coil (Cook Medical, 2023). (C) Terumo AZUR™ CX Peripheral Coil System (Terumo, 2023). (D) Boston Scientific Embold™ Detachable Coil (Boston Scientific, 2023).

A surgeon already has "so many devices you're remembering how to use". Where Dr Khanna has used multiple types or brands of coil, the deployment systems have been either *very similar* to one another or very *intuitive*. So, the wide range and variation, e.g., in instructions for use, is an issue.

4.2.1.1.1 Personalisation & Customisation of Care Using OTS Coils

Opinion was held that a broad range of sizes and shapes offers a level of customisation in a surgical procedure. Added to this was the availability of liquid embolics, plugs, beads and the like. Dr Sachin Modi agreed that every single procedure was personalised as such.

4.2.1.1.2 Scaffolding/Framing Coils

OTS framing coils were not only used with packing coils but also used in conjunction with *liquid embolics*, one example that was given was *Onyx*™, a Medtronic product (Medtronic, 2023). In this case a Boston Scientific 35 Interlock framing coil was used to open up a splenic aneurism, allowing it to be filled with the liquid embolic. However, per Prof. Mark Little, framing coils "can obscure visibility and affect the packing."

4.2.1.2 Liquid Embolics

Liquid embolics (LEs) were discussed with regard to their usage. Per the interviews these can be in the form of hydrogels, glues, and polymers. Michael Mohs pointed out that one of the first things considered in a procedure is how to navigate to the target site and what embolic agent or devices to use. Coils can be used in conjunction with LEs as a scaffold (as mentioned in 4.1.1.1), or an LE may be introduced after coiling has been performed to ensure there is full coverage of the vessel. A liquid can reach distal vasculature and other hard to reach places where placement of coils is difficult. Different viscosities are used depending on the target and the risk of unintended leakage into surrounding anatomy. For a wide neck aneurism one IR said they had used a balloon to cover over the neck of the aneurysm to prevent the liquid embolic from leeching into the parent artery, (a similar containment procedure to BAC). Liquids also *conform* to the shape of the vessel and are especially of use in vessels of less than 3mm. *Cost* was a recurrent theme in the research, and this was the case also in relation to LEs. Emma Brown pointed out that a procedure may be done with two vials of an LE versus multiple platinum coils, and therefore could be a more cost-effective option - LEs were identified as a *competitor* to coils. An Embolization Product Manager for EMEA backed this up by stating that the LE market is growing at a rate 3X times faster than the overall peripheral embolization market - potentially cannibalising 30% of the coils business in 3-5 years' time. In the next two years, six to seven new LEs will be entering the market in Europe, with the projected growth rate and the potential coil cannibalisation rate set to rise as a result. Another factor is the overall procedure cost, this includes the cost of time taken to do the procedure and the devices used, here something also like an embolic plug may be used, though more expensive than coils, yet it allows a speedier procedure time. The IRs pointed out that procedure time and getting through multiple procedures was important, as there are a lot to get through in any given day. So, balancing cost of procedure time with the use of a potentially more expensive, yet expedient embolic device e.g. a plug or liquid embolic, is a factor in cost and consequently a factor in the physicians use of liquid embolics and LE market growth.

4.2.1.3 Physician Habit and Product Loyalty

A very important theme that came through in the interviews with the R&D, IR and Marketing SMEs was physician habit and product loyalty. This was the case with regard to the delivery catheter used during an operation. Feedback from the groups was that 'getting there' [navigating a catheter to the target vessel] is often the trickiest part of an embolization procedure. Two of the marketing group were in unison in suggesting that the first consideration in every embolization case is 'what catheter do I need to get to my target anatomy, and can I do it reliably?' Emma Brown stated that a "catheter is very personal thing – it's what the [physician] trains with". The IR group held that they were used to using either a single model, or selection of micro catheters. Knowing how the preferred device behaved meant that the catheter was an extension of their arms as such. Dr Sachin Modi put it clearly in saying that "if a vessel is in a position that is very difficult to get, you want to use the micro catheter you are used to using". Prof Mark Little emphasized that doing so many cases with a particular "set-up" meant that complications are low.

4.2.1.4 Openness to New Technology

One issue in introducing a new technology is *user preference,* and more directly *"t*rying to make a user do something they are not used to" (Snr R&D Engineer Grigory Severyukhin). The interviewed groups agreed: IRs are open to new technology, under a certain set of conditions.

One IR commented that any new technology needed to be *straight forward* to use. If something better than the current preferred product comes along the clinicians *will use it,* but there was reluctance to change to a more complicated, awkward, or tricky-to-use device. Any new technology

must be better than the current technology. Examples were given of embolic coils that surpassed the previously preferred models due to superior performance and features (such as a fully retractable coil). Examples of market leading 'cannot live without it' devices were also given. The catheter again was highlighted, the marketing group asserting that part of the consideration for end users regarding a new embolic device is, "can I use it with my favourite catheter or with the *market leading catheter.*" The same group said catheter compatibility, as a factor in changing to a new embolic device, was a source of resistance. There was agreement that *stipulating* the use of a *specific* micro catheter would be a major block to a new technology (and that non-compliance with this stipulation had led to product performance problems in the past). One IR explicitly said that they "were more than happy to embrace new technology…but would need a *good* reason for switching the *delivery catheter*."

4.2.1.5 Cost As a Consideration When Using OTS Embolic Devices

The SMEs main consideration was the cost of a device versus the practical purpose it served. Comments on cost compared the procedure outcome with the methods and means to get it done. The SMEs were by in large of the opinion that placing multiple short coils in a vessel was potentially a cheaper option than getting a device custom made to achieve the same end. Similarly, the expense of using a LE may be lower than using *multiple* coils. This fit with the expressed opinion that the IRs are innovative, have a large range of existing tools and will use whatever tools they have to hand to 'get the job done', i.e., there is enough utility in what they have available to effectively carry out procedures. On the other hand, there was opinion among the marketing and R&D group that a device that can be used instead of multiple OTS coils would be an advantage in terms of overall procedure time and could reduce the need to hold a large stock of OTS coils on hand. The main theme identified from the interviews was that there must be a balance of cost versus the expected benefit i.e., completing a procedure successfully, for any new device as OTS devices were apt to the task. The same opinion was expressed in relation to selecting tools from the current devices on the market, such as the use of multiple coils versus an LE and vice versa. The literature review in section 2.4.6 agreed with sentiment that cost was not just about the expense of the device itself but should take into account the overall procedure time and clinical throughput, which agrees with SME views.

4.2.1.6 Gaps in Currently Available OTS Coils

The need for a *longer* coil to reduce the potential complications as detailed in section 4.2.1.1 was expressed. Also, the desire for a coil with a very soft platinum and curved tip, reducing risk of perforation and lengthy procedure time, was detailed by one of the IRs. A need for the development of *resorbable* coils was communicated by one of the IRs. The same is involved in Musculoskeletal embolization (MSK) research and pointed out that development of resorbable coils would "open up that discipline". The complication in using stents with current OTS coils (stent assisted coiling or 'SAC') was identified by Conor O' Sullivan, as future access to the vessel or access beyond the vessel is difficult after the insertion of a stent, a point supported by Michael Mohs. A similar issue was raised where an LE is used, as there also access beyond the embolised vessel/vasculature would be restricted. SMEs detailed that a coil with utility to replace the need for SAC, when treating wide necked aneurisms, would be an advantage. Duygu Besler remarked that such a coil would replace the need for "costly stents" and identified the same "as a gap in the market." Section 2.2.2.4 and 2.2.2.5 detailed the current need for stenting and the issues associated with the same, SME opinion agreeing with the literature. The literature nowhere mentioned the existence of a coil, or potential *use* of a coil, that could negate the need for a stent, highlighting the identified gap in the literature and the need for discussion regarding a device to meet the need – a discussion conducted as part of the primary research.

4.3 A Patient Specific Embolic Coil For Peripheral Vasculature – Why Has This Not Already Been Developed?

The secondary research found a gap in the literature regarding personalised embolic coils (see Section 4.6). The following section explains why, from the point of view of the SMEs, a patient specific embolic coil has not yet been developed.

4.3.1 Devices Available are Sufficient for Peripheral Intervention

As already discussed in 4.2.1, there are a myriad of OTS coils available to the Interventional Radiologist. Added to the coils is a wide array of other embolic devices including gels, glues, embolic particles, gel foams, PVA plugs and conformable polymer embolics. A form of personalisation of care is already facilitated by the same and the SMEs believed that there were indeed already enough tools existing to successfully treat patients. One marketing manager believed that "embolization is a 'one size fits all'" treatment and that most IRs can 'make do' with what is already marketed. Adding to this, Marie Claire Anderson commented that current coils are flexible and can be made to conform to *whatever shape is required*, while cautioning that there are limitations to that. The SMEs indicated that neuro interventional radiologists (NIRs) require something far more specific to each vessel and work within an area of the body where a bleed can lead to severe disability or death. Several of the SMEs commented that neuro vascular coiling entails a *target* aneurism filling volume (25%), which is critical to the success of the procedure. However, IRs on the other hand do not need something as specific to the vessel, and do not have the same sensitivity to filling volumes. Instead, embolization for *peripheral intervention* relies more on thrombosis in the body. A rupture in the visceral system can be plugged with a large coil or other embolic and does not lead to the poor patient outcome that the same complication causes in neuro embolization.

4.3.2 Emergency Versus Scheduled Procedures

Duygu Besler stated that 70% of coils are used in an emergency situation. Incidence of *emergent* versus *scheduled* embolization was a strong theme discussed by the other SMEs. In short: in a trauma situation physicians don't have time to wait for something patient specific to be built and need a device that they can pull of the shelf to stop the bleeding. For emergent cases there would be an immediate need for intervention, scans and rendering a 3D model would not be viable. One IR communicated that hospitals are struggling to get supply of OTS coils as it is. Waiting for a patient specific coil was not seen as a feasible option for unplanned cases. *Use of a patient specific coil would require a great degree of planning.* For scheduled/planned cases, opinion was that there may be some utility in a patient specific coil, but this would be niche at best and would be better suited to the field of neurology. Planning using 3D modelling was deemed useful, but this in only a subset of cases, with one IR commenting that it would be a 'once a year scenario'. SME opinion was that 3D imaging was "a luxury", "not completely required", and was deemed unnecessary as a scan of cross-sectional anatomy is adequate enough to work out what devices to use. Even *with* planning there was an element of the unknown regarding which coils were best suited to the case until the procedure was underway. Those interviewed stated that some cases are very difficult to image with CT, so the required tools and sizes, including coil length, are not known until the radiologist is actually in the anatomy where they can then use dynamic angiography. An illustration of the limitation of planning was given by Prof Mark Little where he gave an example that in a planned case it may be decided that a 30Cm coil is required to fill a vessel, only to discover after packing the aneurism that the coil is too long and sticking out into the parent vessel.

4.3.4 Turnaround Time for A Patient Specific Device

The IRs interviewed were concerned that they would have to wait for delivery of a patient specific coil, this being potentially the case even for a planned procedure. Another SME stated that having medical staff required to follow the device's manufacturing progress and tracking the delivery of the same, would be overly burdensome. One senior marketing respondent stated that production time would have to be no more than a day to be practical. The general feeling was that the device would have to be *on the table and ready for use* within a week. The question of physician confidence in the *framework* to produce the coil, in a reasonable turnaround time, was raised by the non-clinical SMEs. Conor O' Sullivan remarked that in order to get the coils to where they are required in a timely manner, a whole network of people would have to be built around the framework; those conducting the imaging, those transferring images, manufacturing, and sales. An example of a similar process for 3D printing custom devices, already existent in medical device company in Ireland, was given: the physician visits the manufacturing site to consult on the specifics of the custom device, the device is manufactured, any required adjustments made, all within 24 hours from the time of the visit.

Overall, confidence was low that the turnaround time for a patient specific device would meet the demanding timelines required by physicians.

4.3.5 Cost Versus OTS Coils and Other Embolic Devices

As already discussed in 4.2.1.2 and 4.2.1.5, weighing the cost of OTS coils versus LEs versus procedure time versus operating theatre *throughput* is a theme that came through strongly in the research. The cost versus benefit of a patient specific coil as opposed to just using OTS coils was queried. "Cost is most important," is the statement that one marketing SME made, saying that "the cost [of embolic products] must be reduced," the sentiment being that new products won't be adopted readily if they are not cost effective. A U.S. based marketing manager stated that Group Purchasing Organisations (GPOs) dictate what a hospital is allowed to purchase, so can be a constraint when it comes to considering the procurement of more expensive products [such as a personalised embolic coil]. The UK based IRs said the situation there was more open - they rarely get told a product they want to use is off limits due to cost but commented that there are only finite resources available and that different procurement procedures are in place elsewhere. The IR group felt that they would gain no marked benefit to the clinical procedure for the extra expense incurred.

The majority feeling was that a custom device would undoubtably be more costly than an OTS coil and that the advantage gained would not outweigh the extra expense, except maybe in limited cases.

4.4 Can Patient Specific Coil Address Coiling Complications?

4.4.1 Wide Neck Aneurysms

For wide neck aneurisms some SMEs expressed that a patient specific coil would work if the coil can exert a high radial force on the aneurism wall and be kept from migrating out of the same. If that problem were solved by the patient specific coil design the need for SAC and BAC, and their associated complications, would be negated (see section 2.4 for complications). As Grigory Severyukhin stated in relation to the same, "do that and you've got a good technology." Marie-Claire Anderson backed up these statements, her opinion being that a custom shape coil could help to exert the radial force required. However, SMEs pointed out the that the high radial force required in the aneurism may lead to friction in the catheter. Shane O Driscoll advised that a technical solution

to this can be provided by tailoring the parameters used to make the platinum wind i.e., by varying the pitch in each section of the wind.

4.4.2 Stent Assisted and Balloon Assisted Coiling

Andrew Sorensen pointed out the issue with stenting is it hinders vessel patency and therefore would see a benefit in having a personalised coil to remove the need for a stent. Another complication that could be helped by a patient specific coil is *extended procedure time*, which may be decreased where a patient specific coil reduces the necessity for (a) multiple coils and (b) secondary devices, such as stents and balloons. Multiple devices being advanced to the target site can cause the catheter to be dislodged. As discussed, getting the catheter to the target vessel is problematic and having to repeat the advancing procedure multiple times increases the risk of complications and procedure length.

4.4.3 Other Complications

Other scenarios where a patient specific coil was deemed to be potentially useful is where blood flow is very fast [making coil placement or use of an embolic difficult], or a situation where an OTS coil may have trouble anchoring. Additional complications identified that could potentially be helped by the use of this technology were post-transplant embolization, endo leaks, failed endovascular aneurism repair (aka EVAR), large spaces, or tortuous/tricky anatomy.

4.4.5 An Aid to Scaffolding Issues?

Opinion was mixed whether a custom *scaffolding* coil was of benefit. One Consultant IR stated that OTS scaffolding coils can obscure imaging and can get in the way of vessel packing, therefore there may some advantage in having a patient specific coil. Another in the IR group thought OTS scaffolding coils were adequate and therefore saw no need for a patient specific device for scaffolding use. R&D SMEs were of the opinion that as OTS scaffolding coils were only *semi controllable* (and so may not go into the desired shape), a patient matching scaffolding coil would be of benefit.

Overall, scaffolding complications did not feature highly as a major problem for clinicians when discussed in the interviews. However, regarding the research aims, seeking to establish if a patient specific scaffolding coil could be of benefit, the weight of SME opinion is *yes*. This is based on the fact that complications, regardless of the scale and frequency, *do exist*, which was highlighted by Professor Mark Little. Additionally, the opinion of the R&D SMEs was that a coil exclusively designed to take the shape of a specific aneurism would be of benefit.

4.5 Proposed Workflow For Using 3D Models To Produce Patient Specific Embolic Coils

4.5.1 3D Rendering to a Secondary Mandrel

See Sec 2.5 and Sec 2.5.2 for detail on what a ‘mandrel’ is, it’s use and design. There was agreement among the R&D, 3D, & Process Development SMEs that producing a mandrel from a 3D scan /DICOM was possible, which agrees with the secondary research.

4.5.1.2 Anatomical 3D Image To Mandrel Design

There was a consensus among the R&D and PD SMEs that a mandrel could be used to produce the desired coil shape. The 3D technology SMEs were highly confident that, with the software currently available, an anatomical scan could be transferred successfully into a 3D format compatible with industry standard tooling computer aided design software (CAD), an example given was SolidWorks™. Manipulation of the imported image would not be technologically beyond current 3D

tool design practice or capabilities. Per Darren Carroll, the 3D image of a vessel could be analysed and measured in the CAD software and the information used to generate a mandrel. Secondary research showed that constructing implants and phantoms from scans was possible and becoming more widespread, therefore the SME feedback was very much in agreement with the current landscape as presented in the literature review.

4.5.1.3 Common Coil Design Features

4.5.1.3.1 Distal Small OD

Incorporation of industry standard coil features (such as a small Outer Diameter section at the coil distal end) were deemed not to pose any issue for patient specific mandrel design.

4.5.1.3.2 Scaling of Mandrel

Scaling up the mandrel design to include the percentage increase essential to embolic coil design poses no difficulty (scaffolding coils are required to be larger than the vessel they are going to embolize - see 2.2.2.3). All of the 3D SMEs were in unison: scaling up the model was not complicated and scaling itself, as a technique, was a routine practice in 3D modelling.

4.5.1.4 Mandrel Manufacture

Shane O Driscoll, a front-end PD engineer and SME in coil winding, shapes, annealing and materials stated the mandrel *could* be 3D printed or machined. Conor O' Sullivan agreed, adding that he was 100% confident that the mandrel could be generated from the 3D patient scan model. The opinion of the 3D Design SMEs opinion was in agreement with that of the PD Engineers.

4.5.1.4.1 3D Printing of Secondary Wind Mandrel (Manufacturing Method #1)

Expert opinion was that mandrels can be 3D printed as either a solid or hollow shape. Selective Laser Sintering (SLS) was suggested as a current technology to achieve this. [Selective Laser Sintering melts selected layers of metal powder to form a solid form to the desired geometry (Iveković *et al.*, 2018)]. The author brought up a question regarding the heat-up and cool-down time with respect to the annealing/heat treat process i.e., a solid mandrel may take a long time to reach temperature and subsequently to return to ambient temperature. SMEs did not see this as an issue. One SME did suggest that a 3D printed hollow mandrel would help with reducing the heat sink effect, the benefit being it would speed up the annealing process. The secondary literature on the advances made in 3D printing technologies, such as SLS, supports the SMEs proposal for fabrication of a 3D printed mandrel.

4.5.1.4.2 Machining of Mandrel (Manufacturing Method #2)

SMEs agreed that the mandrel could be machined per current industry tooling fabrication practice. If 3D printed, a mandrel could also be finished using machining processes.

4.5.2 Personalised Coils and Their Manufacture From Current Materials

SMEs agreed that personalised coils can be made from current platinum wind. Not just that, but the characteristics of the wind can be altered to allow stiffer and softer sections in one continuous length of material, as may be required by a custom design. A host of parameters can be adjusted to accommodate the same, including wire gauge, wind pitch and wind diameter to ensure the material is the desired stiffness level. A large coil is softer and may not hold its shape as well, but where a high radial force is required a larger gauge wire can be used to achieve the same (see 4.4.1 regarding the radial force required for wide neck aneurisms). As seen in the literature review section 2.2.2.3, radial force is a key characteristic of a scaffolding coil, secondary research agreed that the design of the platinum wind is critical to coil performance. Primary research showed that the platinum wind specifications can be modified to suit the requirements of a patient specific coil.

4.5.3 Winding Pattern

One 3D SME stated that a winding pattern [the way the coil is wound onto the mandrel, such as a criss-cross, overlap, side by side wind etc] could be produced by the 3D CAD software. The winding pattern was not a major concern for the Process Development SMEs, as their opinion was that there is a lot of experience and knowledge held within the traditional coil manufacturing sphere regarding winding pattern generation.

4.5.4 Downstream Coil Processing

Downstream or 'back-end' processing of patient specific coils was deemed to be no different than currently manufactured OTS coils. Examples given of downstream processing steps were *unwinding* [removal of the shaped coil from the mandrel] and forming an atraumatic [distal] tip. Shane O' Driscoll stated that "as a general top-level rule the downstream processes don't change much, the biggest change is upfront with the coil OD."

4.5.5 Coil Fabrication Turnaround Time

The PD Engineers were the most detailed in their assessment of coil turnaround time. In order to produce coils in a rapid manner it was suggested that existing technology such as automated secondary winding could reduce processing time. 3D design SME, Darren Carroll, put forward a concept on how to make a mandrel from premade sections. The same could be configured to make one off shapes from a winding pattern matching the 3D scans, thereby removing the need to *fabricate* a new mandrel for every build, one only need be *assembled* to a given pattern. Consideration was given to how advanced the 3D printing of metals has become vis-a-vis mandrels potentially being produced in a very short time period. A single day was the estimated time to produce a coil *if* the mandrel were available on the manufacturing floor. Use of a *hollow* 3D printed mandrel would provide a processing time advantage (reducing the coil annealing time due to faster thermal response). The SMEs were confident that a speedy manufacturing lead time was achievable and suggested the process could be streamlined if a dedicated manufacturing line was set-up for personalised 'one-off' coils. The rapidity of 3D phantom manufacture and device manufacture were detailed in the literature review and agreed with the SME statements on the rapid nature of current 3D printing technology.

Conclusion to Chapter 4

The SMEs were very knowledgeable and forthcoming with information and were clearly very experienced in their fields. There was overwhelming agreement that a patient specific coil could be produced from an anatomical scan, using current manufacturing practices and materials. Winding mandrel design based on the scan and subsequent fabrication were not deemed to be beyond current technology, software, or expertise. The cost-benefit associated with a patient specific coil, versus currently available OTS products, and the *need* for the former were questioned. However, there *were* uses for a patient specific coil identified, but the general opinion being that these would be niche. Optimism was expressed when considering the potential advantage gained by using custom coils for wide neck aneurisms - specifically where that would remove the necessity for use of a secondary device (e.g., a balloon or stent). When discussing the same, potential issues with radial force and stiffness were highlighted, however technical solutions were offered by the SMEs to resolve the same. Lead time was a concern for IRs in particular and was highlighted by SMEs in the other groups. Again, a number of technical solutions were proposed by the SMEs to reduce the turnaround time.

Chapter 5 - Conclusion

DICOM/3D imaging

The secondary research agreed with the primary research on their being no technical barrier to the patient imaging, 3D segmentation and image rendering to a 3D file. Technical challenges of accuracy in the rendering, as discussed in the secondary sources, did not feature as an issue with those people consulted as part of the primary research.

Rendering 3D Model to a Winding Mandrel

The SMEs were not only able to discuss the concept and potential flow for designing a mandrel from a 3D patient specific model but had such optimism that this could be achieved as to offer a number of mandrel design concepts that could be used to speed up the manufacturing process, a hollow 3D print, a modular mandrel etc as discussed in Chapter 4. The secondary research did not put forth any barrier to making a 3D model into a patient matching medical device. The agreement between the primary and secondary research shows that the flow of going from patient scans to 3D model and then to a fabricated medical device (or tool for manufacturing the same in this case) has been done and can be done in the case of a patient specific embolic coil.

Technical Challenges Around Coil Design from A 3D Scan

While the manufacture of the custom mandrel for making a coil did not pose any major difficulty, the technical challenges were around the coil design itself. The secondary research discussed coil features such as coil stiffness, wind pitch and wind diameter. Primary research highlighted related characteristics such as *radial force*. Having sufficient radial force in the coil design to stay in the wide neck aneurism, and not protrude in the parent vessel, was seen as a potential technical challenge. Expert opinion of the PD Engineers was that this could be overcome by incorporating the specific characteristics required into the platinum wind via varying pitch, wire outer diameter and wind pitch - characteristic changes that agree with the secondary literature.

Coil winding pattern on the mandrel to achieve the desired technical characteristics (such as bridging the neck of an aneurism) was seen as possible using the CAD software for mandrel design. A potential challenge in making a 4D shape, where the platinum wind criss-crosses and fills the space in the centre of the coil secondary shape, was called out but a solution was again offered as to how this could be overcome. Overall, no major challenge precluding coil design from a 3D scan was given; where a challenge was highlighted a solution was offered by the SMEs.

Patient Specific Material Softness/Stiffness

How to determine the stiffness, or inversely, the softness of the platinum wind required based on the 3D model of anatomy, was not discussed and would be a technical feature to be investigated further. However, the secondary research and primary interviews show that there is enough knowledge and experience in the coil manufacturing industry, regarding the demands of different sized vessels, to determine the platinum wind to be used. This experience is based on currently used platinum wind stiffness versus indications for vessel size and morphology on OTS coils. The downstream processes involved in coil manufacturing, which require welding etc, would have to be tailored to deal with platinum wind of varying thickness, again this would have to be factored in when generating a coil design from a 3D model of anatomy, a factor not seen as a technical barrier by the SMEs. Though an important feature of coils is their stiffness, no technological solution was offered as to how to determine the target stiffness from a 3D image of a vessel. The primary and secondary research did however opinion that current knowledge and reckoning of the appropriate

stiffness, based on vessel characteristics, is sufficient to allow a patient specific coil to be manufactured.

Overall, opinion was that a patient specific coil could be manufactured from a 3D patient scan using current materials and manufacturing methods.

Are Patient Specific Coils Needed?

The SMEs consulted agreed that there is enough OTS coils and other embolic devices available to the Interventional Radiologist to do their job capably. If asking if patient specific coils for peripheral intervention are *needed* to get a good patient outcome, the answer from the SMEs was 'no', OTS coils are sufficient. That does not mean that there was no value or use for a patient specific coils put forward by the SMEs. Opinion was almost unanimous that there are *niche* uses and though an IR can treat a patient amply with OTS coils, a custom device may reduce procedure time, negate the need for secondary devices (stent and balloons) and improve theatre throughput. Opinion was also that challenging cases may be helped if a coil is made specifically for a difficult vessel, complicated procedure, or tortuous anatomy.

One very important point was brought up by Dr Kunal Khanna relating to the question, 'are patient specific coils needed?' Dr Khanna stated, "the difficulty in answering that question is knowing what kind of things/shapes could be produced." In essence it was hard to say if a custom coil is useful if it *doesn't exist*. An example given to illustrate the point was that of the Cook Tornado® coil. Dr Khanna stated that he could not say that the Tornado® coil shape was useful until someone *made it.* In that instance someone did manufacture the coil and the Dr Khanna said he finds it *really useful*.

Recommendations and Further Research

A number of areas for further research were identified during the interviews conducted with the SMEs and are laid out below.

Resorbable Coils

Research should be put into identifying suitable resorbable materials for embolic coil manufacture. The same should be investigated with a view to widening treatment options in Musculoskeletal (MSK) embolization. MSK embolization is still an area of research and could potentially be opened up to more indications if resorbable coils were developed.

Coil Shapes/Morphology

As part of R&D into embolic coil design, various shapes should be trialled even if there is no *present* indication that they may be of use. Their utility may only be identified during in vivo trials and therefore there should be a greater push to develop a wider range of shapes with a view to utilization discovery.

Coil Softness and Length

Feedback from the research showed a desire for development of a very soft, long coil with a 'J' shaped tip for treating larger vessels with a friable wall. The desired end result would be that the coil would not pose a perforation risk and that the number of coils used in a procedure can be reduced. Also, interest was expressed to investigate the design of a "curved straight coil" (an arc) for embolizing smaller vessels, this should be prototyped and investigated for potential benefit.

Modular Mandrels

Development work into a modular mandrel that can be configured easily to a host of custom shapes and sizes should be conducted. This would allow for an expansion of patient specific capabilities within the current embolic coil manufacturing arena and allow for rapid prototyping of coil shapes.

Neuro Applications

Though a patient specific coil was identified as being of niche use in the peripheral vasculature, the vast majority of the SMEs, including two of the Interventional Radiologists, proffered that there may be much more utility in Neuro Interventional Radiology. Opinion was that Neuro IRs prefer *custom* tools designed for a *very specific* end purpose. One IR remarked that *it would work in the brain* and would have advantages. The reasoning was that there would be much more benefit in elective aneurysm coiling for Neurology as neuro elective procedures are more common than elective procedures to treat the peripheral vasculature. The justification from a number of the SMEs was that there is more planning involved in neuro as the risk/reward is much greater. Rationale given for the statement on risk/benefit was that a rupture in a cerebral aneurism can cause immediate profound disability or death. Whereas a rupture in the visceral system can be dealt with by embolising the inflow to the ruptured vessel and generally has no profound side effects or immediate risk of death. Research should be carried out into the potential benefit of a patient specific coil for neuro applications.

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