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FACTORS AFFECTING BIOCOMPATIBLE 3D PRINTING PHOTOSENSITIVE RESINS USED FOR MEDICAL APPLICATIONS

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Declaration

I hereby declare that my submission is the result of my own work and is not substantially the same as any that I have previously made or am currently making, whether in published or unpublished form, for a degree, diploma, or similar qualification at any university or similar institution.

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"Some man for one man" – N. Mulcahy

Abstract

3D printing has been increasingly used to manufacture medical devices in the last twenty years (Tack *et al.* 2016; Kermavnar *et al.* 2021). The traditional production of medical devices is carried out in line with strict regulations put in place to protect those involved in the supply chain (Kramer *et al.* 2020). The development of regulations for 3D printed medical devices are yet to be fully established due to difficulties in defining their parameters (Ricles *et al.* 2018). Currently, existing regulations are applied to 3D printing where possible (Di Prima *et al.* 2016). This has raised concerns regarding the future adoption of 3D printing into key industries (Horst 2020). Of particular focus on this topic, is the use of biocompatible 3D printing photosensitive resins (Alifui-Segbaya *et al.* 2017; Lupuleasa *et al.* 2018; González *et al.* 2020). These materials require specific post-processing to achieve their intended material properties (Jindal *et al.* 2020; Kim *et al.* 2020). Post-processing generally consists of washing parts in an alcohol solution such as isopropyl alcohol, drying the parts, and then post-curing with ultra-violet light and sometimes heat for a prescribed amount of time. Post-processing information is provided by material manufacturers generically with the caveat that post-processing should be extended for 'large' or more 'complex' geometries but do not define these parameters (3DSystems 2020c; Formlabs 2022).

The initial research of this thesis explores how 3D printing is utilised to benefit the production of medical devices. Firstly, its use to rapidly replenish PPE and other devices during the COVID-19 pandemic, whilst highlighting issues arising from the use of a decentralised 3D printing supply chain. Secondly, a review to assess how the ability to produce bespoke geometries is used to create patient-specific devices for palliative medicine. As palliative medicine often requires a rapid and bespoke solution for patients, 3D printing is often used at the point-of-care. This review aimed to gain a better insight into the literature,

and systematically identify recent 3D printed developments within the field. The review identified no correlation between the device being produced and the machine/material used to make it. This would suggest that education and availability of 3D printing systems at the point-of-care needs improving. Research is then directed towards the efficacy of 3D printings application by investigating the information supplied with biocompatible materials. A review of the grey literature identified 99 rigid, and 31 flexible biocompatible 3D printing resins. The information supplied with those materials varied in quantity, quality and terminology used. From this, two experiments were performed to test the outcomes of extending post-curing times on simulated 'large' and 'complex' geometries using commercially available biocompatible 3D printing resins. In chapter 6, the cure depth of 'large' geometries are tested. The results of this experiment showed that materials containing opaque pigments were unable to cure to the full depth of the test model even when exposed to 500% of the recommended post-curing treatment. The second experiment tested further post-curing times on 'complex' geometries, and was quantified by testing the materials mechanical properties. The results showed that extending the post-curing time was insufficient in curing opaque pigmented resins. In one case, specimens in the outer exposed layer showed a tensile strength of 58MPa, whereas specimens from the inner layer only showed 19MPa.

The outcomes of this research suggest that standardisation needs to be implemented concerning the information provided by material manufacturers, and that the success of post-curing photosensitive resins is largely dependent on the pigmentation of the material.

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List of Abbreviations

3D	Three-Dimensional
3DP	Three-Dimensional Printing
ANOVA	Analysis Of Variance
ASTM	American Society for Testing and Materials
BJ	Binder Jetting
CAD	Computer Aided Design
CAPA	Corrective And Preventative Action
CDLM	Continuous Digital Light Manufacturing
CE	Conformité Européenne
CLIP	Continuous Liquid Interface Production
CT	Computed Tomography
DED	Direct Energy Deposition
DLP	Digital Light Processing
DLS™	Digital Light Synthesis™
DMD	Digital Micromirror Device
DMLM	Direct Metal Laser Melting
DMLS	Direct Metal Laser Sintering
EBM	Electron Beam Melting
FDA	Food and Drug Administration
FDM	Fused Deposition Modelling
FFF	Fused Filament Fabrication
G-CODE	Geometry Code
GMP	Good Manufacturing Processes
HCP	Health Care Professional
IPA	Isopropyl Alcohol
ISO	International Standards Organisation
LCD	Liquid Crystal Display
LED	Light Emitting Diode
LFS	Low-Force Stereolithography
MDD	Medical Device Directive
MDR	Medical Device Regulation Group
ME	Material Extrusion
MJ	Material Jetting
mSLA	Masked Stereolithography
OBJ	Object Wavefront
PBF	Powder Bed Fusion
PMD	Patient Matched Device
POC	Point-Of-Care
PPE	Personal Protective Equipment
PRISMA	Preferred Reporting Items for Systematic Reviews
R&D	Research and Development
RBG	Red Green Blue
SEO	Search Engine Operative
SLA	Stereolithography
SLS	Selective Laser Sintering
STL	Standard Tessellation Language

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Publications directly related to this research:

1. Guttridge, C., O'Sullivan, A., O'Sullivan, K.J. and O'Sullivan, L.W. (2021a) 'Three-Dimensional Printed Devices for Health Care in Response to the Coronavirus Disease 2019: Lessons Learned to Date', *3D Printing and Additive Manufacturing*, 8(5), 340-342.

   https://www.liebertpub.com/doi/full/10.1089/3dp.2020.0266

2. Guttridge, C., Shannon, A., O'Sullivan, A., O'Sullivan, K.J. and O'Sullivan, L.W. (2021) 'Biocompatible 3D printing resins for medical applications: a review of marketed intended uses, biocompatibility certification, and post-processing guidance', *Annals of 3D Printed Medicine*, 100044.

   https://www.sciencedirect.com/science/article/pii/S2666964121000394

Publications associated with this research:

1. Kermavnar, T., Guttridge, C., Mulcahy, N.J., Duffy, E., Twomey, F. and O'Sullivan, L. (2022) '3D printing in palliative medicine: systematic review', *BMJ Supportive & Palliative Care*.

   https://spcare.bmj.com/content/early/2022/09/06/bmjspcare-2021-003196.abstract

   Association: Kermavnar led the study design, paper search, data extraction, synthesis, reporting and paper writing. Guttridge and Mulcahy contributed to the paper search, data extraction, synthesis and paper writing. Duffy, Twomey and O'Sullivan contributed to the study design, synthesis, reporting and paper writing. O'Sullivan is acting as guarantor of this research.

Chapter 1: Introduction

1.1. Research Background

3D printing is expected to replace as much as 40% of traditional manufacturing processes by the year 2040, with many industries already seeing disruptive changes to their prototyping and manufacturing methods, of particular focus is the field of 3D printing in and for healthcare (Berman 2020; Freund *et al.* 2022). In the last twenty years there has been a considerable increase in the use of 3D printing to produce medical devices (Tack *et al.* 2016; Kermavnar *et al.* 2021). Traditionally, the production of medical devices is heavily regulated with stringent frameworks in place to protect stakeholders, particularly end users. The development of standards concerning 3D printing however, has been slow. This has been attested to challenges in parametrically defining the technology (Pierrakakis *et al.* 2014; Ricles *et al.* 2018). As 3D printing is commonly used as a 'batch-of-one' manufacturing process, applying existing batch control systems such as ISA-88 and ISA-95, is difficult and time consuming as a control needs to be established for each 'batch-of-one' (ANSI/ISA 1995; ANSI/ISA 2020).

In lieu of specific 3D printed medical device manufacturing standards, it has become commonplace for regulatory bodies to apply existing medical device manufacturing standards such as, ISO 10993 and ISO 13485 (ISO 2001; Di Prima *et al.* 2016; ISO 2016). This has created difficulty in defining user responsibility within 3D printing supply chains, as well as often leading to the misinterpretation and sometimes, a complete disregard of regulations (Lindenfeld and Tran 2015b; Choong *et al.* 2020). This raises many concerns as to what the future holds for the longevity and adoption of 3D printing into key industries (Schniederjans 2017; Horst 2020).

One such area of concern and of particular focus within the literature is the application of biocompatible photosensitive resins (Alifui-Segbaya *et al.* 2017; Kessler *et al.* 2020). These are materials specifically engineered for medical uses, offering desirable material characteristics such as prolonged skin and mucosal membrane contact (Nakano *et al.* 2019). Biocompatible is an umbrella term for materials specifically engineered to interact with living tissues without causing an immunological response (Remes and Williams 1992). The definition of a biocompatible material refers to the materials ability to perform with an appropriate host response i.e. if a material's intention is to be used in contact with skin for 24 hours, the material must be certified to remain chemically stable and not cause an immunological response for that duration (Remes and Williams 1992; Barrère *et al.* 2008). Whilst biocompatible materials exist for other 3D printing methods, the post-processing of photosensitive resins is crucial in achieving the proper biocompatible and mechanical properties and eradicating the material of toxic uncured resin. (Bagheri and Jin 2019). Information for post-processing is provided by the material manufacturer and is given generically with the caveat that post-processing time should be extended for 'large' or more 'complex' models - the parameters of which are not defined, therefore, research is required to investigate the efficacy of these statements (3DSystems 2020c; Formlabs 2022).

As 3D printing is most commonly used for its ability to create bespoke models it could be expected that size and complexity will often vary. There is a need to investigate the efficacy of these statements regarding post-processing and consider the process from a regulatory point-of-view.

1.2. Thesis Structure

A review of the current literature was performed in chapter two exploring the evolution of 3D printing and its role in medicine. The review investigates the

current and prospective regulatory aspects of 3D printing, and considerations for their prolonged establishment. The review then focusses on the applications of vat-polymerisation 3D printing, the methods within it, its applications, and challenges with post-processing. A summary of studies that customised methods of post-processing is also provided.

Chapter three is a narrative review on 'lessons learned' from the 3D printing in response to the initial emergency phase of the COVID-19 pandemic. This study focusses on the regulatory aspects of the decentralised 3D printed supply chain that was mobilised to replenish much needed PPE during the pandemic. Considerations are made as to how these regulatory aspects were in some cases overlooked, and recommendations for how future responses might perform better.

Chapter four provides a systematic review on the topic of 3D printing's use in palliative care. This area was considered as palliative care is often faced with patients for which there are no commercially available solutions for their care needs, as often in palliative care bespoke personalised medical devices can be necessary. The paper and research was led by a colleague in the research group (Dr. Tjasa Kermavnar). The current author was one of two independent researchers who performed and synthesised the actual search of the literature.

Chapter five reviews the grey literature of biocompatible 3D printing materials. The search aimed to include all 3D printing photosensitive resins that stated biocompatibility, with the intention of assessing the quantity and quality of information provided in reference to cited certifications, intended uses and post-processing information.

Chapter six and seven detail two experiments that were performed to test the efficacy of the statement made by material manufacturers regarding extending post-processing times for 'large' or more 'complex' models. Chapter six

focusses on simulating a large geometry, using direct measurements to record the curing depth achieved from varying intervals of post-curing. Chapter seven simulated a complex geometry with internal components. Mechanical testing was performed on the specimens of the models to understand how material properties are affected by extending post-curing duration.

1.3. Research Objective

There has been an increase in the use of 3D printing at the point-of-care. With this increase, and growth in the technology, there has also been a change in its application. Initially used to produce devices that are not in direct contact with patients, the literature suggests a move towards devices that are used to directly treat patients. With this change in use, the regulatory requirements for those devices have also changed. As there is a current lack of regulations and standards relating to the 3D printing of medical devices, many users must heavily rely on the information that is provided to them by materials and machine manufacturers. This research aims to explore the recent developments in 3D printed point-of-care devices whilst testing the efficacy of the information that is given to users.

1.4. Research Questions

Research question 1: During the COVID-19 pandemic, 3D printing was utilised to manufacture PPE and medical devices that were in short supply. What can be learned regarding the use of 3D printing during the emergency response?

Research question 2: The literature details that 3D printing is utilised in some medical disciplines more than others. Palliative care is an example of a medical discipline where 3D printing could be utilised to respond to unique individuals

needs where existing devices are not commercially available. How is 3D printing being used to treat palliative care patients in the current literature?

Research question 3: The increase in the use of 3D printing to manufacture medical devices has created a demand for biocompatible materials. These materials are required to provide specific instructions detailing the certification, intended uses and post-processing technique. As user's heavily rely on this information, what can be learned from the grey literature regarding the quantity and quality of this information?

Research question 4: Manufacturers provide generic post-processing guidance per material, however some manufacturers recommend extending post-curing times for models that are '*larger or more complex*', without providing specific details. How does extending post-curing times affect the depth of cure of large geometries?

Research question 5: Building on the results of chapter 6, how does extending post-curing times affect the mechanical properties of material within a complex geometry?

1.5. Contribution

This thesis contributes to the knowledge of post-processing 3D printing photosensitive resins. Specifically, the results of the two experiments performed show that materials with opaque pigments are unable to cure to full depth even when post-curing is extended to 500% of the manufacturer's guidance. It is suggested that opaque pigmented materials be avoided when possible, that users scrutinise the post-processing information supplied to them, and seek to design their own post-processing steps for their specific device.

Chapter 2: Literature Review

2.1. Introduction to 3D printing

3-Dimensional (3D) printing is a manufacturing process that produces parts by adding material layer upon layer (Weller *et al.* 2015; Oropallo and Piegl 2016). 3D printing is an "*additive*" technology as opposed to traditional "*subtractive*" or "*formative*" manufacturing methods such as milling, turning, or injection moulding (see Figure 1). The materials used are generally thermoplastics, photosensitive resins or metal alloys, however some are capable of printing in ceramics, foodstuffs, and living cells (Bechtold 2016). There are several synonyms used in industry, such as additive processes, additive manufacturing, rapid prototyping, layered manufacturing or freeform fabrication (Mellor *et al.* 2014). For the purpose of this review, the term 3D printing will be used.

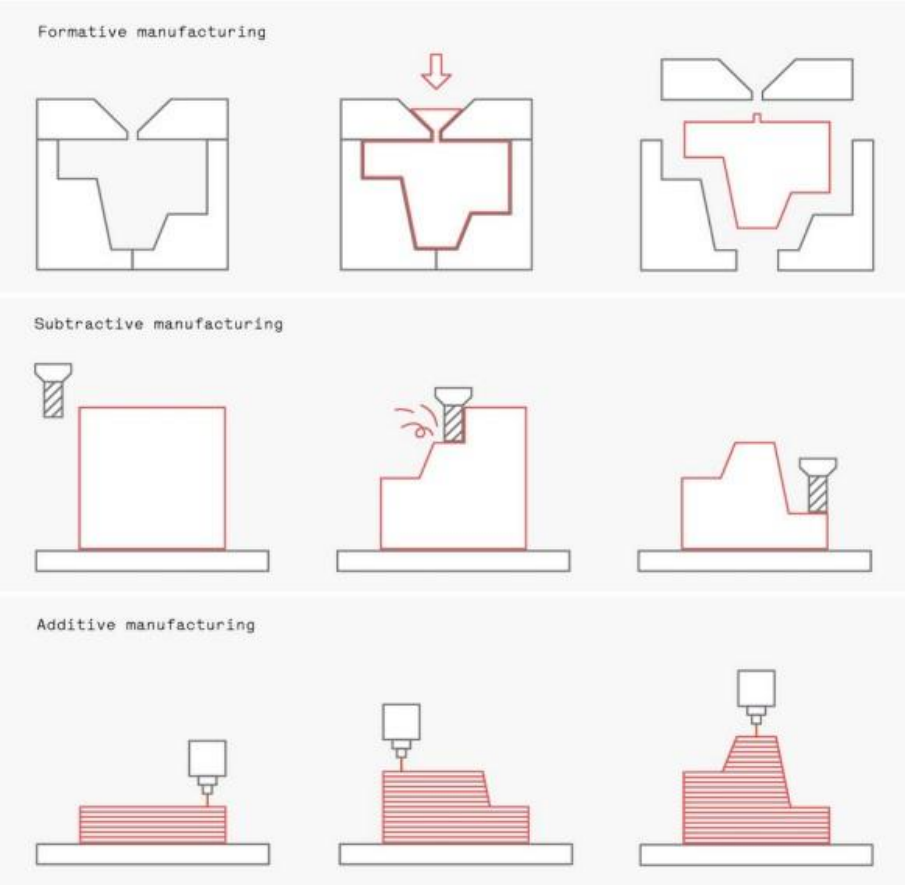


Figure 1: Manufacturing processes (Redwood *et al.* 2017)

The process of 3D printing begins with a 3D file. This is typically a Standard Tessellation Language (STL), or a Wavefront Object (OBJ) file (Mitsouras and Liacouras 2017). The 3D file is imported into a slicing software that slices the part into layers of a defined thickness, along one axis (Oropallo and Piegl 2016). These layers are then used to generate a series of movements and commands that the machine can interpret, called Geometry Code (g-code), to build up the part to a complete object (Balletti *et al.* 2017). There are various methods of 3D printing, but all follow the same basic process and can be defined with eight key steps (Gibson *et al.* 2021):

1] Creating the 3D model

2] Generating a compatible file

3] Transfer and orientation of the file

4] Machine setup

5] Build

6] Part removal and clean up

7] Post-processing of part

8] Application

2.1.1. Methods of 3D Printing

The international standard ISO/ASTM 52900 (ISO 2015) categorises the various methods of 3D printing into several categories: material extrusion; vat polymerisation; powder bed fusion; material jetting; binder jetting; directed energy deposition; and sheet lamination. The key differences between each technology are the materials used, and the method(s) used to deposit and/or join the materials (Gibson *et al.* 2021). The scope of the current research is focussed on polymer printing systems. Specifically, vat-polymerisation systems

are investigated, as the user is ultimately responsible for the post-processing of the material to achieve its optimum biocompatible and mechanical properties. Therefore, technologies that use metal powders, ceramics, and composites are outside the remit of this research and are not included in this overview.

2.1.1.1. Material extrusion

Fused Deposition Modelling (FDM), or Fused Filament Fabrication (FFF) is a method of 3D printing where a continuous filament of a thermoplastic material, is extruded through a heated nozzle and deposited onto the print bed (Fuenmayor *et al.* 2018). Typically, a material with a diameter between 1.75mm and 3mm is fed from a spool and is driven by an extruder into the heat block, where a heating element and thermocouple keep a constant temperature to liquify the material, where it is extruded out of the nozzle (see Figure 2). The required print temperature depends on the material. The material is in a molten state as it is extruded through the nozzle, but cools and solidifies once it comes into contact with the bed within the ambient environment (Chua and Leong 2014).

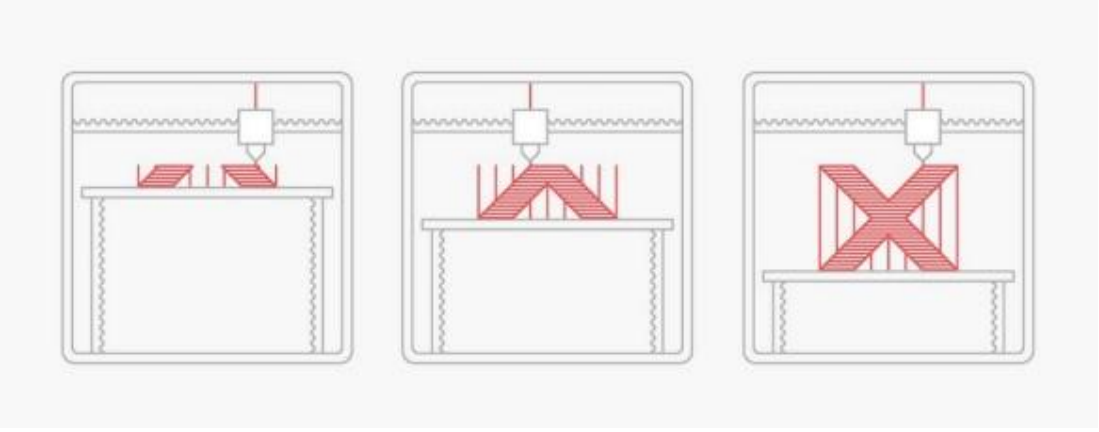


Figure 2: Material Extrusion (Redwood *et al.* 2017)

There are a number of factors that impact the extrusion such as; the diameter of the nozzle, the flow rate, and the rate of speed at which the nozzle is travelling (Gibson *et al.* 2021). Once the first layer has been completed the printer moves on the z-axis a predefined amount known as the "l*ayer height*", and the next layer will be extruded on top of the previous layer. The heat in the material in each subsequent layer re-melts the previously printed layer and bonds them together with each layer printed sequentially until the part is complete (Redwood *et al.* 2017).

FDM printing methods require the manual removal of support material. As the surface finish is rough due to 'stepping' artefacts, users may choose to post-process parts using finishing techniques such as sanding and painting, machine finishing techniques such as bead blasting, or chemical treatments such as acetone dipping (Chohan and Singh 2017). Compared with other methods of 3D printing, the dimensional accuracy and surface finish of FDM printed parts is lower in quality, but the process is often favoured as a low-cost solution for rapid prototyping (Redwood *et al.* 2017).

2.1.1.2. Powder bed fusion

Selective Laser Sintering (SLS) is a form of Powder Bed Fusion (PBF) 3D printing that uses powdered polymer materials (King *et al.* 2015). Other PBF

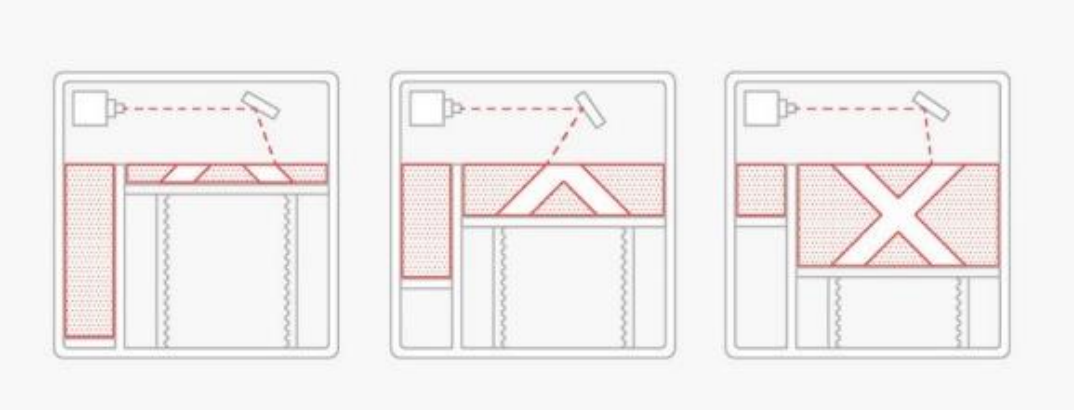


Figure 3: Powder Bed Fusion (Redwood *et al.* 2017)

technologies differ from SLS in material used, and in the material fusion technology, although, the process of layer creation is similar. Powdered material is swept onto the bed as a flat layer and an energy source emitting concentrated heat is used to fuse the powder together into the desired shape (see Figure 3). Excess material is swept away and a new layer of powder is distributed by the material recoater on top of the previously fused layer. PBF systems do not require fabricated supports as the models are held in suspension by excess powder (Chatham *et al.* 2019). Therefore, in some methods, a portion of the unused powder can then be re-used for later printing. Post-processing of PBF parts generally consists of brushing excess powder away in a dedicated powder station where the necessary Personal Protection Equipment (PPE) is worn. If required, media blasting or tumbling techniques can be used to improve the surface finish of parts. Common materials used in SLS are Nylons and Thermoplastic Polyurethane's (TPU).

2.1.1.3. Material Jetting

Material Jetting (MJ) coined as '*Polyjet*' by Stratasys (Stratasys, USA) works by depositing droplets of photosensitive resin onto a bed layer by layer to construct a part. Droplets are deposited by the piezoelectric constriction of print nozzles during the first pass of the print block, on the return pass the z-axis slightly raises allowing a roller to flatten droplets. A UV bulb on the side of

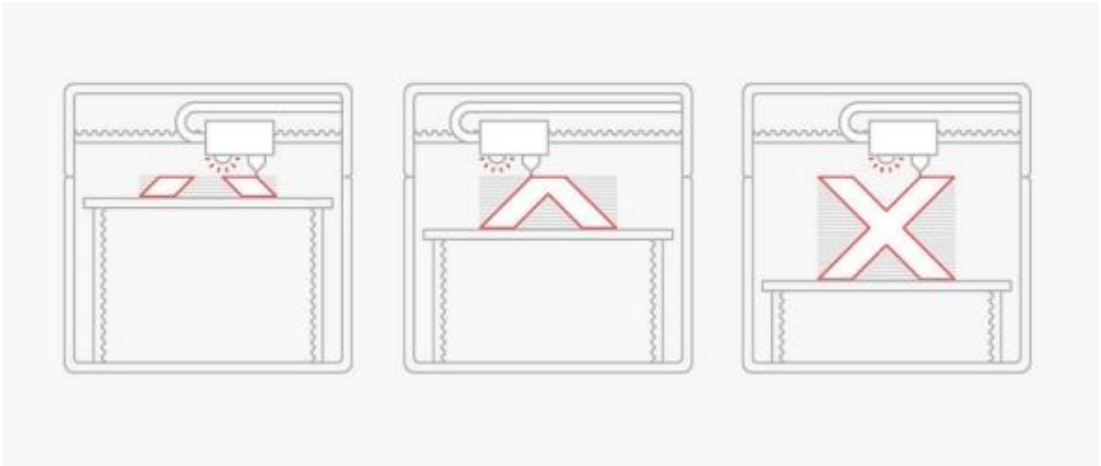


Figure 4: Material Jetting (Redwood *et al.* 2017)

the print block cures the photosensitive resin during the printing operation (see Figure 4), therefore post-curing is not required after printing (Redwood *et al.* 2017). As some MJ systems feature multiple print heads, multi-material printing is made possible. The inclusion of a rubber like material such as Stratasys' Tango and Agilus range enables users to program the shore rating of specific components. Similarly, Red, Blue and Green (RGB) colours can be loaded to create pantone colour palette options for models. Due to these advanced material options, MJ methods are often utilised for product demonstration and anatomic training models where interaction is required.

2.1.1.4. Vat-polymerisation

There are several methods of Vat-Polymerisation (VP): Digital Light Processing (DLP); Stereolithography (SLA); Masked Stereolithography (mSLA/LCD); Digital Light Synthesis ™/Continuous Liquid Interface Production/Continuous Digital Light Manufacturing (DLS™/CLIP/CDLM). These methods share many similarities and are mostly distinguished by the energy (light) sources employed. To help inform the reader, a summary of each technology is provided in the sections below.

VP methods operate by solidifying photosensitive resins using ultra violet (UV) light. A vat of photosensitive resin sits above a UV light source, separated by a thin transparent membrane (Ngo *et al.* 2018). At the beginning of a print, the bed will move down the z-axis until the gap of a predetermined layer height remains between the print bed and vat-membrane. The light source outlines the shape of the print layer for a programmed duration known as 'exposure time'. The layer will solidify, the bed will then raise up to allow resin to flow back underneath, before returning to solidify the next layer. The part is printed upside down, this is known as '*top-down*'' 3D printing (see Figure 5). The various light sources used in VP 3D printing methods include: scanning laser beam (SLA); projected light source (DLP); array light source, liquid crystal

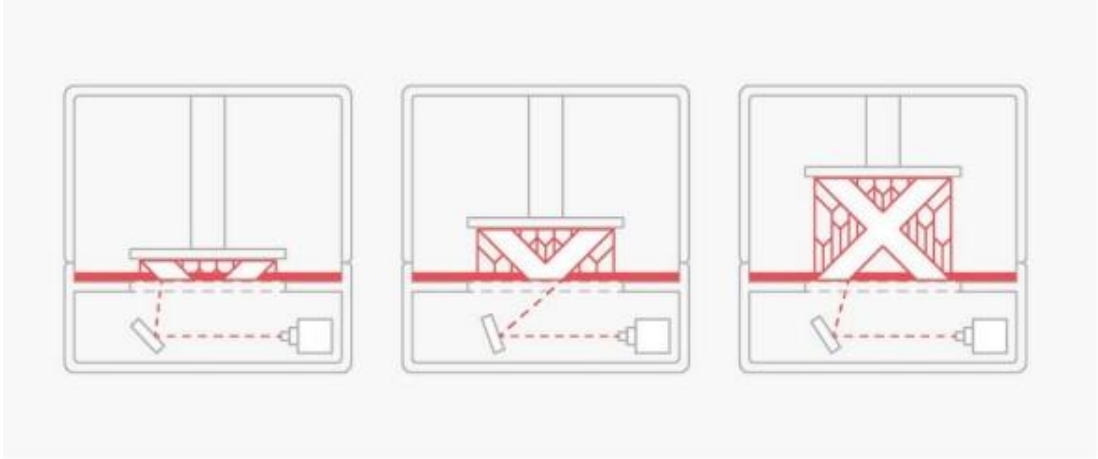


Figure 5: Vat Polymerisation (Redwood *et al.* 2017)

display, and digital mask (mSLA/LCD); LED '*light engine*' (DLS™/CLIP). The wavelength of UV emitted from the light source is between 355-405nm, depending on the machine and resin (Gibson *et al.* 2021).

VP 3D printing techniques are often favoured for their near-isotropic properties, smooth surface finish, and wide range of specifically engineered materials. Most commercially available systems are capable of printing at layer heights between 25-100 microns. This technology is often favoured for injection mould-like prototypes, jewellery, dental applications, surgical guides and microfluidic chambers (Redwood *et al.* 2017).

After printing, support and adhesion material is stripped away manually. As photosensitive resins are only semi-cured (or green) after printing, they require post-processing to achieve their intended biocompatible and mechanical properties. Post-processing of photosensitive resin parts usually consists of an agitated wash in an alcohol solution, typically isopropyl alcohol (IPA). Parts are then placed into a curing tank for a prescribed amount of time and exposed to UV light (and in some cases, heat), until the desired properties are achieved (Melchels *et al.* 2010). Information for post-processing is supplied by the material manufacturer and is heavily relied upon by the user.

2.1.2. Methods of vat-polymerisation

2.1.2.1. Stereolithography

Sterolithography (SLA), deriving from the Latin words *'Stereos'* (firm, solid) and *'Lithograph'* (to write) is a common technique of VP 3D printing (Glare 1982). Taken literally from its translation, SLA uses a UV laser (355-400nm) refracted through an X-Y scanning mirror to write/trace and solidify each layer as shown in Figure 6 (Redwood *et al.* 2017). Once a layer has been traced, the build platform retracts along the z-axis allowing resin to flow back and recoat the area between the previous layer and vat membrane (Bártolo 2011). The laser velocity, or scanning speed, denotes the exposure time of UV to photosensitive resin (Jacobs 1992). The laser utilised in SLA 3D printing has a circular pixel shape, as opposed to square, that benefits SLA in its geometric capabilities and surface finish.

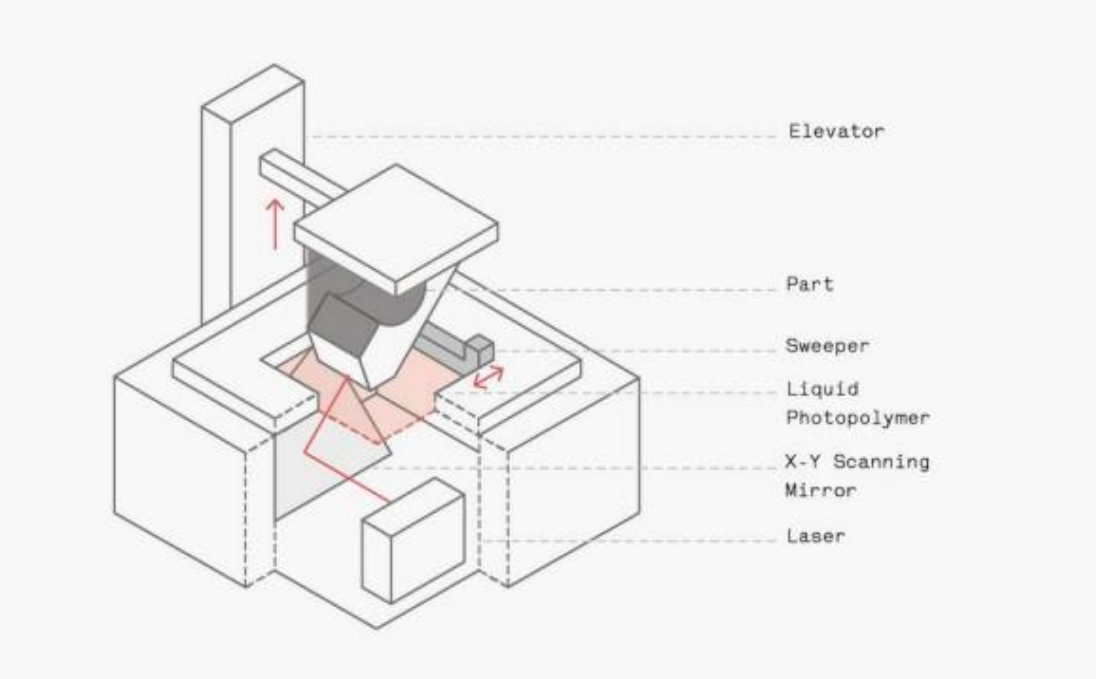


Figure 6: Stereolithography (Redwood *et al.* 2017)

In some models of SLA printers, such as the Formlabs (Formlabs, USA) Form3, the addition of a flexible film bowed by the convex roof of the light unit reduces the pressure during retraction allowing for the use of light-touch supports. This process is known as Low-Force Stereolithography (LFS), and boasts a slightly smaller laser spot size (Wang *et al.* 2022). Typically, SLA systems print at layer heights of between 25-300 microns (Formlabs 2019a; Stratasys 2020).

2.1.2.2. Digital Light Processing

The key difference between Digital Light Processing (DLP) and SLA printing is that a projector is used in place of the SLA laser. UV light is projected onto and reflected off of a Digital Micromirror Device (DMD) consisting of microscopic-size mirrors that rapidly toggle between lenses to direct light towards the bottom of the vat membrane (Formlabs 2020b). The light is exposed for a programmable amount of time dictated by the material used. As the entire layer is being solidified at once, DLP 3D printing is significantly faster than SLA (Redwood *et al.* 2017). The quality of DLP printing is dictated by two factors: layer height and pixel count (Hornbeck 1997). Typically, DLP printers come in

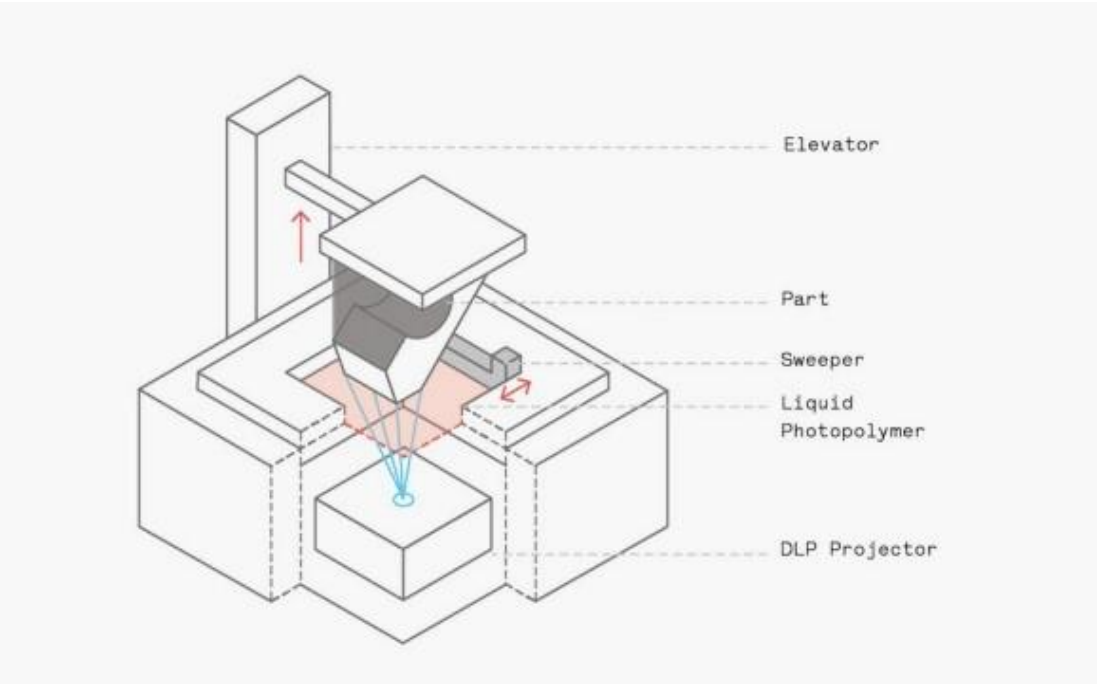


Figure 7: Digital Light Processing (Redwood *et al.* 2017)

resolutions of 1080p, 4k, and 8k whilst achieving layer heights of between 10-175 microns (3DSystems 2020a; EnvisionTec 2021b). Similar to other techniques of VP, once a layer has been solidified, the z-axis will retract allowing resin to flow back over the vat membrane in preparation for the next layer (see Figure 7).

2.1.2.3. Masked Stereolithography – Liquid Crystal Display

Masked Stereolithography (mSLA), often referred to as Liquid Crystal Display (LCD) 3D printing, utilises an LCD screen to mask a UV backlight. By changing the pixels activated on the LCD screen, UV is let through in the desired spots to form each layer (Borra and Neigapula 2022). Due to the simplicity of the technology, mSLA systems tend to be much cheaper than other VP 3D printers whilst achieving similar print qualities. mSLA printers are capable of layer heights of 10-30 microns and are available at resolutions ranging from 1080p to 8k (Borra and Neigapula 2022). As the printing process is similar to DLP, where an entire layer is able to cure at once, mSLA 3D printing is also considerably faster than SLA printing.

2.1.2.4. Digital Light Synthesis™ – Continuous Liquid Interface Production – Continuous Digital Light Manufacturing

Continuous Liquid Interface Production (CLIP) is a VP technique that was later trademarked by Carbon 3D (Carbon 3D, USA) as Digital Light Synthesis™ (DLS™). The process is similar to that of DLP printing, whereby a projector and DMD is used to project and reflect the light source. The key difference in DLS™ is that an oxygen permeable glass membrane is used in place of the traditional membrane (Manoj *et al.* 2021). This enables the machine to continuously print in the z-axis direction without the need to retract for recoating (Balli *et al.* 2017). DLS™ is therefore a faster method of VP as the time taken for retraction is removed. DLS™ is limited by the materials currently available, and by the

creation of a dome shaped voxelation that appears on printed parts as a result of the oxygen flow. Recent developments by 3D manufacturer EnvisionTec (EnvisionTec, USA) have led to the release of Continuous Digital Light Manufacturing (CDLM), a spin off technology of DLS™. In CDLM, a thinner membrane is used that does not create the domed voxelation seen in DLS™ but maintains the benefits of continuous z-axis resin printing (EnvisionTEC 2022).

2.1.3. The evolution of 3D printing

There is debate as to when the very first use of 3D printing was, as publicly available information is limited (Jakus 2019). However, it is generally accepted that 3D printing was first practiced in the 1970's by Hideo Kodama, who is regarded to be the first person to create a solid object from 3D data (Gokhare *et al.* 2017). In 1981 Kodama published "*Automatic method for fabricating a three-dimensional plastic model with photo-hardening polymer*" (Kodama 1981), which presents the experimentation of 300-400nm UV light used to solidify photo-polymers into a programmed shape using a fibre optic transmitter. A short summary of the evolution of 3D printing is provided to gain an insight into the stages of development the technology has undergone since its invention.

From the 1980's to the 90's, 3D printing began what could be defined as its first era. In 1984 Charles Hull put forward the patent for SLA and co-founded 3D systems (3D Systems, USA). Whilst Hull was not the first to experiment with the technology, he is credited with being the first to develop the STL file which is still used as the '*de facto*' file format for 3D printing (Chen *et al.* 1999; Jakus 2019). The STL file is colloquially referred to as the 'stereolithography' file, but by definition stands for 'standard tessellation language' or sometimes 'standard triangle language' given that the format of the 3D mesh is made up of triangles (Bommes *et al.* 2013).

Shortly after the patenting of SLA technology, came the subsequent release of several 3D modelling software packages. In 1981 UniGraphics (Siemens, USA) released the first solid modelling system, UniSolids, shortly after AutoDesk (Autodesk, USA) and Dassault Systems (Dassault Systemes, France) were founded, both of which are still developing Computer Aided Design (CAD) software packages in 2023 (Tornincasa and Di Monaco 2010). In 1986 a group of researchers in the United States of America (USA) filed a patent for SLS, and in 1988 Scott Crump patented the first FDM system, and later founded Stratasys (Stratasys, USA) (Balletti *et al.* 2017).

The second era of 3D printing came after the expiration of several key patents. The patents for SLA technology expired in August 2004, the patent for SLS technology expired in 2006, and the patent for FDM technology expired in 2009 (Bechtold 2016). The release of the key technology patents allowed for the open market manufacturing of 'desktop' 3D printing systems (Gershenfeld 2005). This gave amateur makers and engineers affordable access to technology that was previously only obtainable to established manufacturers. In 2011, Jones *et al.* (2011) published the paper "*ReRap – the replicating rapid*

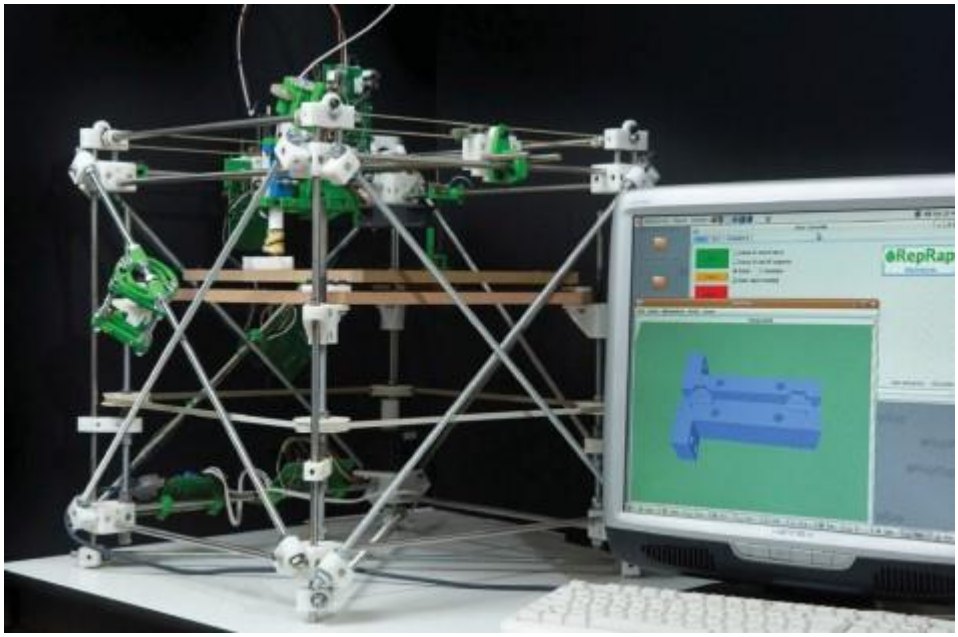


Figure 8: RepRap version 1 "Darwin" (Jones *et al.* 2011)

prototype", which detailed an FDM based 3D printer that was almost entirely made from 3D printed parts, and was capable of printing its own replacement parts (see Figure 8). The files for the design were shared for free on open source networks, and subsequently kick started the open source 3D printing revolution, inspiring designs for further modification and for other competing kits (Mota 2011). Around this time home-assembly 3D printer kits were readily available for purchase, as were pre-built machines based on adaptations of the RepRap project (Mota 2011). Crowd funded projects through the use of Kickstarter (Kickstarter, USA) raised upwards of $100million in 2011 for projects such as MakerBot (MakerBot Industries, USA), an open-hardware 3D printing company, and Quirky (Quirky, USA), a 3D printing service (Anderson 2012). Open source file sharing sites such as Thingiverse (Ultimaker, Netherlands) and GrabCad (GrabCad, USA) were founded, and quickly became populated with files. These sites offered mostly free access to a database of 3D files, designed by amateur or professional CAD users for download (Rayna *et al.* 2015). Access to these sites meant that users who had no experience, or were not interested in learning CAD, could still access files and print on their desktop 3D printers at home. As well as databases, sites such as 3D Hubs (3D Hubs, Netherlands) and Shapeways (Shapeways, USA) offered bureau-style work, where designers could upload files and pay to have them printed, allowing those only interested in CAD to manufacture designs without investing in machines themselves. With such an ease of access into the technology, the 3D printing community was able to expand rapidly. A survey published by Brujin (2010) reported that the RepRap community increased by more than 100% every 6 months. The democratised community lead state of 3D printing, often referred to as 'The Maker Movement' grew at an exponential rate with the rise of industry 4.0 (Anderson 2012; Bongomin *et al.* 2020).

Whilst 3D printing was an essential tool to Research and Development (R&D) and prototyping groups, its adoption into several key industries was relatively

slow. This may be attested to several economic and characteristic limitations of 3D printing, namely: high marginal cost of production, poor surface finish, material availability, synergy with industrial materials, low production throughput speed, and regulatory standards for quality control not being established (Berman 2012; Weller *et al.* 2015). Whilst 3D printing still faces some of those same issues today, its adoption into industries such as aerospace, defence, automotive, healthcare and construction has been prevalent (Schniederjans 2017).

2.1.4. Adoption of a disruptive technology

3D printing is often referred to as a disruptive technology, recognised by the three characteristics as described by Nagy *et al.* (2016):

1) The innovation allows the user to accomplish a new task that was impossible before the innovation was invented (e.g., 3D printing is useful for manufacturing in difficult-to-reach locations or in humanitarian logistics after a natural disaster (Tatham *et al.* 2017)).

2) The innovation generates new markets (e.g., Rapid expansion and innovation of 3D technology and materials as well as online digital marketplaces for cloud based sharing (Bhattacharjee *et al.* 2016)).

3) The innovation uses less costly materials or more efficient technologies (e.g., Accurate estimations for material usage, reduced waste and access to low cost raw materials (Aimar *et al.* 2019)).

Many consider 3D printing one of the most disruptive innovations to impact recent industrial logistics due to the paradigm shift it creates in the global supply chain (Berman 2020), whereas some believe it will only serve to enhance existing techniques (Mohr and Khan 2015). It is estimated that by 2040 as much as 40% of trade could be eliminated due to the implementation of 3D printing

into existing supply chains and manufacturing processes (Freund *et al.* 2022). Whilst 3D printing may replace many existing processes, formative manufacturing solutions still remain the most cost effective solution for mass production (see Figure 9) (Redwood *et al.* 2017).

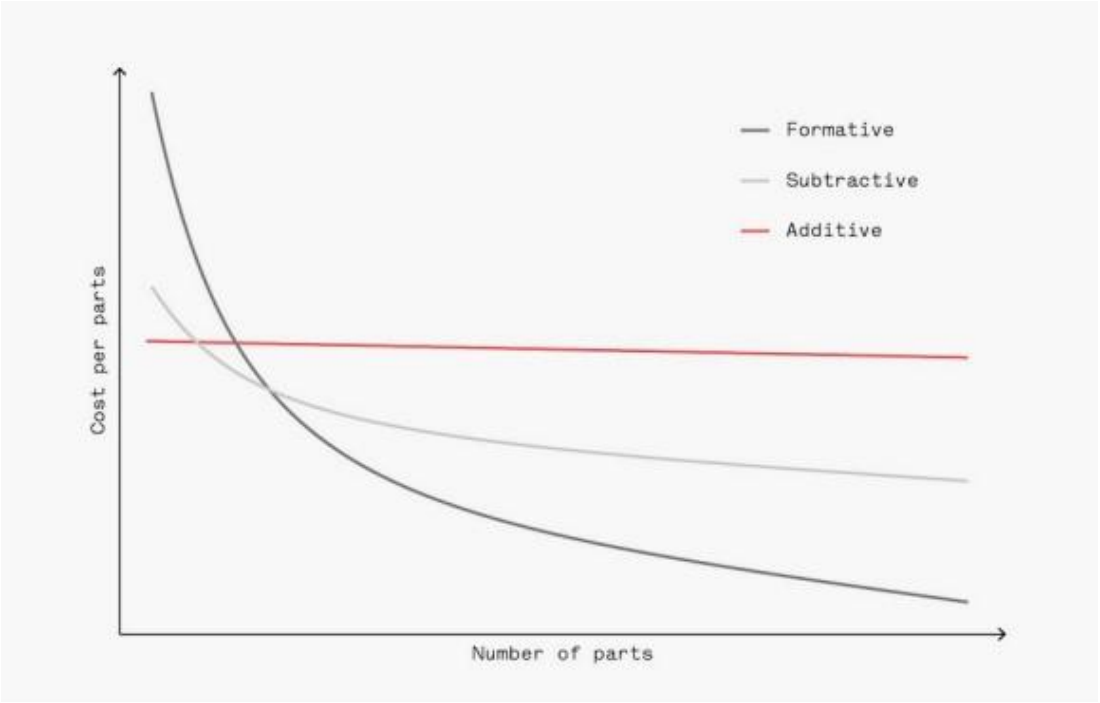


Figure 9: Cost per part of manufacturing processes (Redwood *et al.* 2017)

2.1.5. Use in medicine

3D printing has bolstered the ability to rapidly produce anatomically matched and patient-specific medical devices with high tunability, programmability, and complexity (Liaw and Guvendiren 2017). Used initially to produce training models and pre-planning guides for surgeries, 3D printing is now commonly used to produce devices that directly treat patients with future roles expected to feature automated point-of-care (POC) manufacturing (Jakus 2019; Kermavnar *et al.* 2021). As explained by Trenfield *et al.* (2019), 3D printing has been used to create a range of complex devices that would not easily be produced by conventional manufacturing technologies, or devices that do not

have a commercial market for mass manufacturing. An example includes palliative care where some patients have rare disease states or they require bespoke solutions (Karyakin *et al.* 2017; Jang *et al.* 2020).

2.1.5.1. Initial uses

A systematic review published by Tack *et al.* (2016) reviewed uses of 3D printing in patient specific applications. The review identified 227 papers with 230 uses. The majority of studies were identified between 2011 and 2015 (189), followed by 2006 to 2010 (30), 2000 to 2005 (8) and before 2000 (2) (Tack *et al.* 2016). A total of 60% of the devices were surgical guides, of which 38.7% were used for surgical planning (see Figure 10), 12.7% for custom implants, 3.91% for prosthetic moulds, 1.74% for implant shaping and 0.87% for patient selection models. It can be summarised that the initial applications of 3D printing at the POC were predominantly devices for the practitioner rather than devices for the patient. It should be noted that this study included the use of CAD as an inclusion criterion.

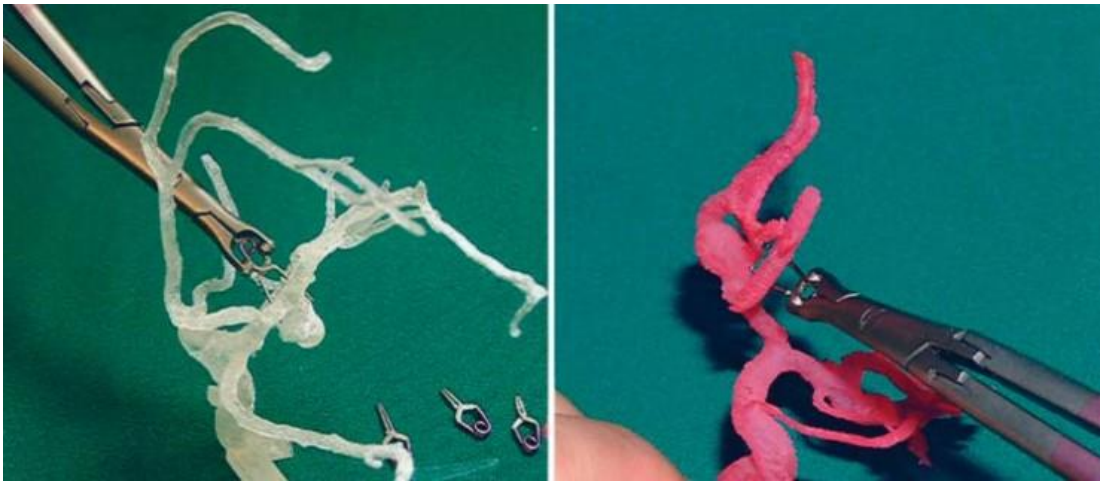


Figure 10: 3D printing guide for cerebrovascular aneurysm surgery (Wurm *et al.* 2004)

2.1.5.2. Current applications

Kermavnar *et al.* (2021) performed a systematic review on the use of 3D printing to directly treat patients. In that study, a total of 119 papers detailing 140 medical devices were reviewed. The majority of the papers identified were

published in 2018 (36), followed by 2020 (29), and 2019 (27), with considerably less studies found before 2018. Most of the devices were employed for orthopaedic surgical use (36%), followed by orthopaedic oncology (32%), maxillofacial surgery (6%), neurosurgery (4%), plastic surgery (1%). A number of the devices employed were for nonsurgical purposes, namely oncology (7%), orthotics (4%), immobilisation (2%), and prosthetics (1%). This review reported on the machine and material used, but as many studies did not specify these details the exact count for the employment of metals or plastics cannot be stated. This review excluded devices that were used for training, or for devices intended for use on cadavers.

Compared with the findings of Tack et al. in the earlier 2016 review, it is clear that the use of 3D printing in medicine to directly treat patients has developed alongside the growth of the technology. With growing availability and innovation alongside specifically engineered materials available to Health Care Professionals (HCP), the application of 3D printing has moved towards devices that are in direct contact, and in some cases permanent implantation (see Figure 11, Figure 12). (Aimar *et al.* 2019).

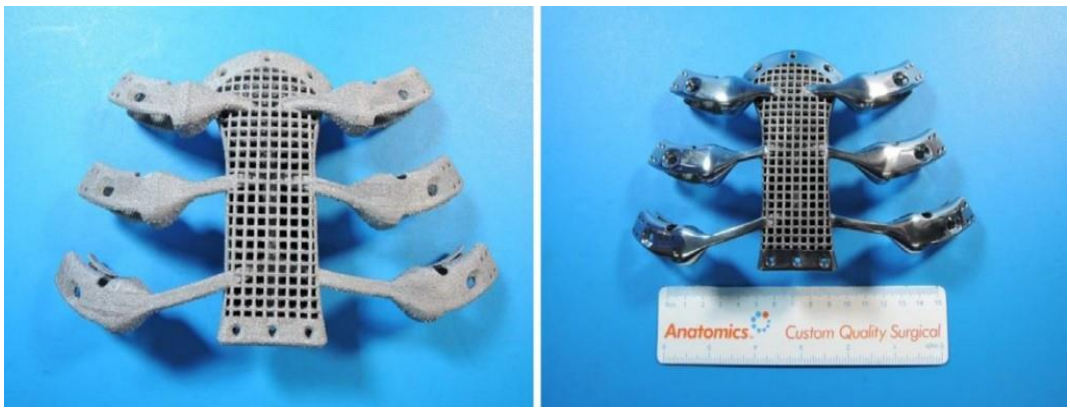


Figure 11: 3D printed titanium sternum implant post-print and post-processed (Thompson 2018; Kermavnar *et al.* 2021)

Amongst other advancements, there has been a considerable research effort towards the 3D bio-printing of soft and hard tissue engineering (Bose *et al.*

2013; Zhu *et al.* 2016). This has led to the development of 3D printed blood vessels, vascular networks, bones, ears, windpipes, dental prosthetics such as jaw bones and corneas (Schubert *et al.* 2014).

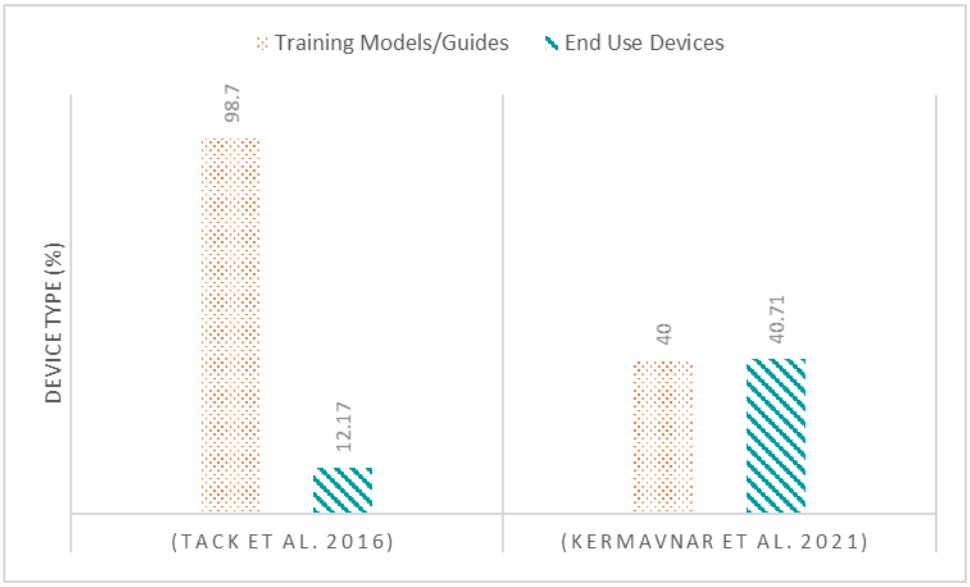


Figure 12: Change in use of 3D printing towards end use devices (Tack *et al.* 2016)

2.1.5.3. Emergency and humanitarian applications

The rapid nature of 3D printing has been implemented in emergency, humanitarian, and palliative care relief (Choong *et al.* 2020; Kermavnar *et al.* 2022). The COVID-19 pandemic saw many professional and domestic users 3D printing much needed PPE and apparatus for HCP's via altruistic community lead pop-up supply chains (Choong *et al.* 2020). Users worked together by open-sharing 3D files for devices to aid front line workers such as shield visors (Wesemann *et al.* 2020), ventilator manifolds (Ayyıldız *et al.* 2020) and other contact relief devices (see Figure 14) (François *et al.* 2021). Many professional 3D printing companies, such as Formlabs, made contributions towards the effort by printing nasopharyngeal swabs for testing (see Figure 13) (Manoj *et*

al. 2021). Whilst there were many responses, it is unclear to what extent these were successful.

Figure 14: 3D printable PPE and contact relief devices (Novak and Loy 2020)

Figure 13: Formlabs SLA printed nasopharyngeal swabs post-wash and packaging (Formlabs 2020a)

2.1.6. Themes emerging from this section

- 3D printing is a form of additive manufacturing that was first invented in the 1970's to the 1980's.
- There are seven key methods of 3D printing that all encompass several iterations of those methods.
- Initially there was a slow uptake by some industries due to the slow establishment of regulatory standards and difficulties converting from existing manufacturing methods.
- Vat-polymerisation is often favoured by areas of medicine because of specific characteristics such as: dimensional accuracy, isotropy, cleanability and wide range of commercially available biocompatible material.
- 3D printing has grown as a technology at an exponential rate and as such has been adopted by many areas of industry as a tool for rapid prototyping.
- 3D printing has been utilised in areas of medicine that can benefit from the ability to produce custom devices. Initially used to produce training guides and fixtures, 3D printing is more commonly used to produce patient-specific, patient-contacting, and implantable devices.
- During the COVID-19 pandemic 3D printing was rapidly deployed to address supply chain shortages in healthcare. However, this decentralised supply chain presented new challenges not seen previously in medical device manufacturing.
- Outcomes from this section have helped to inform the focus of 3D printing in medicine, including its change in application from surgical guides/training models to devices that directly treat the patient

2.2. Regulation of 3D printing in Medicine

2.2.1. Current regulation of medical devices

The regulatory ruleset for manufacturing medical devices is set by bodies such as the International Organisation for Standards (ISO) in Europe, and the Food and Drug Administration (FDA) in the USA. There are multiple standards relating to the manufacture of medical devices. Of particular focus within the literature and field is the regulatory standard ISO-10993 (Biological evaluation of medical devices) (ISO 2001). This standard details 22 individual sections relating to topics such as risk management, material preparation and degradation, toxicity, blood interaction and biological evaluation.

In the USA, whilst the development and standardisation of medical devices is regulated by the FDA, the biological testing of medical devices falls under the United States Pharmacopeia (USP), specifically under the standard USP VI. There are three reactivity tests that must be passed to gain class VI certification (USP). The three *in vivo* biological reactivity tests are as follows: acute systemic toxicity (systemic injection) test, intracutaneous test and the implantation test.

Not all standards must be met for certification. Rather the applicant must decide which of the tests are relevant to the device given its application in relation to manufacturing process, materials used and intended use. To decide what tests a device must pass, the device is classified as either class I, IIa, IIb or III in the EU, or class I, II, or III in the US. The classification is based on the risk of the device and the level of control necessary to assure safety and efficacy (Morrison *et al.* 2015). Classification is decided by the intended site of use, the time scale of use, and whether they are externally powered (Aronson *et al.* 2020). The device will be categorised by its contact site:

- **Surface device** e.g. intact skin, mucosal membrane, breach, compromised surface.
- **Externally communicating device** e.g. blood path indirect, tissue/bone/dentin, circulating blood.
- **Implant device** e.g. tissue/bone, blood (ISO 2001).

Prior to open market release, medical devices must adhere to and meet the necessary requirements of classification governed by the local regulatory body.

2.2.2. Current regulation of 3D printed medical devices

Currently in the USA, one of the few published directives from a regulatory body specific to the 3D printing of medical devices is provided by the FDA entitled *'Technical considerations for additive manufactured medical devices'* (FDA 2016). This document categorises the device in two ways:

A: Overall device design – This section focusses on the repeatability of mass produced 3D printed devices, detailing that manufacturers should compare printed devices to a control specimen for reference to dimension, surface finish and mechanical performance.

B: Patient-Matched Device (PMD) design – This section encompasses everything in section 'A' but adds that as these parts are patient specific, and that parameters for dimensional accuracy, mechanical performance and other clinically relevant factors should be established within a performance envelope prior to the manufacture of said device.

To seek certification for 3D printed medical devices in the EU, a similar strategy is employed. Initially set by the Medical Device Directive (MDD), 3D printed medical device regulation has now been replaced by the Medical Device Regulation group (MDR) (Wilkinson and van Boxtel 2020).

Whilst under the MDD, 3D printed devices that were custom-made and therefore not considered 'mass produced' did not require a CE mark, but did require a prescription from a registered medical practitioner. Currently, under the MDR, changes made to the definition of a custom-made medical device mean that any device that is 'mass produced' will not be considered custom-made. This strongly depends on the interpreted definition of 'custom-made' (BSI 2019).

Some believe that these regulations are not adequate in the face of considerations that the 3D printing process poses being a technology that is often used to produce bespoke devices. A review by Horst (2020) commented on the uncertainty of 3D printing regulation and calls for more nuanced and detailed consideration of the issues that arise for 3D printed medical devices such as; the placement of liability, difficulties in defining IP, difficulties in determining the classification of a bespoke device, difficulties in standardising the various methods of the technology universally. They define the issue as not stemming from the product being made using 3D printing, but because of specific characteristics of the process such as personalisation and decentralisation (Horst 2020).

2.2.3. Difficulties and considerations in the regulation of 3D printing

The unique building process of 3D printing brings with it new challenges in developing regulatory standards and in meeting Good Manufacturing Practice (GMP). Whilst the advancement of 3D Printing technologies is progressive, there are many factors that must be considered within a regulatory framework. These factors create difficulties for regulatory bodies to define parameters for certification and are convoluted further by the ever evolving technology

(Morrison *et al.* 2015). The multifaceted challenges regarding 3D printing regulation have caused the development of standards to be slow and difficult to parametrically define (Chua *et al.* 2017; Ricles *et al.* 2018).

Regulatory standards are still being developed and as such there are no fully established standards specific to the 3D printing of medical devices at the time of this research. Instead, existing medical device regulation and manufacturing frameworks are applied to 3D printed devices as regulation is agnostic to the manufacturing process used (Horst 2020). Therefore, consideration is made of the finished artefact, whereby the device is inspected and tested by in-house developed protocols, or exported to a third party registered body. The process of manufacture, regulation, feedback and iteration is however slow and often relies on the use of third parties, which adds to the manufacturing cost (Chua *et al.* 2017).

A study by Morrison *et al.* (2015) highlighted how the changing of printing parameters significantly impacted on the aesthetic and mechanical characteristics of a manufactured device. These parameters related to the machines profile setup, e.g. laser beam energy, density, scanning speed, deposition velocity and humidity within the build environment. As users are able to modify these settings and the option for configuration is almost infinite, establishing regulation for these settings is particularly difficult. This aligns with comments made by (Horst 2020), whereby the personalisation and configuration of the 3D printing process can have a dramatic effect upon the output of a machine.

Whilst facilities and operators can use regulations set by existing standards such as ISO 13485 (quality management systems) (ISO 2016), and ISO 5900-52950 (additive manufacturing) (ISO 2021), variation in 3D printing can occur from a number of factors, namely: machine choice, material choice, slicer settings, orientation, pre-processing, post-processing, calibration, cell

structure, topological optimisation, isotropy, sterilisation, error control, and human error (Oropallo and Piegl 2016). These factors create difficulty regarding repeatability and reproducibility within the technology. Studies by Shah *et al.* (2016) and Pilipović *et al.* (2020) demonstrate the use of Computed Tomography (CT) as a means of demonstrating the varying repeatability and reproducibility of common 3D printing systems and using CT to set confidence intervals for those specific 3D printing systems. As regulatory bodies cannot insist that a particular brand of 3D printer, process, material, or slicing format is used, and the options for the latter are expanding, standardisation cannot be set in the same way as it is for conventional manufacturing. Therefore, the process presented by Shah *et al.* (2016) and Pilipović *et al.* (2020) is an example of how a new approach could be used to overcome some of the challenges specific to 3D printing technologies, and employed by regulatory bodies to create standardisation envelopes for specific printing methods.

2.2.4. Themes emerging from this section

- The ruleset for the production of medical devices is set by the ISO in the EU and the FDA/USP in the USA
- There are many standards relating to the manufacture of medical devices such as: ISO 10993, ISO 13485, USPVI
- Devices are first categorised by their risk factors and sites of use, these risk factors help to inform the manufacturing process and to determine the class of the device. This research is aims encompass devices of any classification
- There are only a few published standards relating to the regulation of 3D printed medical devices
- Generally, 3D printed medical devices are split into two categories: general medical device, patient-matched medical device

- Some studies believe that the current regulatory framework for 3D printed medical devices is inadequate in the face of its utilisation
- There are many factors affecting the consolidation of regulatory standards for the 3D printing of medical devices, such as: multiple iterations of the technology, constant expansion of the technology, repeatability and reproducibility

2.3. Stakeholder responsibility in the 3D printing of medical devices

2.3.1. Liability relative to user roles

The slow development of regulation, standardisation and certification within the 3D printing of medical devices also poses risk in terms of liability for those involved in the supply chain. Consumers that are injured as a result of a 3D printed medical device will have significant medical bills but will struggle to be compensated as an adequate liability framework is yet to be established in the growing technology (Lindenfeld and Tran 2015b).

The traditional supply chain consists of a designer, manufacturer and retailer (Harris 2015). Within this supply chain, liability can be identified by the nature of the failure. For example: if a device has a defect that other devices in the batch do not, the manufacturer is likely at fault, if the entire batch of products fail during use, the designer is likely at fault, and if the product is sold with a defect caused during storage or transportation, the retailer is likely at fault (Engstrom 2013). The system of identifying and correcting error in the traditional supply chain is clearly defined under standards such as ISO 13485 (ISO 2016). In section 8.5.2 the process of Corrective And Preventative Action (CAPA) is described, whereby supply chain stakeholders must establish procedures for implementing corrective and preventative action, this process is prescribed by the regulatory body. Negligence in the context of 3D printing poses unique difficulties and challenges for stakeholders as the position of responsibility is less clear (see Figure 15) (Lindenfeld and Tran 2015a). There are considerations to be made with respects to liability as many new stakeholders are introduced in the 3D printed medical device supply chain (Wang 2016), namely:

- CAD file designer/seller

- 3D printer manufacturer
- Material manufacturer
- Slicer program operator
- Post-processing operator
- Health Care Professional

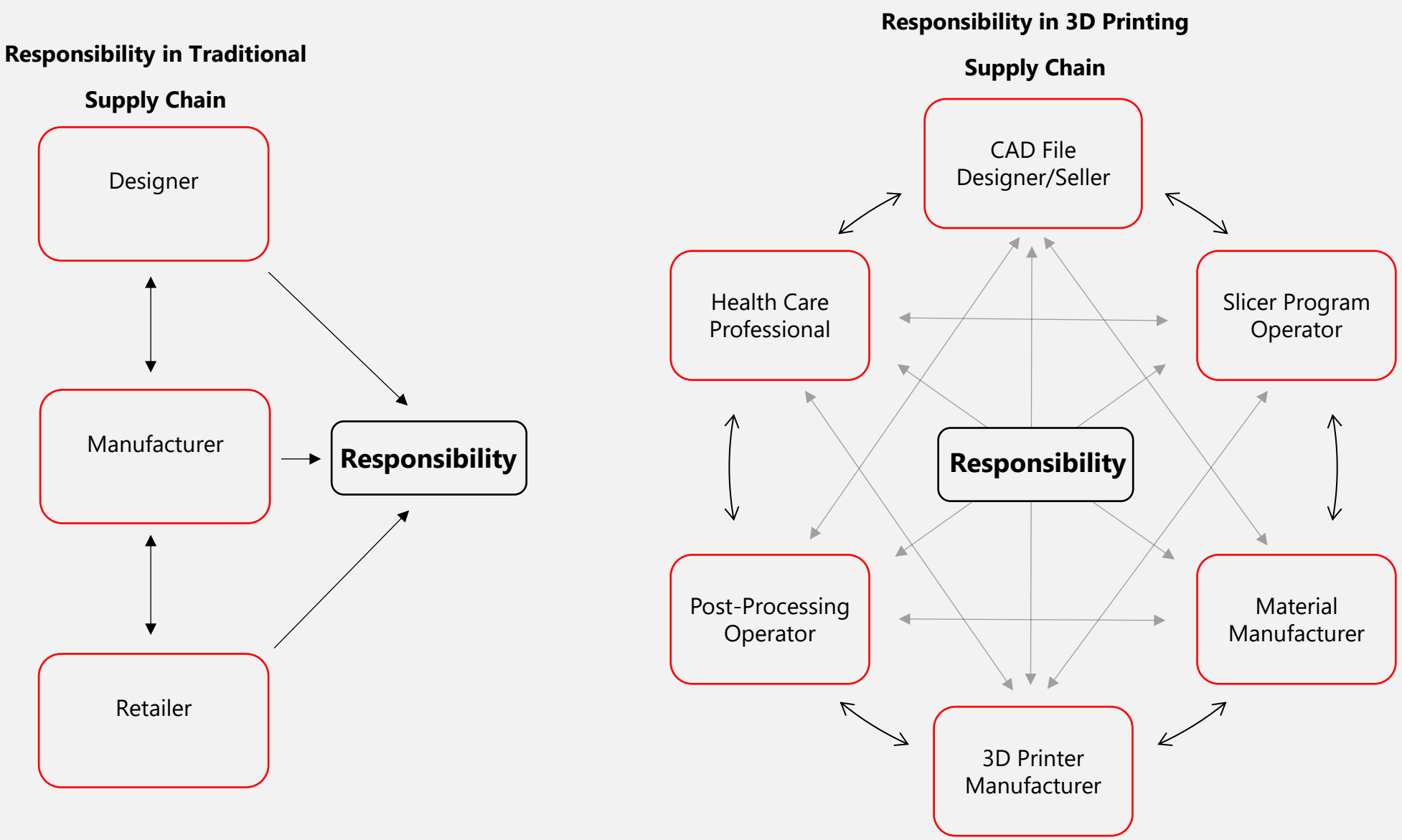


Figure 15: Responsibility in traditional and 3D printing supply chains

2.3.1.1. CAD file designer/seller

Argued by Lindenfeld and Tran (2015a), liability is most likely to fall to the designer of the 3D object in the 3D printing supply chain. However, the CAD designer will be able to defeat a lawsuit on the grounds that they are simply the creator of a digital product as opposed to being a distributor of a physical one, as a '*blueprint*' it is a product of interpretation. The complex nature of work surrounding CAD design makes it difficult for liability to be positioned and upheld in court (Lindenfeld 2016).

2.3.1.2. 3D printer manufacturer

As the model being printed by the machine is the defective item rather than the CAD file itself, 3D printer manufacturers are also responsible for the liability of a printed device upon failure (Wang 2016). Whilst possible, it is unlikely that the Plaintiff will be able to prove that the machine is defective, furthermore prove it was defective upon leaving the manufacturer's factory.

2.3.1.3. Material manufacturer

A category for liability that is almost unique to 3D printing is the supplier of the material (Wang 2016). The use of an ineffective or insufficient material may lead to the failure of the product, especially if the reason for failure was mechanical and the breaking force was significantly less than of that advertised in the material's specifics data sheet.

2.3.1.4. Slicer program operator

Another possibility for liability within the 3D printing supply chain is the operator that creates the g-code file for the machine to follow (Scott 2007; Berkowitz 2014). As there are infinite ways in which a CAD file can be sliced

prior to printing, it is highly possible that using incorrect settings may lead to the device failing. However, it is highly unlikely that the operator was given exact instructions by the designer of the file as to how the settings should be configured (Wang 2016).

2.3.1.5. Post-processing operator

Post-processing, particularly for 3D printing methods that use photosensitive resins, is a vital step to ensure printed devices are safe for use. Several studies have identified toxic leachates in parts that were post-processed in accordance with the material manufacturer's instructions (Macdonald *et al.* 2016; Oskui *et al.* 2016; Walpitagama *et al.* 2019). These studies noted that by customising the recommended post-processing technique the concentration of leachates were mitigated. However, by deviating from the material manufacturer's given guidance, the operator becomes liable and would therefore share responsibility if the device was to cause injury due to insufficient post-processing (Remes and Williams 1992; Barrère *et al.* 2008).

2.3.1.6. Health care professional

Health Care Professionals (HCPs) are liable under a negligence rule of malpractice. There is a considerable framework in place to protect healthcare workers in the case of malpractice (Danzon 2000). However, assuming that the HCPs are not the persons manufacturing the device, it is generally the direct manufacturer who will incur liability through negligence laws of a defective product (Park 2015). In the case of 3D printed devices, the '*learned intermediary*' doctrine will more than likely shift liability from the HCP. Under this doctrine HCP's have a duty to warn their patients of the danger of a

medical device (Twerski 2006). This is especially pertinent with respects to 3D printed devices as they are a relatively new breakthrough (Park 2015).

2.3.2. Themes emerging from this section

- The slow development of regulatory standards for 3D printing poses risks for stakeholders as liability and responsibility is unclear in the supply chain
- The 3D printing supply chain has new stakeholders, creating difficulty for those involved to work lawfully and safely
- New stakeholders include: CAD designer, 3D printer manufacturer, material manufacturer, slicer program operator, post-processing operator, health care professionals

2.4. Photosensitive resins used in vat-polymerisation 3D printing

2.4.1. Photosensitive resins

Photosensitive resins present specific material advantages and have attracted attention from chemists, materials scientists, HCP's, and engineers (Layani *et al.* 2018; Bagheri and Jin 2019). As previously explained, photosensitive resin is a liquid in its raw state and is solidified during the printing process. Due to its raw liquid state, photosensitive resin can be printed at very high resolutions with excellent dimensional accuracy, isotropy, smooth topography, and is capable of achieving a high anatomical likeness to the original 3D object due to its low-shrinkage (Keßler *et al.* 2022). Similarly, materials scientists often benefit from the raw liquid state by synthesising custom resins using additives that offer characteristics such as radiopacity (Shannon *et al.* 2020). Significant innovations have been made in the engineering and development of photosensitive resins with the necessary biocompatibility, bioactivity and biodegradability to further medical 3D printing (Lim *et al.* 2020).

VP 3D printing systems that use photosensitive resins are of particular focus within the literature where the production of medical devices is concerned (Kermavnar *et al.* 2021). In a review by Melchels *et al.* (2010) the benefits of using VP techniques over other 3D printing techniques for biomedical applications were discussed. The review focusses on the advantages SLA holds for the manufacture of high-risk and low-risk patient-specific devices such as, implantables, tissue engineering scaffolds and hearing aids. However, with the absence of clear regulatory standards and confusion surrounding stakeholders liabilities, the use of VP 3D printing techniques for manufacturing medical devices is of concern and has attracted attention within the field (Rogers *et al.* 2021).

Whilst VP techniques have many clear benefits for the production of medical devices, the key drawback identified within the literature is the post-processing and chemical composition of the material. Unlike other methods of 3D printing, VP techniques require users to post-process printed models to ensure that the material achieves its optimum biocompatible and mechanical properties by completing the process of solidification (Alifui-Segbaya *et al.* 2017).

2.4.1. Photo-crosslinking

The process of photosensitive resin being solidified is known as *'photo-crosslinking'* (Zhang and Xiao 2018). Photo-crosslinking occurs when an energy source, (typically UV light), is emitted into the resin. Photo-initiators in the resin react and form polymer chains from oligomers and monomers and begin to join to other polymer chains creating a solid material (see Figure 16) (Alifui-Segbaya *et al.* 2017; Bagheri and Jin 2019; Kessler *et al.* 2020).

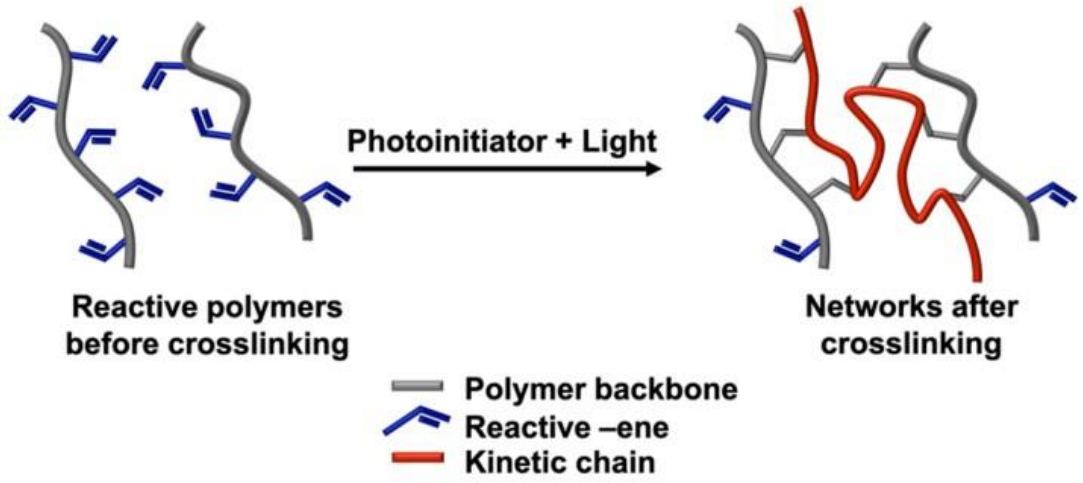


Figure 16: Photo-crosslinking (Lim *et al.* 2020)

After printing, photosensitive resin has not fully completed the process of photo-crosslinking, leaving semi-cured resin within the structure of the model, and raw liquid resin on the surface (Rogers *et al.* 2021). The conversion rate of

photosensitive resin after printing is not exact in the literature, and is listed by several studies with varying conversion percentages. A study published by J.L. Ferracane and J.R. Condon (1990) lists the post-print conversion rate between 35-77%, whilst Kessler *et al.* (2020) lists it as >50%.

2.4.1. Composition of photosensitive resins

The composition of a photosensitive resin needs to contain a reactive UV-curable monomer or oligomer, or a blend of them that are capable of cross-linking. They must also contain a photo-initiator capable of converting physical energy into chemical energy that then degrades forming cations or radicals that will activate the process of photo-crosslinking (Taormina *et al.* 2018; Gibson *et al.* 2021).

In 3D printing, most photosensitive resins are either epoxy based, acrylate based, or a hybrid of both (Yu *et al.* 2017). The rest of the material is made up of chemical plasticisers, elasticisers and pigment additives (Decker *et al.* 2001). In VP 3D printing, resins are almost exclusively acrylic based as they are able to begin cross-linking faster than epoxy based, allowing for faster printing speeds (Decker *et al.* 2001; Uzcategui *et al.* 2018).

Commonly used chemical components such as Bisphenol A and poly-phenylene are known to have a number of harmful toxicological and irritant effects in their uncured liquid state (3DSystems 2020c). Therefore, printed parts require post-processing after printing to increase the conversion rate to >90% and finish the process of photo-crosslinking (Kessler *et al.* 2020).

2.4.1. Post-processing of photosensitive resins

Post-processing guidance is usually provided by the material manufacturer and is material dependant. The information generally details post-washing, post-curing and support removal. It is observed in the grey literature that this guidance changes depending on the brand of material. Post-processing instructions encompass any model that is produced using that material. The guidance insinuates wash/cure times are universal to any geometry capable of being manufactured within the build parameters of the proprietary system.

2.4.1.1. Post-washing

As parts are submerged in the liquid resin during printing, excess resin must first be washed away from the model prior to curing (Kalaskar 2022). Typically, solvents such as IPA or tripropylene-glycol-monomethyl-ether are recommended (Formlabs 2022). Post-washing is performed by hand, or in a washing tank depending on the brand of material. Guidance provided by the manufacturer will detail the method of washing, solvent refresh rates, and washing times required.

2.4.1.2. Post-curing

Post-curing involves exposing printed parts to UV and sometimes heat. Manufacturers will provide detail of how to post-cure models specific to individual resins. Post-curing is essential to insure that photo-crosslinking has reached a higher conversion rate and that the appropriate mechanical properties have been achieved (Ammoun *et al.* 2021; Piedra-Cascón *et al.* 2021).

Often material manufacturers recommend extending post-curing processes for parts that are larger or feature complex geometries, however, they do not detail what is considered larger or more complex (Formlabs 2022). Many also

provide statements informing the user that test coupons were used to inform the post-processing guidance but do not detail the dimensions of the coupons. Furthermore, manufacturers state that it is the responsibility of the user to conduct their own testing to ensure that the printing process and post-processing of the material is safe and lawful in line with the intended use (3DSystems 2020c).

2.4.2. Customised post-processing

The guidance provided by many material manufacturers in relation to post-processing guidance are ambiguous and suggest that post-processing technique should be customised by taking model geometry and size into account. They also confirm that liability is placed on the operator responsible for carrying out post-processing. It is therefore important to consider the findings of the literature that has experimented with post-processing technique in reference to the guidance given by material manufacturers.

The studies detailed in Table 2, modify post-processing and assess the results using mechanical or biocompatible properties, they also include control groups that test the given guidance from the material manufacturer to test if deviating from guidance was beneficial. The results of the table were used to inform the research questions and the methodology of the experiments carried out in chapters six and seven.

It is clear from the studies listed within the table that deviating from the material manufacturer's given guidance often results in significant changes to the material properties of photosensitive resins.

Table 1: Customised post-processing effects in the literature

Study/Author	Aims	3D Printer (3DP)/Method/Material	Independent Variable(s)	Dependant Variable(s)	Outcomes	Material manufacturer guidance control
Effects of postcuring temperature on the mechanical properties and biocompatibility of three-dimensional printed dental resin material - (Bayarsaikhan *et al.* 2021)	This study aimed to evaluate the effects of alternative post-curing times and temperatures on the mechanical and biocompatible properties of SLA denture material.	**3DP:** Formlabs Form 3 **Method:** SLA **Material:** Formlabs Denture A2	**Cure Times:** 15, 30, 90, 120 minutes **Cure Temperatures:** 40, 60, 80^{oC}	**Mechanical:** Flexural strength, flexural modulus, Vickers hardness, degree of conversion, **Biocompatibility:** Protein absorption, cell viability	Two-way ANOVA showed that post-curing time and post-curing temperature had a statistically significant effect on flexural strength. Past 60^{oC} effects plateaued. Flexural modulus increased with extended postcuring time up to 90 minutes. Extending post-curing time significantly affected degree of conversion, with the highest result of 63% at 120 minutes at 60^{oC}.	Formlabs recommends to post-cure Denture A2 for 30 minutes at 80^{oC} then to turn the part and repeat for a further 30 minutes. The study did not replicate this, but did test past the recommended curing time resulting in a higher flexural strength, conversion rate, and a better rate of cell viability.
Effects of post-curing conditions on mechanical properties of 3D printed clear dental aligners - (Jindal *et al.* 2020)	This study assesses the effects of post-curing conditions and mechanical properties of 3D printed dental aligners.	**3DP:** Formlabs Form 2 **Method:** SLA **Material:** Formlabs Dental LT clear	**Cure Times/Temperatures:** 80^{oC} for 20 minutes, 80^{oC} for 10 minutes, 80^{oC} for 5 minutes, 60^{oC} for 20 minutes, 40^{oC} for 20 minutes.	**Mechanical:** Compression tested under 1000N load cell	Temperature had the most effect on compressive load. 80^{oC} for 20 minute test withstood 700N, and 60^{oC} for 20 minutes only withstood 473N.	Formlabs recommends curing Dental LT clear for 20 minutes at 80^{oC}. This was replicated in the study and showed that it had the highest compression, therefore deviating from the manufacturer's guidance did not had a positive result.
3D-printed material for temporary restorations: Impact of layer thickness and post-curing method on degree of conversion (Reymus *et al.* 2019)	This study aimed to investigate the impact of print layer thickness and post-curing method on the degree of conversion of 3D printed temporary restoration material.	**3DP:** Rapidshape D20 **Method:** DLP **Material:** NextDent C&B dental resin	**Curing tanks:** LC-3DPrint Box – 30 minutes, Octoflash G171 – 2000 flashes (x2)**,** Labolight – 3 minutes (x2), PCU LED – 5 minutes	**Layer thickness:** 25, 50, 100 microns **Mechanical:** Conversion rate	Results showed that specimens cured in the Octoflash G171 curing tank had the highest degree of conversion, followed by the LC-3DPrint Box. Print layer thicknesses of 100 and 50 micron also showed a consistently higher degree of conversion than 25 micron specimens.	NextDent recommends curing C&B dental resin for 30 minutes in the proprietary LC-3DPrint Box curing tank. This was performed in the study, and the results showed that using the Octoflash G171 tank resulted in a higher degree of conversion.

Effects of two postprocessing methods onto surface dimension of in-office fabricated stereolithographic implant surgical guides - (Ammoun *et al.* 2021)	This study aimed to evaluate the effects of two postprocessing methods in terms of surface finish using intaglio and cameo surface dimensions on SLA printed surgical guides.	**3DP:** Formlabs Form 2 **Method:** SLA **Material:** Formlabs Dental SG resin	**Wash/Cure Times:** (Group 1) 10 specimens washed and cured according to manufacturer. (Group 2)10 specimens washed using 30 second IPA hand wash, 10 minute IPA ultrasonic bath, 30 second IPA hand wash, 5 minute IPA ultrasonic bath **Curing:** (Group 1) 10 specimens cured in Formcure for manufacturer recommended time. (Group 2) 10 specimens were cured for 60 minutes at 60^{oC} in NextDent LC-3DPrint Box	**Mechanical:** Cameo and intaglio surface analysis using CT scan data to compare to digital STL file	Results showed that (Group 2) alternative washing and curing methods resulting in additional surface material compared with (Group 1) the automated washing and curing methods that had lost surface material. Results were tested by comparing CT scanned specimens to the digital model.	This study replicated the material manufacturer's recommended guidance (Group 1), the results showed that alternating from guidance removed less surface resin.
Effect if post-rinsing time on the mechanical strength and cytotoxicity of a 3D printed orthodontic splint material - (Xu *et al.* 2021)	This study aimed to investigate the effect of post-rinsing time on the flexural strength and cytotoxicity of SLA printed orthodontic splint material.	**3DP:** Formlabs Form3B **Method:** SLA **Material:** Formlabs Dental LT clear	**Wash/Cure Times:** Specimens were washed for 5 min, 12 min, 20 min, 30 min, 1 hour, 12 hours using an unnamed ultrasonic IPA bath. Curing was performed in the Formcure tank for 20 minutes at 80^{oC}	**Mechanical:** Three-point bend test performed to analyse flexural strength **Biocompatibility:** Extract test and direct contact test using mouse fibroblasts	Results showed that from 5 minutes to 1 hour, flexural strength remained around 185MPa with a large drop off at 12 hours at 92MPa. The increased post-washing time had no difference on the cytotoxicity tests.	Formlabs recommends curing Dental LT clear for 20 minutes at 80^{oC} and to wash parts for 20 minutes, this was replicated in the study. However, deviating from the recommended guidance showed so significant improvement on the mechanical or biocompatible properties.
Effect of print orientation and duration of ultraviolet curing on the dimensional accuracy of a 3-dimensionally printed orthodontic clear aligner design (McCarty *et al.* 2020)	This study aimed to investigate the effect or print orientation and post-curing duration on the dimensional accuracy of clear aligners.	**3DP:** Formlabs Form 2 **Material:** Formlabs Dental LT clear **Method:** SLA	**Wash/Cure Times/Temperatures:** Parts were washed for 2 minutes in one IPA ultrasonic bath, then for a further 3 minutes in a separate IPA ultrasonic bath. Sets were then cured for (Group 1) no cure, (Group 2) 20 minutes at 80^{oC} (Group 3) 40 minutes at 80^{oC} in the Formcure tank **Print orientation:** Sets of specimens were printed	**Mechanical:** Cameo and intaglio surface analysis using CT scan data to compare to digital STL file	Results of the study reported that the no cure (Group 1) were excluded as they could not be scanned due to surface resin. It also showed that print orientation had no significant effect on the surface accuracy and that both intervals of post-curing resulted in specimens that were both clinically acceptable.	Formlabs recommends curing Dental LT clear for 20 minutes at 80^{oC} and to wash parts for 20 minutes. As the curing was replicated but the washing was not, as well as the study finding no significant difference at the two tested intervals, it cannot be said that deviation had a positive or negative effect on the specimens.

			vertically, horizontally and at 45°.			
Effects of post-curing time on the mechanical and color properties of three-dimensional printed crown and bridge materials - (Kim *et al.* 2020)	In this study, crown and bridge photosensitive resins are evaluated by mechanical properties, cytotoxicity, and colour changes at varying lengths of post-curing treatment.	**3DP(s):** Veltz D2, Zenith D **Material(s):** NextDent C&B, Nextdent C&B MFH, ZMD-1000B temporary, DlOnavi C&B **Method:** DLP	**Cure Times/Temperature:** (Group 1) no cure, (Group 2) 15 minute, (Group 3) 30 minute, (Group 4) 60 minute, (Group 5) 90 minute, (Group 6) 120 minute. All curing was done at 60°C.	**Mechanical:** Flexural strength, Weibull analysis, degree of conversion and Vickers hardness were tested. **Biocompatible:** Cytotoxicity and cell viability testing was performed using a CELLOMAX™ viability kit.	Flexural strength was increased from the control group (Group1) in all cases. Most materials increased in flexural strength until the 90-minute interval where they plateaued or dropped off. The same pattern was seen in the Vickers hardness. In some materials the pigment of the material appeared more saturated after extended curing exposure. Degree of conversion increased in all materials in each increased interval of curing. Cell viability in all materials increased with the highest viability seen at the 120-minute interval.	The Nextdent materials tested in this study require 30 minutes at 60°C. Whilst this was performed in the study, the specified curing tank was not used, however the output settings of the used and specified curing tanks are similar in wattage and wavelength. Therefore, the authors have shown that increasing the curing time of these resins has resulted in an increase in mechanical and biocompatible properties.

2.4.3. Themes emerging from this section

- Photosensitive resins are the material used in vat-polymerisation and material jetting 3D printing processes
- They offer unique material characteristics such as: smooth surface finish, near-isotropic parts, high dimensional accuracy, good likeness to original 3D model
- The process of photosensitive resin solidifying is known as photo-crosslinking and occurs when UV light comes into contact with the resin
- The composition of photosensitive resins is made up of oligomers, monomers and photo-initiators
- After printing, the process of photo-crosslinking is not complete and therefore vat-polymerisation printed parts requires post-processing to achieve a higher conversion rate
- Material manufacturers supply guidance on how to properly post-process materials. This information is unique to each material and is carried out by the user. Often, guidance detail recommendations that users should extend UV exposure duration if the model being produced features larger or more complex geometries - however do not detail specific guidance regarding durations and parameters
- Many studies have tried to customise the given guidance of and assess the effects using mechanical properties, surface properties and biocompatible properties to evaluate the affects
- There are several biocompatible 3D printing resins available. There is a need to review the quality and availability of information on the materials to ensure they are safe in their end use.

2.5. Research questions

The following research questions have emanated from the findings of the literature review, and are investigated in the following chapters.

Research question 1: During the COVID-19 pandemic, 3D printing was utilised to manufacture PPE and medical devices that were in short supply. What can be learned regarding the use of 3D printing during the emergency response?

Research question 2: The literature details that 3D printing is utilised in some medical disciplines more than others. Palliative care is an example of a medical discipline where 3D printing could be utilised to respond to unique individuals needs where existing devices are not commercially available. How is 3D printing being used to treat palliative care patients in the current literature?

Research question 3: The increase in the use of 3D printing to manufacture medical devices has created a demand for biocompatible materials. These materials are required to provide specific instructions detailing the certification, intended uses and post-processing technique. As user's heavily rely on this information, what can be learned from the grey literature regarding the quantity and quality of this information?

Research question 4: Manufacturers provide generic post-processing guidance per material, however some manufacturers recommend extending post-curing times for models that are '*larger or more complex*', without providing specific details. How does extending post-curing times affect the depth of cure of large geometries?

Research question 5: Building on the results of chapter 6, how does extending post-curing times affect the mechanical properties of material within a complex geometry?

Chapter 3: 3D printed devices for healthcare in response to COVID 19 – lessons learned to date

Publication associated with this chapter:

1. Guttridge, C., O'Sullivan, A., O'Sullivan, K.J. and O'Sullivan, L.W. (2021a) 'Three-Dimensional Printed Devices for Health Care in Response to the Coronavirus Disease 2019: Lessons Learned to Date', *3D Printing and Additive Manufacturing*, 8(5), 340-342.

3.1. Pre-Chapter Synopsis

During the COVID-19 pandemic there was a global response by the 3D printing community to help replenish much needed PPE and other devices. Due to the lack of fully established regulations for the 3D printing of medical devices, this movement was mostly unregulated. As such, users had to heavily rely on the information supplied to them by material manufacturers. It is important to report on what was observed during the response with relevance to 3D printing being used as a point-of-care manufacturing method.

3.2. Abstract

During the first surge of the COVID 19 pandemic there was a tremendous global response from 3D printing communities and individuals to support local healthcare systems and staff. The responses involved a range of 3D printer users from amateur makers to conglomerate manufacturers creating PPE and other supplies of which there were shortages. These new supply chains resulted from the democratisation of 3D printing, open source file sharing, mass production of desktop machines, and the relatively cheap cost of 3D printers. The democratised state of 3D printing facilitated an altruistic movement of makers with ranging experience, to work alongside traditional manufacturers to make medical supplies. With the critical nature of the shortages and the sharp increase in COVID 19 infections, many standards and regulations were bypassed, and good manufacturing processes disregarded, in cases. The outcomes from this article is a set of 6 lessons learned from the author's perspective regarding the use of 3D printing during the initial phase of the COVID 19 pandemic. We note challenges experienced around volume manufacturing, infection control requirements of produced parts and the clean-ability of devices, mechanical strength considerations, good

manufacturing practices, product and IP liability, and the role of involving clinical stakeholders.

3.3. Introduction

The first cases of COVID-19 were reported by officials in Wuhan City, China, in December 2019 (Jovičić *et al.* 2020). By January 2020 the first cases of COVID 19 were confirmed in Europe and the United States. Italy, Spain and Germany saw dramatic rises in cases until April 2020, and were then surpassed by rates in the USA, Brazil and India. By September 2020 the virus spread to 188 countries globally and infected upwards of 31,000,000 people, of which over 900,000 people are estimated to have died (JHU 2020). As the pandemic spread, healthcare systems ran out of PPE and other medical supplies (Eneko Larran˜eta 2020). With quarantine restrictions in place many manufacturers also struggled to meet demands due to the closure of manufacturing lines and/or sub manufacturers/suppliers (Rance Tino1 *et al.* 2020). Further, as governments issued lockdowns, and in some cases trade embargos on the export of associated equipment, many supply chains froze internationally.

The initial response was largely on the basis that 3D printed devices would be a last resort and were better than nothing (FDA 2020; William Clifton 2020). However, as the infection rate soared, last resort products became more commonplace in some areas (Megan L. Ranney 2020). There was a notable trend regarding communities/individual makers producing 3D printing face visors, face masks, and respiratory equipment, among various other healthcare devices (Eneko Larran˜eta 2020; Stephanie Ishack 2020). While there were deeply commendable individual and community efforts during this time of emergency, our experience was that a great many erroneous assumptions were made, such as the extent of shortages of specific products locally and in supply

chains. Solutions were produced that had design/production challenges that limited their actual use in the healthcare settings. Issues such as sterility, consistency, scalability, and product liability were widely overlooked.

Stringent standards and regulations are in place for medical device manufacturing to protect all members of the supply chain, particularly the end user/patient. With the emergency nature of the pandemic and the risk to frontline workers from extreme shortages of supplies, many, if not all, regulatory requirements were ignored by many in order to deliver solutions (knowingly or otherwise).

The 3DP community internationally responded rapidly during the first wave of COVID 19. Some responses were more fruitful than others. It is appropriate to now reflect on the responses and consider aspects that affected the utility and success of these efforts which should be considered through research activities for future emergencies of this nature. This could help ensure that such efforts in the future are optimised and the opportunities for utilising 3D printing fully exercised. The purpose of this commentary is to detail six lessons learned by the current author on this topic.

3.4. Discussion – Lessons Learned

3.4.1. Volume manufacturing using 3D printing at required quality levels was a challenge during the pandemic

As the production throughput of 3D printing is low in comparison to traditional manufacturing, many machines must be utilised for the output rate to sufficiently meet moderate demands. Quality control of 3D printed relative to traditionally manufactured devices remains a challenge (Chung and Kim 2018; Wu and Chen 2018). Many non-professional maker groups came together to scale up production of some designs, notably visor head bands (Eneko

Larran˜eta 2020; Jesse L. Cox 2020). The very nature of multiple disparate makers producing a single design brings with it the potential for large variability in printer technologies, settings, materials and quality. For example, our experience in Ireland was that many groups donated 3D printed visor headbands to healthcare facilities, with significant variability in overall quality. As a proportion of these donated units were unsuitable for use, some facilities disregarded 3D printed solutions *en masse*. The lesson learned is that for volume manufacturing across various makers, there is a need to produce such devices to a minimum acceptable standard predetermined by a control sample and verified by the recipient stakeholder, even during emergencies such as a pandemic.

3.4.2. Infection prevention and control practices need to be respected or printed solutions will not be used in healthcare settings

Healthcare facilities work under stringent Infection Protection and Control (IPC) considerations. 3D printed components to be used in healthcare must consider infection/sterilisation related aspects as they may affect their use (Bosc et al. 2021). These increased significantly during the pandemic. IPC teams require that solutions are clean (not necessarily sterile) before they can be used in a healthcare facility.

The printing technology used can also affect IPC risk. Technologies such as FDM often have small crevices/spaces between print layers, and in such cases, there may be a risk that surfaces cannot be thoroughly cleaned (Changchun Zhou 2016). For single use applications in some healthcare settings this may not be as much a concern as for repeated use in settings where devices require cleaning before reuse.

In our experience, there were cases in which large volumes of devices were produced without any/sufficient IPC team input. Where the IPC team only evaluate devices post manufacturing via 3D printing there is a significant risk the entire batch will be rejected if a concern emerges. This can lead to negative opinions and low adoption of 3D printed devices in those healthcare settings.

3.4.3. Emergency 3D printed devices need to consider mechanical strength characteristics

A response during the early stages of the pandemic when supply chains froze was to 3D print devices locally as an alternative production method (Eneko Larran˜eta 2020). There is significant variability in the mechanical characteristics of 3D printed components depending on the 3D printing technology used. Many of the designs available on open source websites were intended for production on specific systems, but may have been printed using alternatives or lower-end 3D printing technologies. A potential concern is that some devices were printed without sufficient consideration for their mechanical strength and performance, which may give rise to product failure and injury during use (Eneko Larran˜eta 2020; Rance Tino1 *et al*. 2020).

3.4.4. There is a need for guidance on Good Manufacturing Practices for 3D printed devices

Maintaining Good Manufacturing Practice (GMP) in medical device supply chains is central to product safety. This includes protocols regarding sterility, quality control, part validation and verification. Traceability of parts is also important if devices need to be recalled on safety grounds (Horst and McDonald 2020). Products created and supplied to healthcare using 3D printing should be subject to appropriate manufacturing standards. While it is appreciated that in the crisis phase of a pandemic that some supplies are better than none, the devices must still meet minimum safety standards. It is

important that GMP guidance for 3D printed emergency medical devices are established, but in particular in response to pandemics, to ensure they are as safe as is reasonable/feasible, and above all, safe for clinical use.

3.4.5. Makers may be inadvertent medical device manufacturers and responsible for product liability and IP infringement

The emergency response during COVID 19 was a passionate response of many. Several device designs were shared internationally, some with caveats that they were to be used as a last resort, and others with liability warnings (Rance Tino1 *et al.* 2020). Makers may have made assumptions that because designs were made available online that they were "approved" in accordance with requisite regulations and standards. In some cases, makers became medical device manufacturers unknowingly, and in so doing, became potentially responsible for product liability (Horst 2020). In addition, assumptions may also have been made by some makers that they could reverse engineer and reproduce commercial designs without consideration for IP infringement. Inadvertently or not, the maker could be held liable even if they were unaware of, or believed they were exempt from, certain regulations.

3.4.6. It is crucial to involve clinical stakeholders if making or designing solutions

Involving healthcare staff in validating requirements for devices, and in the design of new devices is crucial. During the initial surge of COVID 19 there were chain reactions whereby devices were 3D printed in response to what was happening on an international level. In many cases this was done without first validating the needs for such devices locally (Horst 2020; Jesse L. Cox 2020; Megan L. Ranney 2020; Rance Tino1 *et al.* 2020). Regarding the design of new

solutions, it is imperative that clinical stakeholders are consulted using an iterative design process to arrive at solutions that meet their needs.

3.5. Conclusions

The 3D printing community internationally demonstrated how this technology can be mobilised quickly to provide important supports to healthcare systems during an emergency such as a pandemic. In this article we detail six lessons learned, which, if addressed through research and regulatory/policy guidance, will help optimise the utility of 3D printing during responses to emergency medical disasters in the future, including potentially pandemics.

Chapter 4: The application of 3D printing in palliative care: A systematic review

Publications associated with this chapter:

1. Kermavnar, T., Guttridge, C., Mulcahy, N.J., Duffy, E., Twomey, F. and O'Sullivan, L. (2022) '3D printing in palliative medicine: systematic review', *BMJ Supportive & Palliative Care*.

   Association: Kermavnar led the study design, paper search, data extraction, synthesis, reporting and paper writing. Guttridge and Mulcahy contributed to the paper search, data extraction, synthesis and paper writing. Duffy, Twomey and O'Sullivan contributed to the study design, synthesis, reporting and paper writing. O'Sullivan is acting as guarantor of this research.

4.1. Abstract

Background:

Three-Dimensional Printing (3DP) enables the production of highly-customised, cost-efficient devices in a relatively short time, which can be particularly valuable to clinicians treating patients with palliative care intent who are in need of timely and effective solutions in the management of their patients' specific needs, including the relief of distressing symptoms.

Method

Four online databases were searched for articles published by December 2020 that described studies using 3DP in palliative care. The fields of application, and the relevant clinical and technological data were extracted and analysed.

Results

Thirty studies were reviewed, describing thirty-six medical devices, including anatomical models, endoluminal stents, navigation guides, obturators, epitheses, endoprostheses, and others. Two thirds of the studies were published after the year 2017. The main reason for using 3DP was the difficulty of producing customised devices with traditional methods. Eleven papers described proof-of-concept studies that did not involve human testing. For those devices that were tested on patients, favourable clinical outcomes were reported in general, and treatment with the use of 3DP was deemed superior to conventional clinical approaches. The most commonly employed 3DP technologies were Fused Filament Fabrication with Acrylonitrile Butadiene Styrene, and Stereolithography or Material Jetting with various types of photopolymer resin.

Conclusion

Recently there has been a considerable increase in the application of 3DP to produce medical devices and bespoke solutions in the delivery of treatments with palliative care intent. 3DP was found successful in overcoming difficulties with conventional approaches and in treating medical conditions requiring highly-customised solutions.

4.2. Key messages

4.2.1. What was already known?

Specialists in palliative medicine often require short-term, rapid solutions to alleviate the patients' distressing symptoms and improve their quality of life. Three-Dimensional Printing (3DP) is becoming more common to manufacture complex patient-specific devices and is recognised for its ability to provide cost-effective and customisable rapid solutions. Patients in receipt of palliative care can benefit from the advantages of 3DP; but in order to highlight potential opportunities, it is necessary to systematically review its use in this clinical field.

4.2.2. What are the new findings?

The majority of reports of 3DP use in palliative care were published after the year 2017. The studies showcase a versatile range of potential applications, including for the production of anatomical models, endoluminal stents, navigation guides, obturators, epitheses, endoprostheses, and others. The main reasons for using 3DP are the difficulty of producing patient-specific devices with traditional methods, and the lack of commercially-available solutions to specific patient needs.

4.2.3. What is their significance?

4.2.3.1. A) Clinical

Using 3DP generated applications as a component of the care provided to patients with palliative care needs can lead to a positive impact on palliative care patient outcomes, particularly when cost, time and the possibility of customisation are critical factors. Guidelines are provided regarding the advantages and disadvantages of specific 3DP technologies and materials, both to inform future clinical practice and identify limitations.

4.2.3.2. B) Research

To the authors' knowledge, this study is the first comprehensive systematic review analysing 3DP as a method of producing medical devices that might be applied to patients receiving palliative care.

4.3. Introduction

Three-dimensional printing (3DP), also known as Additive Manufacturing (AM) is becoming increasingly common in modern medicine. Initially it was limited to manufacturing prototypes, and was synonymous with Rapid Prototyping (RP), but it is being increasingly utilized to directly produce finished products and components (Hague *et al.* 2006; Carlström and Wargsjö 2017). Physical objects are built from digital data (i.e. Computer-aided Design (CAD) models) that can be generated anew using 3D-modelling software, or obtained by 3D-scanning of existing objects in the process of Reverse Engineering (RE). The final designs are then 3D-printed directly (direct AM), or fabricated with the help of 3D-printed tools/moulds (indirect AM).

Presently, 3DP is gaining increasing recognition in a range of medical practices, including diagnostics, surgical planning and reconstruction, patient education, rehabilitation, tissue engineering, and pharmacology (Kermavnar *et al.* 2021). In the production of medical devices and tools, 3DP offers a wide range of advantages over traditional methods, most notably the possibility of cost-effective, small-scale, on-demand, in-house fabrication of geometrically and structurally complex patient-specific products in a relatively short time (Holmström *et al.* 2010; Slotwinski 2014). These advantages can add particular value to the delivery of responsive care to patients with palliative care needs. Namely, the possibility of producing highly-customised solutions at low cost allows for individualised management of patients' needs to help them cope with their condition and treatment, and experience optimal quality of life despite the disease. Moreover, reduced lead time enables a quick response to alleviating distressing symptoms and allow a person whose health is deteriorating to spend less time away from their home.

It is of note that in part due to the relatively recent recognition of Palliative Medicine as a specialty, even amongst healthcare professionals a common understanding of the roles of palliative care still needs to be established (Gaertner *et al.* 2014; Rance Tino1 *et al.* 2020). To facilitate this, the International Association for Hospice and Palliative Care published a new 'Consensus-Based Definition of Palliative Care' in 2019 (Aimar *et al.* 2019). For clarity, the authors of the present work also acknowledge the following: (1) specialist palliative care is given alongside treatments targeting the underlying disease; (2) when the intention is potentially curative, the intervention does not qualify as truly palliative; and (3) interventions provided with palliative intent are typically less invasive and less dangerous procedures, although the same medical approaches can have curative effects in some diseases, and palliative in others (e.g. central airway obstruction management with stents, radioactive ^{125}I seed implantation for brachytherapy, bone tumour resection and endoprosthetic reconstruction (Pruksakorn *et al.* 2015; Baltz *et al.* 2019; Heunis *et al.* 2019; Liu *et al.* 2019).

Individual literature reviews exist of 3DP in palliative care, focused on specific types of medical devices, such as central airway stents, oesophageal stents, and orthoses (Seongjae Choi *et al.* 2019; Liu *et al.* 2019; Al-Zogbi *et al.* 2021). However, to the authors' knowledge, no systematic reviews have been published to date in this field. Thus, the aim of the present study is to provide a systematic review of studies reporting the use and the potential uses of 3DP in specialist palliative care, with specific emphasis on the fields of application, technology employed, and the advantages of 3DP over conventional methods.

4.4. Method

4.4.1. Literature search and study selection

A systematic literature search was performed during December 2020 using the following databases: EBSCOhost (including Academic Search Complete, MEDLINE with Full Text, CINAHL Complete), PubMed, Scopus, and Web of Science. Articles of interest included terms related to 3DP in the title (i.e. "3D print*","3D-print*", "three-dimensional* print*", "additive* manufactur*", or "rapid* prototyp*"), terms related to palliative care in the abstract (i.e. "palliat*", "cancer*", "oncolog*", "tumour*", "tumor*", "malignan*", "terminal* ill*", or "terminal* disease*"), and terms related to palliative care in the full text (i.e. "palliat* car*", "palliat*", "end-of-life", "end of life", "quality-of-life", or "quality of life"). If necessary, the search string was adapted to meet the search options of specific databases. An additional search was performed using Scopus to identify studies including any of the terms related to 3DP and the term "palliative" in either the title, abstract or keywords. The study selection was limited to full scientific articles in the English language. All included papers were published prior to the date of the search. Reviews, book chapters and non-scientific papers were excluded from the review, as were studies performed on veterinary patients, involving curative or aesthetic surgical reconstructive procedures, and testing diagnostic technology. Also excluded were studies involving palliative surgical correction of paediatric congenital heart defects, as these are typically managed by cardiologists. Regarding bias, all studies which met the selection criteria were included.

The review protocol was designed according to the PRISMA guidelines (Moher *et al.* 2009). The search and study selection criteria are presented in Figure 17. TK confirmed the outcomes of the search and selection performed by NM and CG. Any disagreements among the reviewers were resolved by LOS.

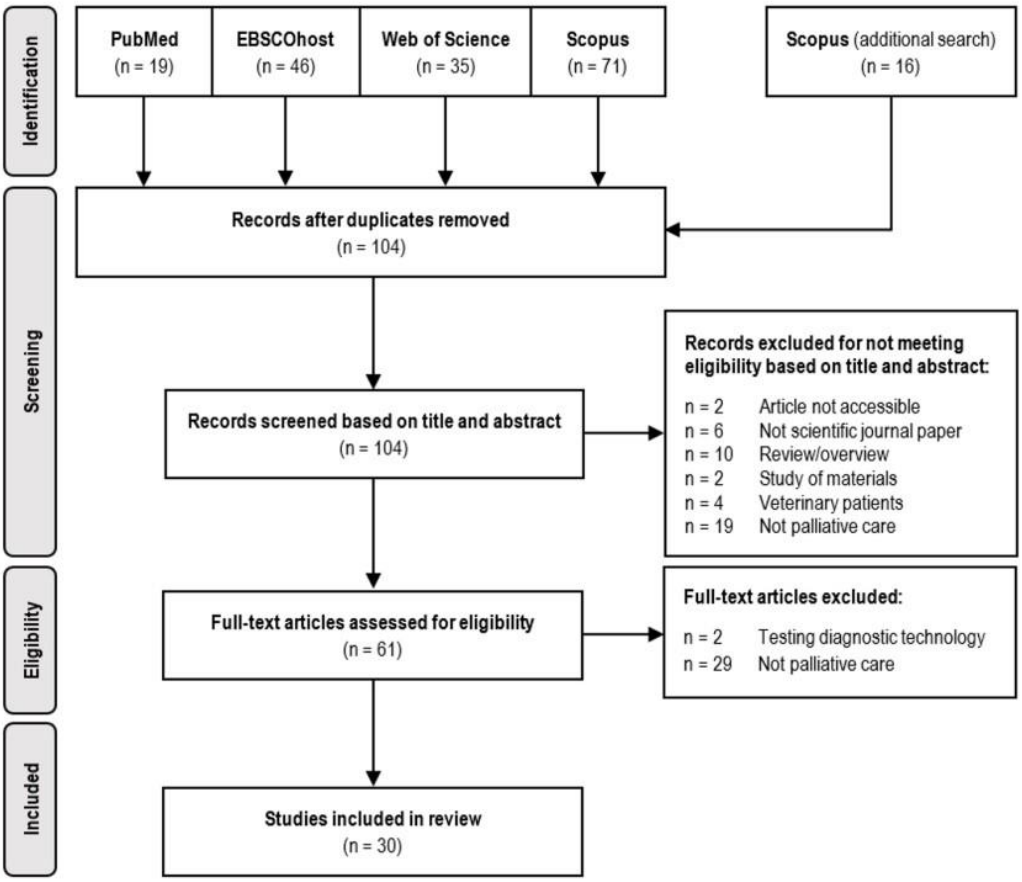


Figure 17: PRISMA flow diagram of literature search and study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

4.4.2. Data extraction and synthesis

The following data were extracted from the selected studies: 1) field of application of 3DP in palliative care, type of 3D-printed device, its stage of development and application; 2) technology used for device fabrication including 3DP technology, 3D-printer make, material, imaging technique, software utilised; and 3) testing of the 3D-printed device, including number of participants, age and medical status, testing method, and outcomes of intervention. 3D-printed device manufacturer, print time and cost were also reviewed.

4.5. Results

4.5.1. Overview

Thirty relevant papers on the use of 3DP in palliative care were identified and included in the review. The first study was published in 2004, and 20 papers were published in the last 3 years, as shown in Figure 18.

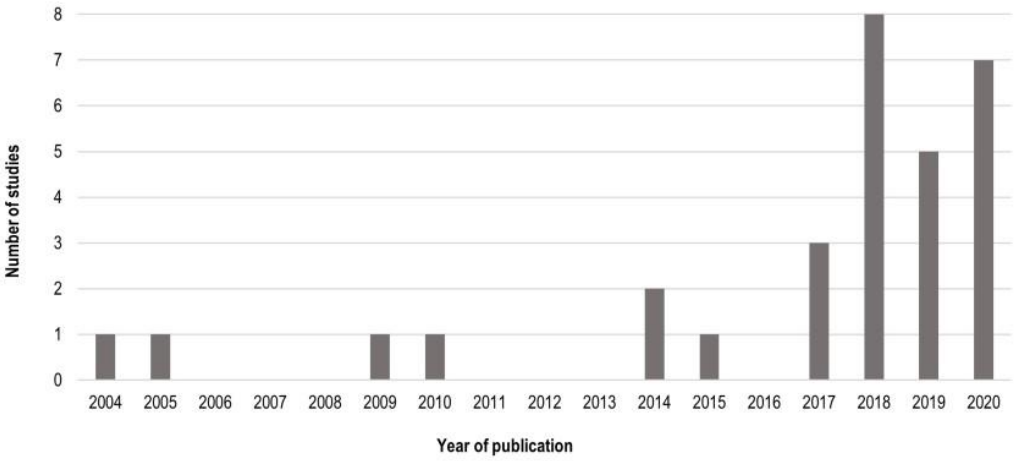


Figure 18: Reviewed studies involving the use of 3DP in palliative care by year of publication. 3DP, three-dimensional printing.

4.5.2. Device type and field of application

3DP was applied to different medical sub-specialties within oncology, predominantly gastrointestinal, orthopaedic and radiation oncology. Only 3 devices were produced for non-oncological applications (Figure 19).

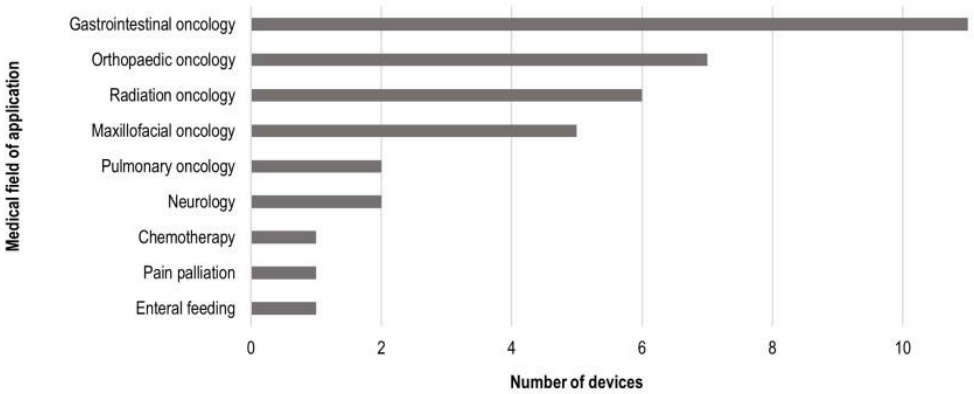


Figure 19: Fields of application of 3DP in palliative care. 3DP, three-dimensional printing.

In the 30 reviewed studies, 36 different devices were produced (Supplemental Table). The most common were endoluminal stents (9), however all were used in proof-of-concept studies. Other most commonly 3D-printed devices were anatomical models (6), brachytherapy navigation guides (5), endoprostheses (including one mould; 4), epithesis casts and moulds (3), and obturator casts (2). In single cases, an injection-moulding chamber, surgical cutting guide, PEG-tube sealing device, respirator mask and positive mould, scaffold for chemotherapeutic delivery, and a robot for ultrasound pain palliation were manufactured. Figure 20 summarises the purpose of the devices.

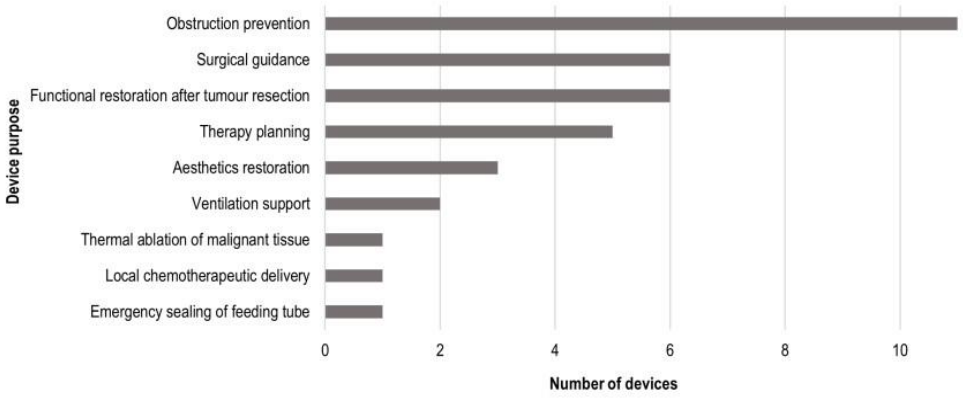


Figure 20: Purpose of the reviewed 3D-printed devices in palliative care. 3D, three dimensional.

4.5.3. Problems addressed by 3DP

The most common purpose of 3DP was to improve the accuracy and/or efficiency of treatment achievable with traditional methods (13 devices). Seven of the thirteen devices were intended to improve the accuracy of drug delivery, two were endoluminal stents with improved patency or drug distribution, and one was an anatomical model for improved surgical planning. A further 3 devices were used to address the lack of efficiency in the traditional method (i.e. 1 cutting guide, 1 endoprosthesis, 1 obturator mould). In 6 studies, 3DP was chosen to address the difficulty of device customisation with traditional methods, including endoluminal stents (3), endoprosthesis (1), epithesis (1),

and respirator mask (1). In 2 studies, 3D-printed anatomical models were used to address difficulties of spatial anatomy comprehension from 2-dimensional images. Four devices were used to reduce the risks for patients associated with conventional methods, and one anatomical model was used as an alternative to human testing (Figure 21).

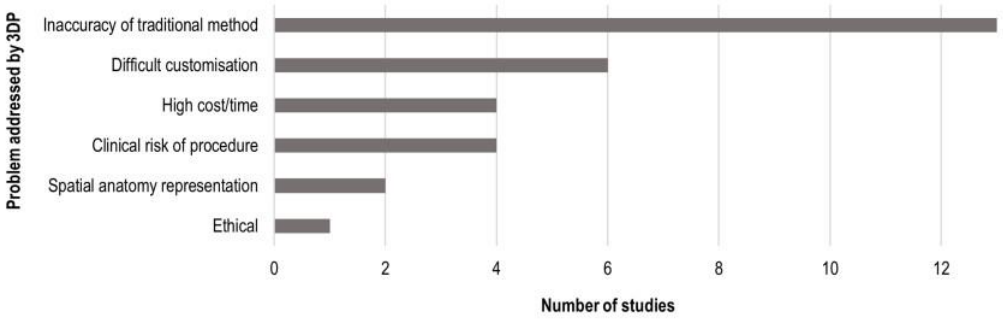


Figure 21: Problems addressed by 3DP in the reviewed studies. 3DP, Three-Dimensional Printing

3DP was used with the intention to reduce the cost and manufacturing time of 2 epitheses and 2 endoluminal stents. Time-efficiency was reported in four studies: the print times ranged from 516 to 36 hours, and 2 studies highlighted the potential for delivering custom 3D-printed devices to patients within 24 hours (Chu Sing *et al.* 2004; O'Sullivan *et al.* 2018; Pham *et al.* 2018). Cost-effectiveness of 3DP was emphasized in two cases ($30 for a head mould to replace a $200-400 CT scan and a $5 custom-fit BiPAP mask16), and one study considered the price disadvantageous ($500 for materials and printing of an obturator definitive cast) (Pham *et al.* 2018; Palin *et al.* 2019).

4.5.4. 3D printing technology

Thirteen devices were manufactured using Fused Filament Fabrication (FFF), (Ciocca *et al.* 2009; Ciocca *et al.* 2010; Ali *et al.* 2014; Karyakin *et al.* 2017; Menikou *et al.* 2017; Ahangar *et al.* 2018; Pham *et al.* 2018; Boyer *et al.* 2019; Lin *et al.* 2019; Fouladian *et al.* 2020; Jang *et al.* 2020; Ha *et al.* 2021) one of which used a custom built FFF gantry specifically designed for the orbital

printing of stents (Al-Zogbi *et al.* 2021). Six devices were produced using Stereolithography (SLA) (Chu Sing *et al.* 2004; Chiang *et al.* 2005; Huang *et al.* 2018; Boyer *et al.* 2019), five using Material Jetting (MJ) (Jiao *et al.* 2014; O'Sullivan *et al.* 2018; S. Choi *et al.* 2019; Q. Han *et al.* 2019; Palin *et al.* 2019), two using Selective Laser Sintering (SLS)(Chu Sing *et al.* 2004; Boyer *et al.* 2019) and in single cases, Direct Metal Laser Melting (DMLM)(Efetov *et al.* 2020) and Electron Beam Melting (EBM)(Boyer *et al.* 2019) were employed. One study reported the use of Selective Laser Lithography (Pruksakorn *et al.* 2015) (the authors of the present review are unfamiliar with this technology). In 7 studies, 3DP technology was not specified; however, 4 of these detailed the type of material used (i.e. photopolymer resin, medical resin, and PMMA).

Ten of the reviewed papers did not detail the material employed. Across the other studies, the most common materials were photopolymer resin (including Flexible Resin, MED610, Tango family and VisiJet C4 Spectrum Core; 8) used with MJ or SLA, and Acrylonitrile Butadiene Styrene (ABS; 6) used with FFF. Also employed were Polycaprolactone (PCL, including in combination with Paclitaxel – PCL/PTX; 2), Polylactic acid (PLA, including in combination with Thermoplastic Polyurethane – PLA/TPU; 2), Polymethyl Methacrylate (PMMA; 2), Polyvinyl Alcohol (PVA, including in combination with TPU – TPU/PVA; 2), Titanium alloy (2), and Polyurethane (PU; 1).

Patient-specific devices were mainly reverse-engineered, which involved surface 3D scanning or CT/MR imaging, and designing the device based on the digital data of patients' anatomy. Devices that were directly designed included 9 endoluminal stents, not tested on patients, a coplanar navigation guide, PEG tube sealing device, scaffold for chemotherapeutic delivery, and robotic system for ultrasound palliation of pain. Unlike RE, these devices were designed independently of the specific patients' anatomy. Indirect AM was used to

create moulds for obturators, epitheses and respirator masks manufactured from silicone; the other devices were directly 3D-printed.

4.5.5. Clinical testing

Eleven papers described proof-of-concept studies that did not involve testing of the devices on human participants. Eight of these were studies of endoluminal stents, one was a phantom model, one a scaffold for chemotherapeutic delivery, and one was a robot for ultrasound pain palliation. In the remaining 19 studies which did include human testing, the number of participants ranged from 1 to 92. The most substantial participant groups were recruited in studies of brachytherapy navigation guides (25-92 participants) (S. Choi *et al.* 2019). The only study that included a control group was of a coplanar navigation guide that was tested on 25 participants (Huang *et al.* 2018). Ten articles were case reports describing the use of 3D-printed devices for clinical care.

The devices were tested using objective methods in 18 studies, 15 of which produced quantitative results and 2 qualitative. Eight studies used qualitative subjective methods. Two studies used a combination of subjective and objective methods, and two did not report any testing of the device.

4.5.6. Outcomes and interventions

All reviewed studies reported generally favourable outcomes. Eleven studies confirmed the feasibility of their concept. Nine of these developed endoluminal stents that showed promising results regarding mechanical and drug-eluting properties (Chu Sing *et al.* 2004; Baltz *et al.* 2019; Boyer *et al.* 2019; Fouladian *et al.* 2020; Jang *et al.* 2020; Al-Zogbi *et al.* 2021). It was also reported that such stents could be delivered to patients within 24 hours or over a weekend at a relatively low cost (Chu Sing *et al.* 2004; Chiang *et al.* 2005). In the other proof-of-concept studies, stent abutment was proven to cause

prolonged passage of soft and solid diets;(S. Choi *et al.* 2019) a scaffold for chemotherapeutic delivery was shown to significantly reduce the viability of prostate cancer cells (Ahangar *et al.* 2018); and MRI safety and compatibility were verified for an ultrasound pain palliation robot (Menikou *et al.* 2017).

Anatomical models produced positive outcomes in therapy and surgical planning. They demonstrated high concordance rate with diagnostic accuracy of invasive procedures (F. Han *et al.* 2019), and facilitated joint-preserving posterior acetabular resection (Heunis *et al.* 2019). In one study, an uncommon anatomical feature was detected that was not recognised in 2D images, but had an important effect on the intraoperative approach (Templin *et al.* 2020). Head models were produced with satisfactory accuracy to make immobilisation masks without the need for additional patient visits, which lowered treatment costs (Pham *et al.* 2018).

All brachytherapy navigation guides were successfully used, with occasional minor side effects related to the treatment itself. One study included a control group and found significantly higher dosimetry values in target tissues when navigation guides were used (Huang *et al.* 2018).

In general, the fit of patient-specific obturators was satisfactory, and few problems were reported in individual cases (e.g. leakage while drinking liquid, nasal voice, numbness, dry mouth) (Jiao *et al.* 2014). Patients' pronunciation, mastication and swallowing were improved, nasal regurgitation was prevented, and the overall psychological and social wellbeing was enhanced (Jiao *et al.* 2014; Palin *et al.* 2019).

Epitheses demonstrated the possibility of improving the patients' quality of life and comfort, both semi-functionally and aesthetically (Ciocca *et al.* 2009). A nasal prosthesis was produced in shorter time and at lower cost compared to traditional techniques (Ciocca *et al.* 2010). Endoprostheses for palliative

orthopaedic reconstruction were successfully implanted, with significant postoperative pain reduction and improved function of the limb (Karyakin *et al.* 2017), and with no cases of poor outcome, severe complications, endoprosthesis failure or migration (Pruksakorn *et al.* 2015; Karyakin *et al.* 2017; Boyer *et al.* 2019; Efetov *et al.* 2020). A PEG-tube sealing device enabled recommenced feeding regime without leakage within 24 hours from the clinicians' request (O'Sullivan *et al.* 2018). Finally, the vast majority of patient-specific respirator masks were rated higher than generic masks in all aspects of comfort, leakage, preference, recommendation and tolerance (Huang *et al.* 2018).

When referring to the technology employed, the term '3D printing' was most often used (25), followed by 'three-dimensional printing' (14), 'rapid prototyping' (12), 'additive manufacturing' (7), and 'computer aided manufacturing' (4).

4.6. Discussion

4.6.1. The use of 3DP in palliative care

This review identified certain trends in the use of 3DP for the purposes of palliative care. The first study was published in 2004, and two thirds of the reviewed papers were published after the year 2017. This indicates a considerable increase in the use of 3DP in palliative care in the last few years, which could be directly related to the release/expiration of 3DP patents. Between 2009 and 2014, the original patents for FFF and SLA expired, leading to the expansion of the 3DP market and subsequent decrease of 3DP entry cost (Hormick 2013). It is likely that the increase in publications presented in this review is directly related to the democratisation of 3DP. The most prominent fields of application that included clinical testing were radiation oncology (brachytherapy navigation guides) and orthopaedic oncology

(anatomical models and endoprostheses). These studies also involved the largest numbers of participants. Brachytherapy navigation guides were among the simplest devices manufactured by 3DP in the included studies, making them relatively easy to implement across a larger number of patients. Anatomical models are relatively easy to make, derived from existing medical imaging, with no ethical constraints or need for regulatory approval, being used for training/education purposes with no body contact, implanting or any procedure directly impacting the patient. 3DP has been used to manufacture anatomical models dating as far back as the early 1990s, recently becoming a more familiar and accessible medical application of 3DP (Mankovich *et al.* 1993). Comparably, there have been enough studies to verify 3DP as a go-to technology for endoprostheses and surgical guides. In a review of 3DP techniques in a medical setting in 2016, surgical guides were listed as the most common devices produced (60%), followed by anatomical models for surgical planning (38.7%) and implants (12.7%) (Tack *et al.* 2016).

4.6.2. Clinical aspects of 3DP in palliative care

Roughly two-thirds of the reviewed studies reported the outcomes of 3DP-assisted procedures, and one third were proof-of-concept studies. In general, the clinical outcomes were considered superior to those of conventional approaches. However, only one study (coplanar navigation guide) included a control group that received the treatment without the device (Huang *et al.* 2018). The lack of a control group can impair the validity of the conclusions drawn, as it is uncertain to what extent clinical results can be attributed solely to the use of the 3D-printed device.

In recent years, 3DP is becoming common practice to treat medical conditions that require highly-customised solutions (e.g. reconstruction after extensive resection in orthopaedic oncology) and/or high-precision treatment (e.g. brachytherapy of unresectable visceral tumours). It can also be used to create

devices that do not otherwise exist (e.g. a PEG-tube sealing device (O'Sullivan *et al.* 2018)) or are difficult to produce with traditional approaches (e.g. obturator for patients with trismus (Jiao *et al.* 2014)).

4.6.3. Technological guidelines for 3DP use in palliative care

4.6.3.1. The choice of 3DP technology

In the reviewed studies, 3DP was predominantly used to overcome the difficulties of producing customised devices with traditional methods. FFF was the most commonly used 3DP technology (13 of the reviewed devices, including anatomical models and oesophageal stents). Despite the poor surface finish with an apparent staircase effect typical for low-resolution desktop FFF printer, it is favoured for its low cost, versatility and wide range of available thermoplastic filaments, allowing clinicians to match material characteristics of the devices with their function (Ciocca *et al.* 2010). However, in the studies reviewed, there was little evidence of correlation between the type of medical device produced and the choice of 3DP technology, which suggests that 3DP technology was selected based on availability to the clinician rather than its suitability for the specific device. This suggests that some or many 3D-printed medical devices are produced using sub-optimal methods due to the lack of funding, accessibility or familiarity with the technology. Table 2 provides a brief overview of the specifications of 3DP technology to inform future clinical practice (Redwood *et al.* 2017; González-Henríquez *et al.* 2019; Al-Dulimi *et al.* 2020; Quan *et al.* 2020).

Table 2: Overview of key characteristics of the most common 3DP technologies and materials (compiled by Kermavnar et al)

	FFF	SLA	DLP	MJ	SLS
Overall cost	Low	Medium	Low	Very high	High
Desktop printers	Yes	Yes	Yes	Yes	Yes
Accuracy	Low	High	High	High	High
Resolution	Low	High	Very high	Very high	Medium
Surface finish	Staircase effect	Smooth	Smooth	Smooth	Grainy
Mechanical properties of printed parts	Satisfactory (anisotropy)	Satisfactory (brittle, affected by moisture and sunlight)	Satisfactory (brittle, affected by moisture and sunlight)	Satisfactory (brittle, affected by moisture and sunlight)	Very good
Complex designs	No	Limited	Limited	Yes	Yes
Multimaterial printing	Yes	No	No	Yes	No
Rigid biocompatible materials—examples	ABS-M30i, PC-ISO, PLA, PMMA, ULTEM™ 1010, ULTEM™ 9085	Accura ClearVue, BioMed Clear, Dental SG Resin, E-Shell 3000, NextDent SG, WaterShed XC 11122	Dental SG Resin, E-Shell 3000	MED610, VeroDent, VisiJet M2R-CL, VisiJet M3 Crystal	CAPA 6501, Duraform PA, EOS PA2200, EOS PEKK, PA 12, PCL
Flexible biocompatible materials—examples	TPU (Tecoflex)	Elastic 50A Resin, E-Guide Soft	E-Guide Soft	MED625FLX, VisiJet M2E-BK70	TPU

ABS, Acrylonitrile Butadiene Styrene; DLP, Digital Light Processing; 3DP, Three-Dimensional Printing; FFF, Fused Filament Fabrication; MJ, Material Jetting; PA, Poly Amide (Nylon); PC, PolyCarbonate; PCL, PolyCaproLactone; PEKK, PolyEtherKetoneKetone; PLA, PolyLactic Acid; PMMA, PolyMethyl MethAcrylate; SLA, StereoLithograPhy; SLS, Selective Laser Sintering; TPU, ThermoPlastic Urethane.

When cost and accessibility are the main concerns, FFF technology is usually opted for, not MJ or SLS. For example, the head mould for radiotherapy immobilization mask would be too expensive to manufacture using other technologies, and the proof-of-concept studies of stents used FFF possibly due to accessibility for research purposes. For devices in direct contact with the skin or mucosa, such as obturators, smooth surface finish is often important, and thus SLA, DLP or MJ are favoured. Likewise, the surface finish of epitheses should resemble the texture of skin, which cannot be achieved with FFF, as pointed out in a study of a nasal epithesis (Ciocca *et al.* 2010). Similar to surface finish, FFF would be rejected for accuracy and resolution in place of MJ, DLP, SLA or SLS, especially when producing highly-detailed parts, such as the thread of the PEG-tube sealing device, or implants.

4.6.3.2. The choice of 3DP materials

Half of the reviewed papers did not detail the material employed. Across the other studies, the most common material, ABS, is used largely for moulds for its high strength, toughness and impact resistance, flexibility, durability, and temperature resistance which allows for mould reusability (Ciocca *et al.* 2010; Tan *et al.* 2020; Al-Dulimi *et al.* 2021). For other FFF applications, PLA can be favoured over ABS due to its biodegradability, accessibility and price (Pham *et al.* 2018). PCL is used to manufacture endoluminal stents because of its biocompatibility and bioresorbability (Al-Zogbi *et al.* 2021). Similarly, biocompatibility is the reason for using MED610 for devices that are expected to stay in prolonged contact with the patient's skin (O'Sullivan *et al.* 2018). Endoprostheses for palliative purposes can stray from the typical use of titanium alloys (Q. Han *et al.* 2019; Efetov *et al.* 2020), as integration between the host bone and endoprosthesis is not expected in patients with bone metastases (Q. Han *et al.* 2019; Efetov *et al.* 2020). In this case, PMMA can be employed as an alternative 3D-printable biocompatible material that is generally available and sufficiently strong to replace non-weight bearing bone, while also being more cost-efficient (Velu and Singamneni 2014; Pruksakorn *et al.* 2015).

Navigation guides for brachytherapy should be safe for skin contact, and are mainly fabricated from photopolymer resins. A common issue with photopolymer resins is the cytotoxicity of the raw material, therefore, a careful balance in its composition is required to preserve printability and ensure safety for use (Aniwaa 2021). Among the most versatile biocompatible polymers used with photo-curing techniques are acrylate- and methacrylate-based resins (Al-Dulimi *et al.* 2020).

4.6.3.3. Manufacturing approaches

Patient-specific devices are reverse-engineered by using digital data (3D/CT/MRI) of patients' anatomy, as opposed to being directly designed. Indirect AM can be used to create moulds for devices that need to be manufactured from non-printable materials, e.g. silicone, like obturators and epitheses. 3DP materials approved for human use with similar properties to silicone are scarce, and most biocompatible silicone resins are not yet commercially available (Aniwaa 2021). Among those currently on the market, 3D-Bioplotter UV Silicone 60A MG (EnvisionTEC) is a transparent medical grade silicone, approved for 29-day direct skin contact, characterised by medium hardness, no odour, and the possibility of colouring prior to printing (EnvisionTec). Similarly, TrueSilTM (Spectroplast AG) is biocompatible and available in different hardnesses for different applications (e.g. mouthpieces, insoles, earbuds, prosthetics) (SpectroPlast). Elastic Resin (Formlabs) mimics casted silicone well, but it is not biocompatible (Formlabs 2019b).

4.6.4. Regulatory aspects of 3DP in medicine

Currently, 3D-printed medical devices must conform to the same regulations as those that are manufactured using traditional methods. The regulations vary across different countries (e.g. Regulation (EU) 2017/745 on Medical Devices – MDR(2017) in the European Union; Title 21 Code of Federal Regulations – 21 CFR(U.S. Food and Drug Administration 2016) in the United States), and have been extensively reviewed in other literature (Tsuyuki *et al.* 2016; Horst 2020). The standard approval process for new medical devices tends to be lengthy, requiring several years of preclinical and clinical testing. As this can present a substantial barrier to urgently treating rare, life-threatening, or severely debilitating medical conditions, not uncommon in palliative care, non-standard regulatory pathways have been established for rapid approval of medical devices in exceptional circumstances. These pathways allow for clinicians

and/or manufacturers to apply for exemptions to use non-certified medical devices on humanitarian grounds. The use must be justified through a significant reduction in mortality or morbidity compared to alternative compliant treatments, and applications are assessed on a case-by-case basis.

The vast majority of studies included in the present review did not detail the regulatory frameworks followed. An overview of the regulatory aspects applicable is provided in the authors' previous systematic review of 3D-printed medical devices used on patients (Kermavnar *et al.* 2021). Especially when bespoke medical devices are 3D-printed to be used without prior testing under the abovementioned humanitarian exemptions, it is of utmost importance that an appropriate quality management system is in place, which can ensure that appropriate technologies and materials (e.g. certified biocompatible materials) are employed in the printing process, and that the post-processing requirements are met to warrant mechanical, chemical and biological safety of the end product (Guidance 2017).

4.6.5. 3DP and design collaboration

This systematic review highlights how 3D printing can potentially be used as part of a design process to address previously unmet clinical needs for which current solutions are either not available or not suitable. The majority of the studies indicated authorships which were interdisciplinary, typically between clinical and design/technical groups. The papers typically focused on the clinical problems and the reporting of the solutions obtained, and therefore, it is not possible to ascertain and synthetise the desgin processes followed across the studies. The current authors anecdotal experience is that clinicians sometimes issue requests to research groups in universities for design assistance with very specefic clinical challenges. Arising from these requests clinical design collaborations are initiated which often form the basis of follow-on 3D printing/innovation research. By way of example, we previously reported

on a clincal request to our group for assistance to produce an alternative eye cover for a teen with Rhabdomyoscarcoma (O'Sullivan *et al.* 2021). Access to 3D printing was not part of the initial request but was used by the design group to make the solution. Arising from the engagement the local palliative care clinical team and the design group thereafter established other research opportunites regarding 3DP in pallaitve care. Hence, once initial experience is established, then follow-on design interactions using 3d printing are made possible.

Our experience is that some clinicians have experience in 3D printing, either through previous clinical innovations or due to access to promoted clinical based 3D printing programs. In these situations such clinicians may develop their own concepts for which their key requirement thereafter is access to designers to collaborate in refining the design and print the concepts/devices.

4.6.6. Limitations

There may be other studies not identified by our systematic search due to the terminology issues addressed above, thus it is possible that some 3D-printed devices intended for palliative care were not included in this review. Moreover, the identified cases of palliative correction of congenital heart defects typically managed by cardiologists were excluded. Nevertheless, the authors expect the key findings of the present work to be a reasonably complete reflection of the current state regarding the use and potential for increased use of 3DP in the provision of care to patients with palliative care needs.

4.7. Conclusions

This systematic review revealed the use of 3D printing in palliative care for approximately two decades, with a considerable increase in its use since 2017. Reviewed were 36 devices produced across 30 studies. The device type, field

of application, problem addressed, technology used, clinical testing methods, and the outcomes of intervention were analysed.

The most common proof-of-concept devices were endoluminal stents, and the most common devices that included clinical testing were anatomical models, brachytherapy navigation guides, and endoprostheses. Of the 3DP technologies, FFF was most frequently employed, followed by SLA and MJ. In most of the studies that specified the material used, ABS was chosen, mainly for creating moulds, followed by unspecified photopolymer resins. The majority of devices were designed using reverse engineering to correspond to the patient's anatomy. The outcomes of interventions were generally favourable, and the difficulties associated with conventional procedures were successfully overcome. 3DP was found especially valuable in the treatment of medical conditions that require highly-customised solutions and/or high-precision procedures, while also ensuring cost- and time-efficiency. With 3DP, entirely new devices can also be created for rapid response to unique clinical situations.

Chapter 5: Biocompatible 3D printing resins for medical applications: A review of marketed intended uses, biocompatibility certification, and post-processing guidance

Publications associated with this chapter:

1. Guttridge, C., Shannon, A., O'Sullivan, A., O'Sullivan, K.J. and O'Sullivan, L.W. (2021) 'Biocompatible 3D printing resins for medical applications: a review of marketed intended uses, biocompatibility certification, and post-processing guidance', *Annals of 3D Printed Medicine*, 100044.

5.1. Abstract

Over the last thirty years, there has been an increase in the adoption of 3D printing by the medical community to create devices for patients that require a custom and rapid solution. In turn, a demand has been created for a variety of specifically engineered biocompatible materials. The aim of this study was to review the information provided with biocompatible photosensitive resins, with regards to their intended uses, cited biocompatibility certifications, and post-processing technique, and arising from this detail challenges for users when making an informed and safe decision regarding material selection.

A primary level search was performed collecting only information from the grey literature available from the websites of manufacturers marketing biocompatible photosensitive resins for 3D printing. Only materials that were stated as biocompatible were included in the study.

The results presented a large range of biocompatible materials with varying intended uses. The majority of materials were specifically for dental applications, followed by general medical use, then specific medical applications. A lack of standardisation was noted with regards to the amount and quality of information that is provided with the materials, therefore, due-diligence should be performed by the user when selecting a material for their specific application.

5.2. Introduction

The application of 3D printing in medicine continues to grow, both in volume and diversity of applications. (Nicholas *et al.* 1993) 3D printing has predominantly been used for the making of anatomic models (60%) and surgical guides (38.7%), with such examples as far back as the 1990's as presented by Tack et al. in their review of 3D printing techniques in medical settings (Tack *et al.* 2016). In the last 5-10 years, there has been a large increase and movement towards the use of the technology for directly treating patients (Chen *et al.* 2016; Girolami *et al.* 2018; Nuseir *et al.* 2019; Kermavnar *et al.* 2021). 3D printing has the ability to rapidly create custom devices which has been adopted by areas of the medical community that require a custom solution. Examples include Endoprostheses (Efetov *et al.* 2020), temporary dental crowns (Li *et al.* 2018), epitheses (Ciocca *et al.* 2010), endoluminal stents (Jang *et al.* 2020), maxillofacial guides (Jiao *et al.* 2014), treatment templates (Jiang *et al.* 2018) and bespoke repairs (O'Sullivan *et al.* 2018). A recent review by Kermavnar et al. of 3D printing used to directly treat patients detailed the most common use of 3D printing to manufacture medical devices were in the fields of orthopaedics (37%) and orthopaedic oncology (33%), followed by maxillofacial surgery (7%) and neurosurgery (4%) (Kermavnar *et al.* 2021). With that, there are many new applications of the technology emerging. Currently, 3D printing methods offer a range of materials from metals, thermoplastics, photosensitive resins, organics and ceramics. This study specifically focusses on the use of photosensitive resins for vat-polymerisation and resin jetting techniques.

Whilst vat-polymerisation printing techniques are very similar in terms or technology, gantry and method, they do have key technological differences, such as light source, light source wavelength and exposure duration. These aspects must be specific to the resin being used to ensure that the resin fully

transitions from a liquid to a solid. (Ng *et al.* 2020) Therefore, in this study, the varying techniques of vat-polymerisation method are detailed separately.

There are clear regulatory requirements regarding the design and manufacture of traditional medical devices in order to ensure patient safety. Normally, medical devices are manufactured in an industrial production facility with a system of validation, verification and control methods in accordance with quality management systems, such as ISO 13485. However, there is relatively little guidance regarding regulatory requirements for the use of polymer based 3D printing techniques in medicine as a mainstream method to produce medical devices. At present, what guidance is available, is focused predominantly on emergency and humanitarian applications. With the move towards 3D printing of medical devices to directly treat patients, there has recently been increasing attention to developing regulatory guidance in this respect. This requires scrutiny of biocompatible aspects relative to their end uses.

Due to the increase in the use of 3D printing for medical devices to directly treat patients, there is a demand for new materials that provide a variety of biocompatible characteristics for different potential applications. Biocompatible is an umbrella term for materials specifically engineered to interact with living tissues without causing an immunological response (Remes and Williams 1992). The definition of a biocompatible material refers to the materials ability to perform with an appropriate host response i.e. if a material's intention is to be used in contact with skin for 24 hours, the material must be certified to remain chemically stable and not cause an immunological response for that duration. (Remes and Williams 1992; Barrère *et al.* 2008) There are many facets to the term biocompatible depending on the intended use. For example, a material could be biocompatible for one or a number of

immunological or toxicological responses e.g. skin irritation and sensitisation, cytotoxicity, reproductive toxicity etc. (Anderson 2001).

Biocompatible materials must be tested and certified with reference to the properties marketed by the manufacturer. The regulatory body for medical device manufacturing in Europe is the International Organisation for Standardisation (ISO). The applicable standard ISO 10993 (Biological Evaluation of Medical Devices)(ISO 2001) includes 22 sections addressing a series of reactivity tests, quality management processes and risk categorisation standards. The intended use of a 3D printed medical device should determine which tests from the standard are applicable. Devices do not necessarily have to comply with all tests in the standard, however, the user must determine the biocompatible requirements as per their intended use and purchase materials which meet those requirements. The equivalent standard in the US is USP VI (the classification of plastics, biological reactivity tests in vivo), regulated by the U.S. Pharmacopeial Convention, which includes three reactivity tests that must be passed to gain class 6 certification (USP). The three *in vivo* biological reactivity tests are as follows: acute systemic toxicity (systemic injection) test, intracutaneous test and the implantation test. Again, the end user must purchase materials which comply with the biocompatibility requirements for their end use.

Resin manufacturers choose which biocompatibility tests they seek certification for, and should only market those materials according to their corresponding intended uses and certification. In some circumstances resins are broadly marketed by manufacturers as biocompatible, but are supplied with either little or no detail of the specific intended uses or related certifications. In order to achieve biocompatibility in use, it is the responsibility of the user to ensure best practice is used throughout the process by implementing a system of validation and control. The user is required to ensure

they use technology and materials which meet the medical device regulations. In the context of applying 3D printing to manufacture medical devices to treat patients, the user has an obligation to ensure they source certified materials corresponding to that use. The manufacturer is required to present information regarding the marketed use of the material, and with that details of the corresponding certification compliance for that intended use.

Studies indicate that for some common 3D printing resins, toxicity has been recorded after post-processing in its fully cured state (Macdonald *et al.* 2016; Oskui *et al.* 2016; Alifui-Segbaya *et al.* 2017; Walpitagama *et al.* 2019; Rogers *et al.* 2021). In one case these effects have been shown to cause reproductive toxicity and genetic mutations, highlighting the need for care (Rogers *et al.* 2021). Certified resins are expected to perform as tested as long as they are printed and post-processed in accordance with the protocols provided by the manufacturer. If an end user deviates from the manufacturer's protocol, then the biocompatible properties may also deviate. In order for a material to maintain biocompatible properties as per the certification, the manufacturer should provide clear guidance regarding printing and post-processing requirements for the user to follow. The user must adhere to these steps and apply them accordingly with respect to their device's anatomy.

The aim of this study was to perform a review of information available to users for making an informed decision regarding selection of biocompatible resins for 3D printing medical devices. This study specifically focused on photosensitive resins as the literature demonstrates increased use of this material form for these applications. We reviewed commercially available biocompatible photosensitive 3D resins in the grey literature regarding marketed intended uses, stated compliance with associated relevant sections of ISO 10993 or USP VI, and post-processing guidance. This review was performed on the biocompatible resin market of 2021.

5.3. Method

A primary level online search was performed of the grey literature during March 2021 using the Google advanced search tool to identify biocompatible photosensitive resins for 3D printing. The grey literature was searched as this is the primary method manufacturers advertise and provide information of their products currently on the market. The search string used was; '"3D print*" or "3D-print* or "3D" and "biocomp*" or "bio-comp*" and "resin". Only materials that were marketed as biocompatible were included in the review. If a biocompatible material was identified, the manufacturer's website was keyword searched for the term 'biocompatible' to collect all relevant materials. All materials had to be commercially available. The specific information recorded was: material name, printing method, manufacturer intended use, post processing information and certification details. A total of 130 biocompatible materials meeting these criteria were identified. The results were separated for rigid and flexible materials.

Information regarding material intended use applications was obtained from text of materials advertisements. If a material specifically mentioned an application or device, this was recorded under intended use. If not, then the key characteristics were recorded and categorised as 'general medical use'.

The extracted data were taken only from publicly accessible pages, material datasheets and 'fill-out' forms from the manufacturer's website. Fill-out forms were also used to make enquiries with manufacturers. With the exception of this, no direct contact was made with the manufacturers to request further information. Also noted were phrases describing the nature of compliance, such as 'capable', 'compliant' or 'compatible' which were often used. The range of quality, consistency, and amount of post-processing information is addressed generally in the discussion.

5.4. Results

Table 3 4 detail the results of the review for rigid and flexible biocompatible photosensitive 3D printing resins, respectively. The review identified in total 99 rigid materials and 31 flexible materials. Regarding rigid materials, the manufacturer with the greatest number of biocompatible marketed materials was 3D Systems (12) followed by Detax (10), Formlabs (10), PrintoDent (9) and Next Dent (8). The printing methods ranged from DLP (46), SLA (14), MJP (6), Polyjet (4), LCD (5) and DLS^{TM} (5). Nineteen materials were available as a tailored option, allowing users to choose the compatible resin for their printing method. Regarding flexible materials, the manufacturer with the greatest number of biocompatible materials was 3D Resyns (12), followed by Detax (4) and KeyPrint (3). Printing methods for these materials ranged from DLP (9), DLS^{TM} (2), SLA (1) and Polyjet (1). Eighteen materials offered a tailored option.

Table 3: Rigid biocompatible photosensitive resins

ID:	Manufacturer / Material / Printing Method:	Manufacturer intended use:	Manufacturer stated certification:
1	3D Systems / Accura ClearVue / SLA	Medical models and medical devices	USP Class VI
2	3D Systems / VisiJet M2R-CL / MJP	Transparent material with medical applications such as surgical guides	ISO 10993 [5, 10] / USP Class VI
3	3D Systems / VisiJet M2R - GRY / MJP	White opaque material with medical applications such as surgical guides	USP Class VI
4	3D Systems / VisiJet M2R-WT / MJP	Injection moulding like finish, applications for medical use i.e. surgical guides	ISO 10993 [5, 10] / USP Class VI
5	3D Systems / VisiJet M3 Crystal / MJP	Translucent material for rapid tooling and medical applications	USP Class VI
6	3D Systems / Figure 4 MED-AMB 10 / DLP	Medical devices, industrial applications. Thermal resistance	ISO 10993 [5, 10]
7	3D Systems / Figure 4 MED-WHT 10 / DLP	Medical devices, industrial applications. Sterilisable in autoclave.	ISO 10993 [5, 10]
8	3D Systems / VisiJet M2S-HT250 / MJP	Heat-deflection 250°C, gas flow, for tooling and manufacturing aids	USP Class VI
9	3D Systems / VisiJet M2S HT90 / MJP	Functional prototypes, medical devices with fine features and internal structures	USP Class VI (Capable)
10	3D Systems / Figure 4 PRO-BLK 10 / DLP	Injection moulding and soft tool processes	ISO 10993 [5, 10]
11	3D Systems / Figure 4 Rigid White / DLP	Smooth-surface medical devices, handles and fixtures for medical application	ISO 10993 [5, 10]
12	3D Systems / Figure 4 Tough 60C White / DLP	Clinical trials and medical devices such as tools, handles, and small plastic parts	ISO 10993 [5, 10] (Capable)
13	3D Resyns / BioTough D70 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
14	3D Resyns / BioTough D80 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
15	3D Resyns / BioTough D90 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
16	3D Resyns / BioTough D70 MF / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
17	3D Resyns / BioTough D80 MF / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
18	3D Resyns / BioTough D85 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
19	B9Creations / BIORES RED / DLP	Medical manufacturing, clinical and consumer tech	ISO 10993 [5, 10]
20	B9Creations / BIORES WHITE / DLP	Medical manufacturing, clinical and consumer tech	ISO 10993 [5, 10]
21	B9Creations / BIORES Micro Precision/ DLP	Prolonged skin contact (up to 30 days)	ISO 10993 [5, 10]
22	Carbon / CE 221 / DLS™	Strength, stiffness and temperature resistant	ISO 10993 [5]
23	Carbon / MPU 100 / DLS™	Biocompatible, sterilisable and chemically resistant	ISO 10993 [5 ,10] / USP Class VI
24	Carbon / RPU 70 / DLS™	High-strength , functional toughness and high ductility	ISO 10993 [5, 10]
25	Carbon / EPU 41 / DLS™	High elastic, tear resistant and energy returning	ISO 10993 [5, 10]
26	Carbon / EPU 40 / DLS™	High elastic, tear resistant and energy damping	ISO 10993 [5, 10]
27	Detax / FreePrint Denture / *Option	Dental use, removable denture bases, total prosthesis.	ISO 10993 [1] (Complies)
28	Detax / FreePrint Ortho / *Option	Drilling templates, orthodontic base components	ISO 10993 [1] (Complies)

29	Detax / FreePrint Splint 2.0 / *Option	Dental splints, fixation and transfer keys	ISO 10993 [1] (Complies)
30	Detax / FreePrint Temp / *Option	Dental temporary crowns & bridges, anterior and posterior tooth restorations	ISO 10993 [1] (Complies)
31	Detax / FreePrint Tray / *Option	Individual impression and functional trays, base resin plates	*Not Found
32	Detax / FreePrint Tray 2.0 / *Option	Individual impressions and functional trays, base plates for dental use	ISO 10993 [1]
33	Detax / LuxaPrint Mould / *Option	In ear monitoring, earmoulds, hearing protection and ITE shells	*Not Found
34	Detax / LuxaPrint Shell / *Option	ITE shells	*Not Found
35	Detax / MedicalPrint Mould / *Option	In ear monitoring, earmoulds, hearing protection and ITE shells	*Not Found
36	Detax / MedicalPrint Shell / *Option	In ear monitoring, foil-earmoulds, hearing protection and ITE shells	*Not Found
37	DSI / Crown & Bridge / LCD	Dental demonstration, models of crowns and bridges	ISO 10993 (Meets)
38	DSI / Gingiva / LCD	For dental demonstration models of gingiva	ISO 10993 (Meets)
39	DSI / Guide / LCD	Surgical dental guide modelling	ISO 10993 (Meets/Satisfies)
40	DSI / Master / LCD	Dental master resin for demonstrational and master-model printing	ISO 10993 (Meets)
41	DSI / Tray / LCD	Aligners, Surgical guides	ISO 10993 (Meets)
42	DWS / DS 3000 / SLA	Printing of dental impression trays, surgical guides,	*Not Found
43	DWS / DS 3500 / SLA	Printing of dental trays	*Not Found
44	DWS / Temporis / SLA	Custom fabrication of dental restorations (class IIa)	CE Class IIa
45	EnvisionTec / E-Guard / DLP	Splints and retainers	ISO 10993 [5,10]
46	EnvisionTec / E-Guide / DLP	High precision dental surgical guides	ISO 10993 [5,10]
47	EnvisionTec / E-Shell 200 / DLP	Hearing aid shells, otoplastics, medical devices (class II)	CE / ISO 10993
48	EnvisionTec / E-Shell 300 / DLP	Hearing aid shells, otoplastics (class IIa)	CE / ISO 10993
49	EnvisionTec / E-Shell 3000 / DLP	Hearing aid shells, otoplastics	CE / ISO 10993
50	EnvisionTec / E-Shell 600 / DLP	Hearing aid shells, otoplastics. Crystal quality	CE / ISO 10993
51	EnvisionTec / KeyOrtho IBT / DLP	Indirect bonding tray	*Not found
52	FormLabs / BioMed AMB / SLA	Short term skin/mucosal membrane contact, implant guides, fixation trays	ISO 10993 [1, 5, 10]
53	FormLabs / BioMed Clear / SLA	Long term skin/mucosal membrane contact	ISO 10993 [1,3, 5, 10, 17, 18] / USP Class VI
54	FormLabs / Custom Tray / SLA	Print impression trays for implants, dentures, crowns and bridges	ISO 10993 [1, 5, 10]
55	FormLabs / Dental Clear LT / SLA	Surgical guides, splints, fixed prosthetic and clear aligner models	ISO 10993 [1,3,5] (Compliant)
56	FormLabs / Dental Clear LT V2 / SLA	Splints and occlusal guards	ISO 10993 [1, 3, 5, 10, 11]
57	FormLabs / Dental Surgical Guide / SLA	Dental surgical guides and similar applications (class I)	ISO 10993 [5,10]
58	FormLabs / Permanent Crown / SLA	Permanent crowns, inlays, onlays and veneers	ISO 10993 [1, 3, 5, 10]
59	FormLabs / Surgical Guide / SLA	Implant guides and templates.	ISO 10993 [1, 5, 10]
60	FormLabs / Denture Teeth / SLA	Dentures	ISO 10993 [1]
61	FormLabs / Denture Base / SLA	Dentures	ISO 10993 [1]
62	KeyPrint / KeySplint Hard / *Option	For rigid dental splints, bite planes, mouthguards and night guards	CE / ISO 10993 [1] / FDA 510k
63	KeyPrint / KeyGuide / *Option	For fabricating transparent surgical guides	ISO 10993 [5,10]
64	KeyPrint / KeyOrtho IBT / *Option	Indirect bonding trays	ISO 10993
65	Mazic D / Surgical Guide / DLP	For guiding course and direction of implant/surgery equipment, drill sleeves.	ISO 10993 [1]
66	Next Dent / C&B MFH / DLP	Crown and bridges, stainable	ISO 10993 [1]
67	Next Dent / Denture 3D+ / DLP	Removable denture bases (class IIa)	ISO 10993 [1]
68	Next Dent / Ortho IBT / DLP	Orthodontic brackets and indirect bonding trays	ISO 10993 [1]

69	Next Dent / Ortho Clear / DLP	Splints and retainers	ISO 10993 [1]
70	Next Dent / Ortho Rigid / DLP	Digital manufacturing of splints (class IIa)	ISO 10993 [1]
71	Next Dent / SG / DLP	Surgical guides for dental implant surgery (class I)	ISO 10993 [1]
72	Next Dent / Tray / DLP	Printing of Multi dental trays	ISO 10993 [1]
73	Next Dent / Try-In / DLP	Try-in devices (class I)	ISO 10993 [1]
74	PrintoDent / GR-10 Guide / DLP	Printing of dental surgical guides	ISO 10993 [3,5,10,11]
75	PrintoDent / GR-11 Tray / DLP	Printing of customised dental trays	ISO 10993 [3,5,10,11]
76	PrintoDent / GR-14.1 Denture / DLP	Printing of custom fit dentures	ISO 10993 [3,5,10,11]
77	PrintoDent / GR-16 X-Ray DLP	Printing of radiopaque scanning templates	ISO 10993 [1,3,5,10]
78	PrintoDent / GR-17.1 Temporary It / DLP	Long term temporary dental restoration and denture teeth	ISO 10993 [3,5,10,11]
79	PrintoDent / GR-17 Temporary / DLP	Printing of temporary crowns and bridges	ISO 10993 [1,3,5,10,11]
80	PrintoDent / GR-19 OA / DLP	Printing of rigid orthodontic splints	ISO 10993 [3,5,10,11]
81	PrintoDent / GR-20 MJF / DLP	Printing of maxillofacial surgery devices	ISO 10993 [3,4,5,10,11]
82	PrintoDent / GR-21Try-In / DLP	Printing of try-in dentures	ISO 10993 [3,5,10,11]
83	SprintRay / IDB 2 / DLP	Printing of brace arches	FDA (Compliant)
84	SprintRay / IBD / DLP	Indirect bonding	FDA (Compliant)
85	SprintRay / Splint / DLP	Printing of splints with high flexural strength	FDA (Compliant)
86	SprintRay / Surgical Guide 2 / DLP	Accurate and distortion free implant guides	FDA (Compliant)
87	SprintRay / Try-In / DLP	For printing try-in dentures	FDA (Compliant)
88	Stratasys / MED610 / Polyjet	Medical applications requiring 30+ days skin contact 24 hours'	ISO 10993 [5,10,3,18] / USP VI
89	Stratasys / MED620 / Polyjet	Approved for temporary in-mouth placement for up to 24 hours	ISO 10993 [1]
90	Stratasys / VeroDent MED 670 / Polyjet	Printing of dental/orthodontic models	ISO 10993 [1]
91	Stratasys / VeroDent Plus MED690 / Polyjet	Printing of opaque dental/orthodontic models, e.g. crown and bridge work	ISO 10993 [1]
92	Voco / V-Print / DentBase / DLP	For production of denture braces for removable dentures	*Not Found
93	Voco / V-Print / Splint / DLP	For generative production of dental splints	*Not Found
94	Voco / V-Print / Splint Comfort / DLP	Generative production of thermoflexible dental, therapeutic splints, palatal plates.	*Not Found
95	Voco / V-Print / Surgical Guide / DLP	For printing of dental surgical guides	*Not Found
96	WhipMix / Verisplint OS / DLP	For printing rigid splints	CE / FDA 510k
97	WhipMix / Dentca Denture / DLP	Dentures	FDA clearance
98	WhipMix / Dentca Crown & Bridge / DLP	Crowns and bridges	FDA clearance
99	WhipMix / Surgical Guide / DLS™	Surgical drill guides	*Not Found

*Option (The manufacturer offers a selection of resins to match machine/method) - Digital Light Processing (DLP) – Digital Light Synthesis™ (DLS™) – Liquid Crystal Display (LCD) – Stereolitography (SLA) – Multi-Jet Printing (MJP)

Table 4: Flexible biocompatible materials

ID:	Manufacturer / Material / Printing Method:	Manufacturer intended use:	Manufacturer stated certification:
1	3D Systems / Figure 4 Rubber-BLK 10 / DLP	High tear strength and biocompatible – suitable for handles/grips	ISO 10993 [5,10]
2	3D Systems / Figure 4 Rubber-65a BLK / DLP	Mid tear strength production grade rubber	ISO 10993 [5,10]
3	3D Resyns / BioFlex MF ULWA UR A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
4	3D Resyns / BioFlex MF ULWA A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
5	3D Resyns / BioFlex MF UR A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
6	3D Resyns / BioFlex MF A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
7	3D Resyns / BioFlex MF ULWA UR A60 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
8	3D Resyns / BioFlex MF UR A60 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
9	3D Resyns / BioFlex MF ULWA A50 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
10	3D Resyns / BioFlex MF A50 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
11	3D Resyns / BioFlex MF ULWA A20 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
12	3D Resyns / BioFlex MF A20 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
13	3D Resyns / BioFlex MF ULWA A10 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
14	3D Resyns / BioFlex MF A10 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
15	Carbon / Sil 30 / DLS ™	Skin contact applications	ISO 10993 [5,10]
16	Detax / FreePrint IBT / *Option	Printing of flexible dental indirect bonding trays (class 1)	ISO 10993 [1] (Complies)
17	Detax / FreePrint SoftSplint / *Option	Printing of flexible dental splints	*Not Found
18	Detax / LuxaPrint Flex / *Option	For generative manufacturing of earmoulds	*Not Found
19	Detax / LuxaPrint Flex Coat / *Option	For generative manufacturing of soft hearing protection.	*Not Found
20	EnvisionTec / E-Shell 500 / DLP	Hearing aid applications	CE / ISO 10993
21	EnvisionTec / E-Guide Soft / DLP	Printing of impact resistant medical devices	ISO 10993
22	EnvisionTec / KeySplint Soft / DLP	Splints and nightguards	ISO 10993
23	FormLabs / IBT / SLA	Indirect bonding trays	ISO 10993 [1,3,5,10]
24	KeyPrint / KeySplint Soft Clear / DLS™	For printing splints, night guards and bleaching trays in Carbon DLS Systems	ISO 10993
25	KeyPrint / KeySplint Soft / *Option	Orthodontic and dental appliances such as bite planes, mouth guards	ISO 10993
26	KeyPrint / Keytray / *Option	Customised impressions trays (class I)	*Not Found
27	PrintoDent / GR-18.1 IBT / DLP	Printing of orthodontic indirect bonding trays	ISO 10993 [5,10]
28	PrintoDent / GR-22 Flex / DLP	Printing of splints with high elastic properties	ISO 10993 [3,5,10]
29	NextDent / Ortho Flex / DLP	Dental Splints and retainers	ISO 10993 [3,5,10,11]
30	NextDent / Ortho IBT / DLP	Indirect Bonding Tray (class I)	ISO 10993 [1]
31	Stratasys / MED625FLX / Polyjet	Flexible medical devices requiring 30+ days skin contact, 24 hour mucosal	*Not Found

5.4.1. Intended Uses

Regarding the intended uses, the materials can typically be grouped into three categories, dental, medical and general medical use. For a material to be classed as either dental use or medical use, they had to mention a specific device that was to be created i.e. temporary dental crown, hearing aid shell. The majority of the rigid materials were of dental resins (61), followed by general medical use (26), and then medical use (12). For flexible resins, general medical use made up the majority (17), followed by dental (11) and then medical use (3). The materials for general medical use were defined by their chemical, mechanical or biocompatible properties with no specific device mentioned.

Regarding rigid materials, the most common specific dental devices were stated as; splints (12), surgical guides (11), try-in or permanent dentures (11), impression trays (10), temporary or permanent crowns (8), master-models (3), gingiva masks (1), brace arches (1), and radiopaque template (1). The second most frequent category for intended use in rigid materials were general medical applications, however the descriptions were mostly material specific and did not tend to state specific applications. Specific medical applications were the least frequent type of intended use with just three recommended uses, in the ear (ITE) shells for hearing aids (8) and surgical guides (3).

Of the flexible materials, 16 were for general medical use and dominated by variants of 3D Resyns 'Bioflex' material, all stating the term 'ultra safe'. The most common stated uses of the dental materials were; trays (5), splints (5) and guards (3). Three flexible materials for specific medical applications were 'LuxaPrint', for manufacturing earmoulds, 'LuxaPrint Coat', for manufacturing soft hearing protection, and 'E-Shell' used for general hearing aid applications.

5.4.2. Certification

Regarding the rigid materials, 86 out of 99 cited a set of standards or a specific certification from at least one regulating body. Those certifications comprised citation of ISO 10993 (68), USP VI (10), FDA (9), and CE (7). Twenty-eight materials cited ISO 10993-1 but only 8 provided details of the risk evaluation endpoints for categorising the material. Of the 99 rigid materials, a section of ISO 10993 containing a specific reactivity test was referenced by 36 materials; ISO 10993-5 (36), ISO 10993-10 (34), ISO 10993-3 (14), ISO 10993-11 (9), ISO 10993-18 (2), ISO 10993-17 (1), ISO 10993-4 (1). Seventeen materials referenced ISO 10993 but did not provide details of which of the 22 sub-sections it was in accordance with. Twenty-three materials used terminology such as 'capable, 'compliant', 'complies', 'meets' or 'satisfies' when referring their stated certification.

Of the 26 biocompatible flexible materials, 14 stated certification from at least one of the regulating bodies. All 14 of the materials referenced ISO 10993 at a high level, and one stated CE certification.

Two materials cited ISO 10993-1 but did not provide detail of the risk evaluation endpoints for categorising the material. Seven of the materials detailed certifications that contained a specific reactivity test; ISO 10993-5 (7), ISO 10993-10 (7), ISO 10993-3 (3) and ISO 10993-11 (1). Five materials referenced ISO 10993 but did not provide details of which of the 22 sub-sections of ISO 10993 it met. One material used the term 'complies' when referring to the passing of the stated certification.

5.4.3. Post-processing

All of the materials provided some information regarding post-processing instruction for their materials. In some cases, a small amount of information was given regarding the cleaning, handling and curing of parts, in other cases, a detailed document with steps for the best practice of post-processing was supplied.

5.5. Discussion

5.5.1. Intended Uses

In this study, 87 materials specifically detailed applications for the material. Seventy-two of those materials were for dental applications and 15 were for medical applications. The remaining 43 materials were categorised by their mechanical, chemical or biocompatible abilities i.e. tear-resistance, water-resistance, skin contact. In many cases, manufacturers provided case-study examples of how the material has been used by customers to help suggest possibilities of use to the prospective user.

The information available for dental materials was the most specific regarding intended use applications, often with clear statements such as use for ‘temporary crowns’. The majority of medical specific applications comprised materials for hearing devices such as ITE shells for hearing aids. Regarding ‘general medical use’ the most common term noted was in the 3D Resyns range ‘ultra safe’ as detailed on all of their biocompatible materials.

It is clear from the review that dental biocompatible materials have a higher consistency of providing clear details regarding end use applications, but this is not the case always for all the other general medical use materials. Without a clear definition of the intended use, it is difficult to determine the boundaries of the material uses with regards to biocompatibility, and also to gauge the

level of post-processing that would be needed in terms of thickness and device geometry.

5.5.2. Certification

The information provided regarding certification typically referred to either ISO 10993, USP VI, FDA exemption or CE marking. The ISO 10993 family of standards was the most frequently cited. In some cases this was cited as just "ISO 10993" without any detail regarding sub-sections. Thirty different materials cited ISO 10993-1, which on its own does not clarify their compliance with biocompatibility certification. ISO 10993-1 is the risk management framework which provides a method to detail endpoints which in turn dictate the reactivity tests required for those intended uses. It is in place to categorise medical devices based on the nature and duration of their contact with the body and to assess the biological safety of the medical device (ISO 2001). Citing ISO 10993-1 just states reference to the risk management framework. No reactivity tests are performed under ISO 10993-1. Hence, referencing just this standard section does not prove biocompatibility certification of the material.

For some materials, however, there were several subsections of ISO 10993 cited. Formlabs BioMed Clear was found to have the highest number of cited certifications with details to 6 subsections of ISO 10993 and also certification within USP VI. NextDent OrthoFlex had the most certifications for flexible materials with a total of 4 cited standards of ISO 10993. Other materials citing compliance with a high number specific subsections included Stratasys MED610 (5), PrintoDent GR-17 (5) and GR-20 (5). PrintoDent GR-20 was the only material found to have been tested and certified for ISO 10993-4, which refers to a reactivity test for hemocompatibility.

It is mostly important for the material to have the necessary certifications to match its intended use. For medical devices, biocompatibility is defined by the

immunological response from the host (Barrère *et al.* 2008). For example, if the intended use is for external skin contact for up to 24 hours, the material is only biocompatible if it can remain in contact with the skin for the stated duration without causing an immunological response. To state 'biocompatibility' a material must be tested and certified according to its intended use, and certified in its final-device form. It is the responsibility of the end user to select a material that is safe for the intended use. Firstly, the user must be aware of their requirements, and secondly, investigate the choice of materials. To make an informed decision, the user will most often rely on marketed information regarding the intended uses and associated certifications regarding biocompatibility. The challenge is that many users perceive they are compliant with "good practice" as long as they procure "biocompatible" resins without performing adequate due-diligence.

5.5.3. Post-processing

If photosensitive resins (biocompatible or not) are under cured they can be highly toxic, and if over cured the mechanical performance is affected. In some common 3D printing resins, toxicity has been recorded after post-processing in their fully cured states (Macdonald *et al.* 2016; Oskui *et al.* 2016; Alifui-Segbaya *et al.* 2017; Walpitagama *et al.* 2019; Rogers *et al.* 2021). Over curing can lead to brittleness and weaken the material beyond its stated properties. (Bagheri and Jin 2019) This could lead to device failure in practice and cause harm to the patient. Curing time for materials may differ from one device to the next due to thicker walls, internal structures, pigmentation and any areas blocked from direct ultra-violet exposure. Because of these factors, curing may not be uniform from one device to the next. Photosensitive resins can only achieve biocompatibility when the material has fully undergone the transition from a liquid to a solid via photo-cross-linking (Bagheri and Jin 2019).

All of the materials identified in this review had at least some instructions for the user regarding technique and good practice for post-processing to achieve and maintain biocompatibility. The information included ultra-violet wavelength settings, safe-handling, washing parts, curing parts and sterilisation. In a number of cases very little information was provided, whereas for others, detailed instructions were provided. At a minimum, suppliers would recommend post-curing parts, but not detail the technique or timings required.

The user is responsible for post-processing so they must be aware of the criticality of this step and the potential risks, so hence must be provided with sufficient information in this respect. The material manufacturer must provide guidelines that can be clearly followed by the user in order to correctly post-process printed parts. The information provided by the material manufacturers, in some cases, recommends extending post-processing lengths if the part being produced was larger. Therefore, the authors implore users to develop their own in-house protocols that test the validity of the given post-processing information against the parts being produced. If the part being produced has internal chambers, complex geometries or thicker geometries, it is likely that post-processing technique may need to be customised to ensure that the optimum mechanical and biocompatible properties are achieved.

5.5.4. Terminology

In the course of this review it was noted that there was a high degree of variability regarding the preciseness and clarity of terminology used when referring to certification compliance. Eighteen materials used terminology such as ‘capable’, ‘compliant’, ‘complies’, ‘meets’, ‘satisfies’, ‘deemed acceptable’ or ‘pending’. Whilst some of these terms are often used as synonyms for ‘passed’,

with regards to biocompatibility, a distinction between passed or not passed must be made in unambiguous terms. The terms listed are open to the interpretation of the user as to whether the material has been certified.

5.5.5. Limitations

As this study was performed of the grey literature findings will naturally vary from time to time. The review is based on marketed information available on a single web search engine. It is possible that there are more materials available than identified. It is also possible that manufacturers hold more information regarding certification compliance than is either available publically, or was identified in this search.

The authors wish to acknowledge that there are other aspects to achieving and maintaining biocompatibility such as: regular printer calibration, maintaining post-processing equipment, using in-date resin, using PPE to avoid contamination and sterilising printed parts with the appropriate method.

5.6. Conclusions

There is a considerable range of specifically engineered biocompatible photosensitive resins available to purchase on the commercial market for a variety of medical applications. The majority of these are marketed specifically for dental applications. The information provided to the user with regards to the intended use, certification and post-processing is highly variable.

When selecting a material, users should perform proper due-diligence to ensure they are choosing a material that will be appropriate for their application, and that the material manufacturer is able to provide sufficient information to achieve and maintain biocompatibility. As the responsibility of achieving the correct biocompatible and mechanical properties rests on the end user, it is imperative that post-processing technique is scrutinised. Where necessary, users should develop their own protocols that test the validity of the recommended post-processing technique, especially when printed parts feature large or complex geometries

Chapter 6: Impact of increased UV curing time on the curing depth of photosensitive resins for 3D printing

Status: In preparation for submission

6.1. Abstract

6.1.1. Background

3D printing (3DP) photosensitive resins are commonly used to produce patient-specific solutions in the fields of medicine and dentistry. These resins are toxic in their liquid state. To ensure that all resin has solidified and parts are safe for use, post-processing must be carried out after printing. Parts are first washed in IPA, allowed to dry, and then post-cured under ultra-violet light (UV), and sometimes heat. As 3DP is commonly utilised for its ability to create custom and rapid solutions, it is expected that a different geometry will be produced almost every time. Currently, post-processing guidance is supplied specific to a material, with the caveat that post-curing times should be extended for larger or complex parts. The aim of this study was to assess the effect of extending post-curing times for photosensitive resin printed parts.

6.1.2. Method:

Two commercially available vat-polymerisation 3DP systems were used to print hollow 60mm diameter spheres. Two opaque white, two opaque black, and two translucent amber resins were used. The spheres were filled with liquid resin, then UV post-cured at intervals of 100, 200, 300, 400 and 500% of the recommended guidance. The spheres were sectioned along the centreline and radial measurements taken of the cured depth.

6.1.3. Results

The results showed that both translucent amber materials cured to full depth at the 100% interval, whereas none of the white or black opaque materials cured to full depth, even at 500% of the recommended guidance.

6.1.4. Conclusions:

This suggests opacity has a considerable effect on the depth of cure in photosensitive resins, and that the use of opaque resins increases the possibility of uncured resin remaining inside parts.

6.2. Introduction

The potential of 3D printing (3DP) was first recognised in the medical community as early as the 1990's (Cima *et al.* 1994; Wu 1998; Tack *et al.* 2016). In the last two decades there has been a significant increase in the adoption of 3DP being used to directly treat patients (Tack *et al.* 2016; Kermavnar *et al.* 2021). 3DP offers customised and rapid solutions whilst reducing manufacturing time and costs (Ventola 2014). Fields such as surgery, biomedicine, dentistry, and microfluidics utilise 3DP as a manufacturing method often at the point-of-care (Masaki *et al.* 2014; Bagheri and Jin 2019; Lin *et al.* 2019; Jovičić *et al.*). However, 3DP is still relatively novel with regards to many of its applications, particularly when used to directly treat patients. The framework for regulation is still in its infancy and is yet to be fully established (Pierrakakis *et al.* 2014; Christensen and Rybicki 2017; Horst and McDonald 2020). It is therefore important to evaluate current practices and procedures to ensure the safety of users and end users.

Vat-polymerisation 3DP methods are often favoured over other methods for characteristics such as dimensional accuracy, isotropy, cleanability, and the wide availability of industry specific materials (Juneja *et al.* 2018; Unkovskiy *et al.* 2018; Kim *et al.* 2020; Kermavnar *et al.* 2021). Vat-polymerisation 3DP uses UV light to change the state of the liquid resin to a solid, layer by layer, to form a 3D part. When exposed to UV light, photo-initiators in the resin react and form polymer chains from oligomers and monomers: a process termed photo-crosslinking (Alifui-Segbaya *et al.* 2017; Bagheri and Jin 2019; Kessler *et al.* 2020). The UV light is projected from a focussed energy source such as a refracted laser (Stereolithography [SLA]), projector (Digital Light Processing [DLP] or Digital Light Synthesis™ [DLS™]), array light source and digital mask

(Masked-Stereolithography [MSLA]), or from a masked projected light source or digital screen (Liquid Crystal Display [LCD]). The light source cures a 2D cross section of the 3D model between the vat membrane and the build platform, the z-axis moves the bed away from the membrane to allow resin to flow back, and this process then repeats to form the next layer until the part is complete (Kodama 1981; Hull 1984; Alifui-Segbaya *et al.* 2017).

The intention of post-curing is to ensure that the semi-cured resin in the model has fully undergone the transition from a liquid to a solid (Piedra-Cascón *et al.* 2021).Vat-polymerisation printed parts are removed from the machine in their 'green' state and so require post-processing to ensure all semi-cured resin is fully cured, and that any liquid remnants are washed off. Materials are supplied with instructions for use and information for users regarding best practices for post-processing. Typically, isopropyl alcohol (IPA) or a solution such as tripropylene glycol monomethyl ether, is firstly used to remove liquid remnants. Washing is carried out manually or in an automated wash station specifically designed for washing vat-polymerised parts. Parts are allowed to air dry and then placed into a UV curing tank where they are exposed to a specific wavelength of UV light and sometimes heat, for a prescribed duration.

Post-processing is a vital step for vat-polymerisation 3DP methods as photosensitive resins are toxic in their liquid state (Oskui *et al.* 2016; Alifui-Segbaya *et al.* 2017). When supplied, the material safety data sheet informs the user that the raw resin is toxic and that improper use may cause an immunological response from the host (Remes and Williams 1992; Barrère *et al.* 2008). It is inferred from the manufacturer's guidance that after post-processing parts will be free from harmful liquid resin and safe for the intended application. However, several recent studies have found that even after post-

processing has occurred, harmful toxic leachates have been identified on parts printed using photosensitive resins (Macdonald *et al.* 2016; Oskui *et al.* 2016; Alifui-Segbaya *et al.* 2017; Walpitagama *et al.* 2019; Rogers *et al.* 2021).

Post processing guidance supplied by the manufacturer is material specific and so applies universally to all geometries that may be produced with that material. As a method, 3DP is utilised for its ability to create bespoke and complex parts. Therefore, a printer is expected to produce different geometries almost every time it is used. As such, some parts may feature thicker or complex geometries and may feature internal chambers, channels, and areas that will be shadowed from the UV light source during post-curing. Material manufacturers recommend extending post-curing durations for parts that are large or feature complex geometries, and for the user to apply their own judgement for post-processing technique. This suggests that post-processing guidance should be customised in relation to part geometry and that due diligence must be performed to ensure that the process is successful in curing parts and any liquid resin remnants.

The aim of this study was to evaluate the effects of extending post-curing by increasing intervals of the recommended post-curing guidance for photosensitive resins using their respective curing systems.

6.3. Method

6.3.1. 3D printer technology

One DLP printer, the Figure 4 Standalone (3D Systems, USA), and one SLA 3D printer, Form 3B (FormLabs, USA) were used for this study. The systems were

chosen as they are both commercially available, offer a comprehensive range of specifically engineered functional and biocompatible materials, and have their own proprietary post-processing equipment supplied with specific post processing guidance. The Figure 4 uses the LC-3DPrint Box UV Post-Curing Unit, for curing parts, and the LC-3DMixer for mixing the resin bottles prior to printing. The Form 3B uses the FormCure for curing parts and the FormWash for washing parts.

6.3.2. Test Model

The test model used was a hollow 60mm diameter sphere with a nominal wall thickness of 2mm. The sphere featured a filling hole of diameter 4.4mm with a 45^{o} chamfer. The hole was designed to fit a 25ml syringe (Terumo, Japan) whilst also allowing air to escape (Figure 22a, b). A plug for the filling hole was also designed. The plug had a 4.4 x 1.2mm shaft attached to an 8 x 8 x 2mm square pedestal used to balance the sphere during curing and to orientate the sphere during cutting (Figure 22c, d).

The models were drawn in SolidWorks 2020 (Dassault Systems, USA) then exported as a standard tessellation language (.STL) file to the appropriate slicing program. The slicing software for the Figure 4 system is '3D Sprint' (3D Systems, USA) and for the Form 3B system, 'Preform' (Formlabs, USA).

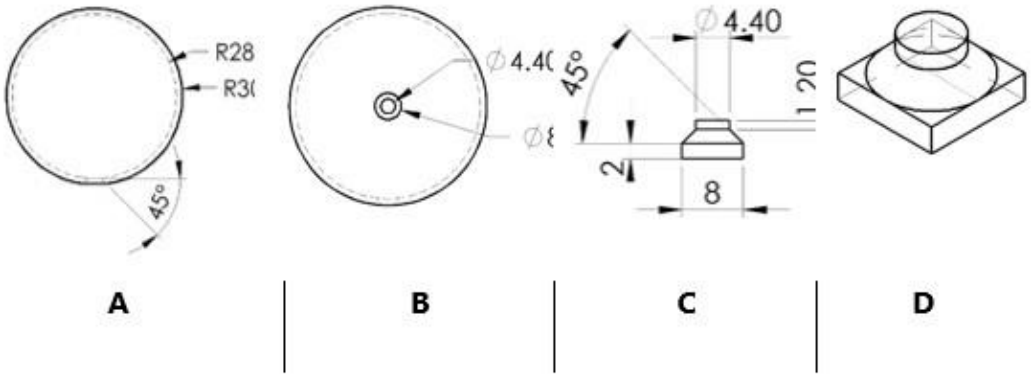


Figure 22: Sphere and plug dimensions

6.3.3. Materials

Six materials were chosen for the study, two opaque white, two opaque black and two translucent ambers (Formlabs White, Formlabs Black, Formlabs BioMed Amber, Figure 4 MED-WHT 10, Figure 4 Pro BLK 10 and Figure 4 MED-AMB 10). Black and white pigments were chosen as they were expected to produce the broadest range of results based on their light transmittance (Levinson *et al.* 2005; Wilson *et al.* 2008). The translucent resins were chosen as they would allow light to pass with minimal refraction (Bohren 1988). Where possible biocompatible materials were chosen. At the time of the experiment, the equivalent coloured resin was not available as a biocompatible, so the non-biocompatible version was used (i.e., FormLabs Black, FormLabs White).

6.3.4. Sample Size

Five spheres were printed for each material, one for each time interval (100%-500%), giving a planned sample size of n=30. However, as the translucent

resins cured fully at 100% the other samples were not further considered, giving an actual sample size of n=22. Each sample was radially measured 360 times by the ImageJ macro to create an average depth of cure from each.

6.3.5. Material and machine preparation

Prior to printing on the Figure 4 system, resin bottles were placed on the 3D Systems LC-3D Mixer and rolled for 60 minutes for PRO-BLK 10 and 150 minutes for MED-WHT 10 Rolling is not required for the MED-AMB 10 as per the manufacturer's guidance. The Formlabs material did not require pre-mixing. Prior to each print, print beds were also inspected and cleaned as prescribed.

For slicing, a layer height of 50µm was chosen on Preform and 3D Sprint. 3D Sprint allows the user to choose from 'draft', 'standard' and 'premium' print speed settings, the 'standard' setting was chosen as a middle ground. During the slicing process, care was taken to remove all internal supports that were generated inside the spheres and only one sphere and one plug was printed at a time. Spheres were orientated with the fill hole towards the bed to counteract an airlock being created between the part and the bed. The plug was printed with the square face away from the bed to avoid a rough finish.

6.3.6. Washing

As washing was not a variable of this experiment, a standard protocol was used to ensure consistency. To remove liquid resin from the parts, spheres were filled with 20ml of IPA using a 25ml syringe, shaken for ten seconds, and then

allowed to drain. This was repeated until the liquid draining from the part was visibly clear. A brush was used to clean the outside of the spheres, and the plugs. The IPA was changed between each material to avoid contamination. After washing, parts were left to air dry for 60 minutes.

6.3.7. Filling of spheres

Each sphere was filled using a 25ml syringe with its corresponding resin to the brim and allowed to overflow, then sit for ten minutes to allow any air bubbles to form at the surface. If necessary, the sphere was topped up with resin, then the plug inserted into the filling hole. Cyanoacrylate (M5100 H.B. Fuller, USA) was used to secure the plug in place. Once applied it was left to dry for ten minutes, as recommended.

6.3.8. Post-curing

Spheres were placed in the centre of the appropriate curing tank standing upright on the square faced plug. Spheres were cured at 100, 200, 300, 400 or 500% of the recommended durations, as provided by the manufacturers (Table 5).

Table 5: Manufacturer curing guidance

Material	Curing
Formlabs White	100% = 60 min @ 60°c
Formlabs Black	100% = 60 min @ 60°c
Formlabs Biomed Amber	100% = 30 min @ 70°c
Figure 4 MED-WHT 10	100% = 60 minutes
Figure 4 PRO-BLK 10	100% = 90 minutes
Figure 4 MED-AMB 10	100% = 60 minutes

6.3.9. Draining

After curing two holes were drilled into the spheres to drain any liquid resin remaining inside. A drilling jig was designed and printed on an FDM printer (Raise 3D N2+, USA) in PLA (Polymaker, Netherlands) filament. The jig was designed so that both holes could be drilled into the sacrificial half of the

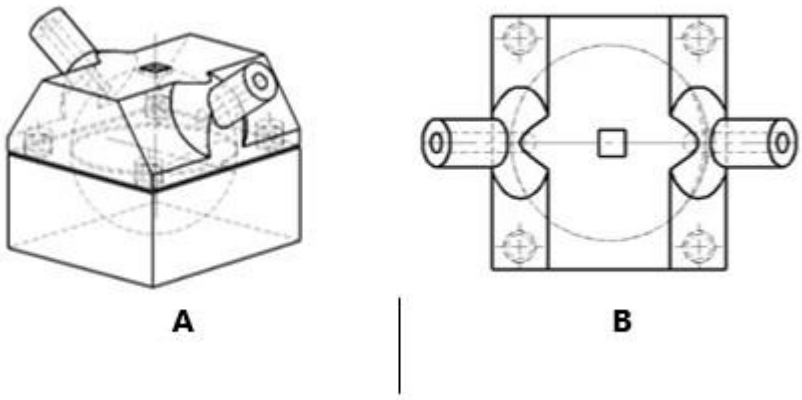


Figure 23: Drilling jig

spheres (see 'cutting section' below) and penetrate exactly to the centre of the sphere. A 5mm drill bit and cordless drill were used to create the two holes. The drilling jig is shown in Figure 23a, the location slot for the sphere pedestal can be seen in Figure 23b, and the drilling jig in use can be seen in Figure 24: Drilling jig in use. The spheres were left to drain into a waste container for ten minutes. They were then washed using the same technique described previously and left to dry for 60 minutes.

Figure 24: Drilling jig in use

6.3.10. Cutting sphere

A cutting jig was designed so that the cut would be offset by 2mm from the centre of the sphere allowing the larger hemisphere to be sanded back to its mid-point, as shown in Figure 26 and Figure 25. The smaller hemisphere featured the plug and drainage holes and which discarded after cutting (sacrificial half).

Spheres were placed into the jig with the square pedestal slotted into the extruded square gap, this was to prevent spinning during cutting. The spheres were cut inside the jig using a band saw. The cutting jig and thumbscrews were printed in Vero Clear resin and the gaskets were printed in Tango Black on a Connex 500 polyjet printer (Stratasys, Israel). A range of sandpapers, 240 through 1500 grit, were used to finish the flat face of each hemisphere.

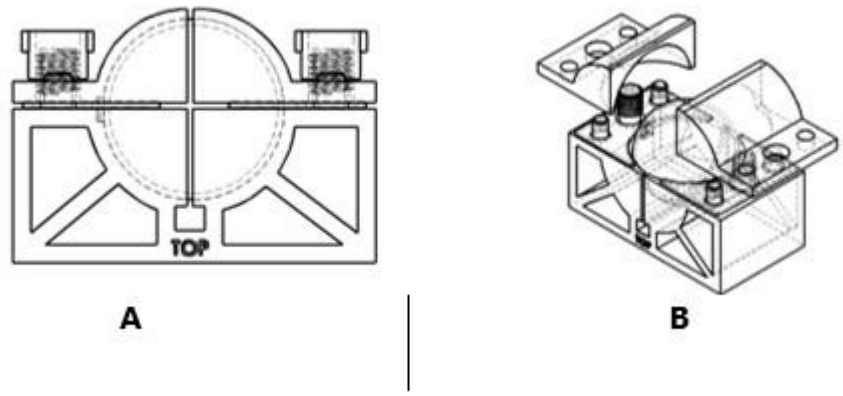


Figure 26: Cutting jig

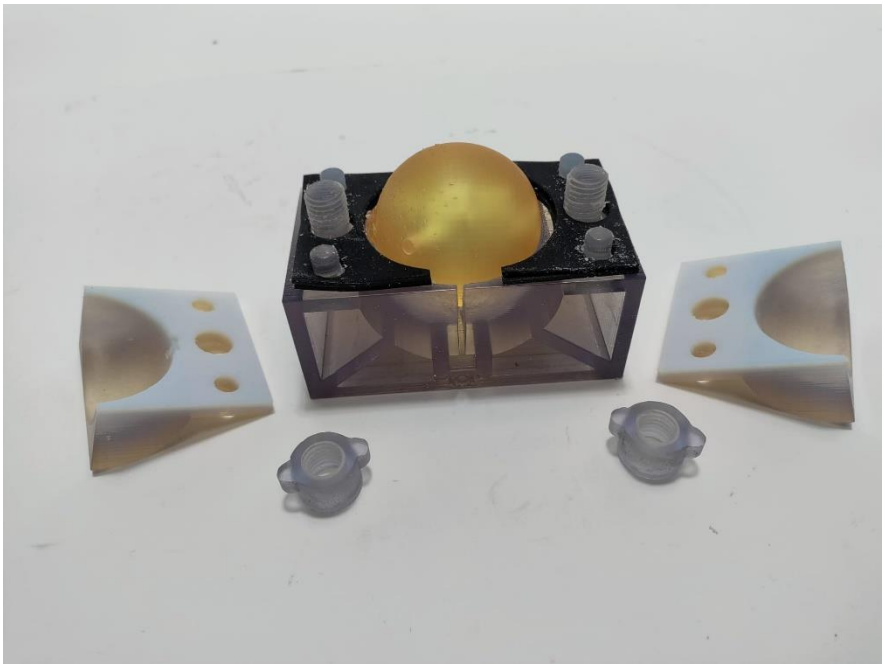


Figure 25: Cutting jig in use

6.3.11. Measurement of wall thickness

An alignment tool and a measurement jig were designed and printed on the FDM printer to aid in the scanning process. The jig and tool were sat against the straight edge of the scanner (Figure 28a) with the hemisphere faced down on the scanner. The tool was used to centre the hemisphere in the jig (Figure 28b) and thereafter removed (Figure 28c) leaving an 8mm gap offset from each side of the hemisphere. The jig in use is shown in Figure 27: Measuring jig in use. Scans were taken using a standard 2D paper scanner at 600DPI and

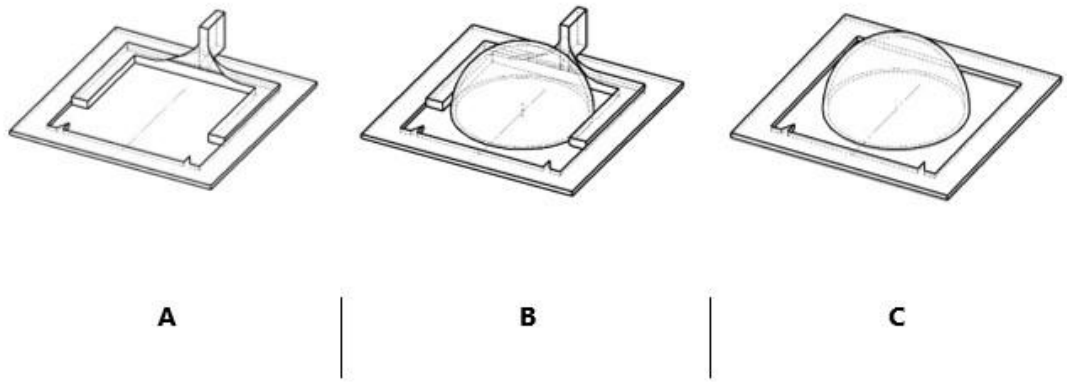


Figure 28: Measurement jig and alignment tool

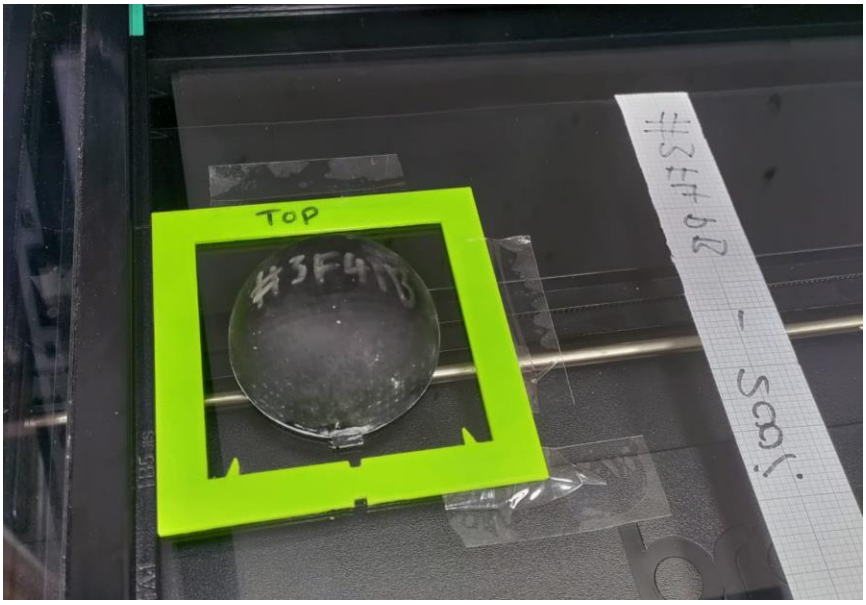


Figure 27: Measuring jig in use

exported to a media drive as a JPEG file (Brother, MFC-J6510DW, Japan). As the black and amber hemispheres did not show up clearly when scanned, white paint was applied to the sectioned face using an airbrush to increase the contrast.

The scanned images were cropped to the inner edge of the measurement jig, leaving an 8mm gap tangent to the sphere and the two prongs of the measurement jig visible. The two prongs of the measurement jig (60mm apart) were used as a reference dimension. Image J (Rasband, W.S., ImageJ, USA) was used to convert the scans to 32-bit greyscale and the contrast adjusted to maximum to ensure all of the cured depth was detected during measurement.

A radial measurement plugin for ImageJ was used to take 360 radial measurements from the image, the setup of the software can be seen in Figure 29. The images were cropped purposefully so that the plugin measures from the centre of the hemisphere each time. The arm then rotates, recording points from the outer printed edge of the hemisphere, to the inner post-cured depth using the grayvalues to determine start and end points. The settings used for

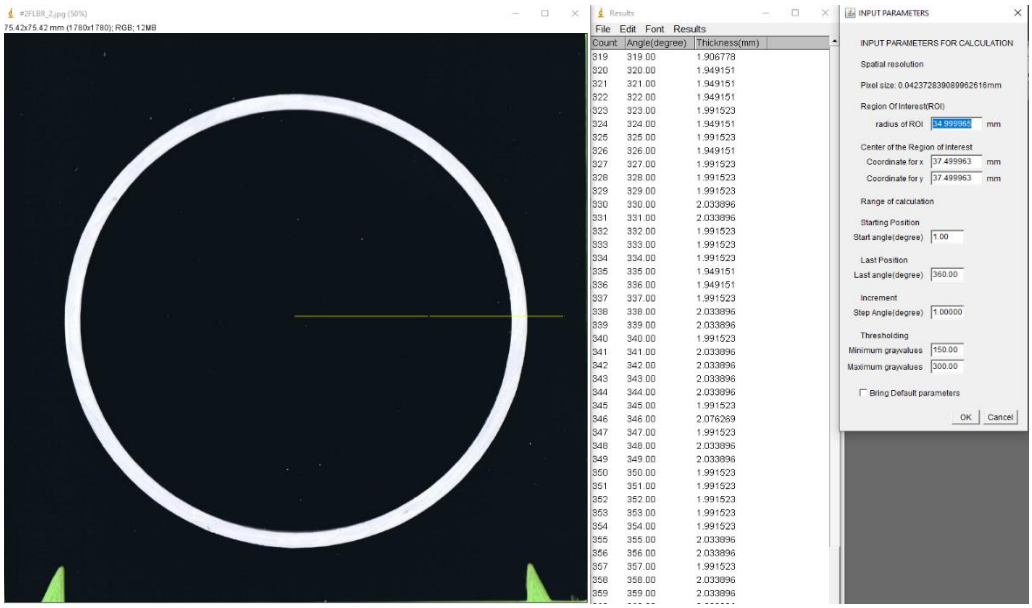


Figure 29: ImageJ radial measurement macro

the macro can be seen in Table 6.

Table 6: Settings for ImageJ radial measurement macro

Settings:	Values:
Radius of Interest (ROI)	35
Coordinates for X (mm)	37.5
Coordinates for Y (mm)	37.5
Start Angle	1
Last Angle	360
Angle Increment	1
Minimum Grayvalues	150 (100 for Black and Amber)
Maximum Grayvalues	250 (300 for Black and Amber)

6.4. Results

Images of the cross-sectioned spheres are shown in Table 8 and the results of the radial measurement data reported in Table 7. Three out of four of the opaque resins showed an increase in curing depth when exposed to extended curing times, but none cured to full depth. Both translucent amber materials cured to full depth at the first interval of post-curing. Figure 30 highlights the difference in cured depth between the opaque and translucent materials.

From the nominal depth to the cured depth recorded at 500%, the Figure 4 MED-WHT 10 showed an increase in maximum cure depth of 8.72mm and a mean increase of 8.06mm (Table 7). The internal circumference of the cured

depth is visually noncircular after the 100% interval and is emphasized more with each interval. The external shape remained circular and no deformation was noted.

From the nominal depth to the cured depth recorded at 500%, the Figure 4 PRO-BLK 10 showed an increase in maximum cure depth of 2.15mm and a mean increase of 1.74mm (Table 7). The shape of the cured depth is visually non-circular after the 100% interval (Table 8b) and more emphasized with each interval thereafter. A change in the external shape can be seen after the 300% interval where the model began to deform and become non-spherical.

The Figure 4 MED-AMB 10 resin cured to full depth at the 100% interval (Table 8c). Accordingly, no further curing intervals were assessed.

From the nominal depth to the cured depth recorded at 500%, the Formlabs White resin showed an increase in maximum cure depth of 6.46mm and a mean increase of 6.22mm (Table 7). No change in shape was noted in the internal or external circumference (Table 8d).

The Formlabs Black resin showed no increase in cure depth from having the curing time extended. The maximum cure depth of each sphere was within ±0.09mm, and the mean cure depth within ±0.05mm (Table 7), it is expected that the value shown is the error of margin in the printer's accuracy. No change in shape was noted in the internal or external circumference (Table 8e).

The Formlabs BioMed Amber cured to the full depth at the first interval of 100%, as it could not cure any further, no more intervals were tested. A large irregular shaped cavity was found in the centre of the sphere (Table 8f). The sphere was drilled to release any liquid resin still held inside the centre, but none was found. The 100% interval was repeated two more times to check for

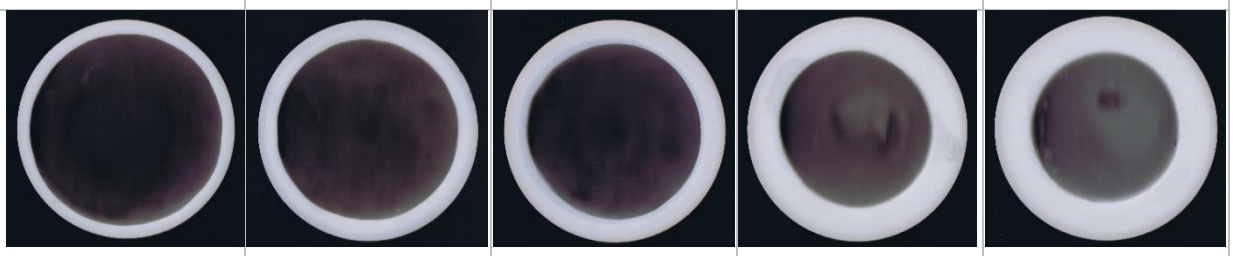
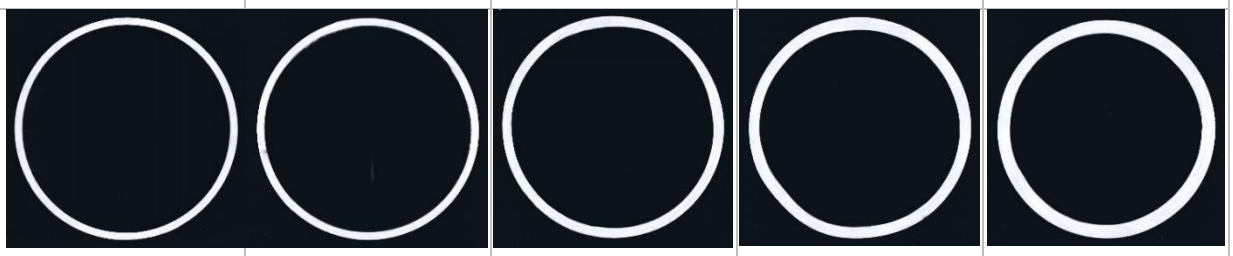
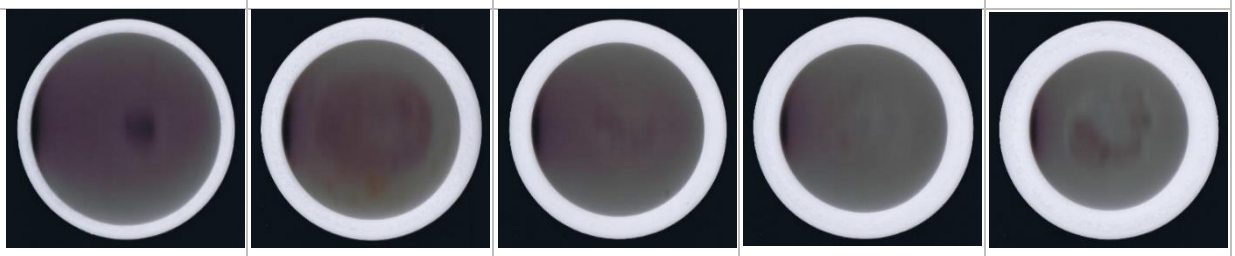
user error (Figure 31). No change in shape was noted in the external circumference.

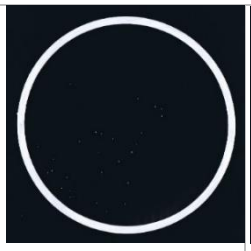
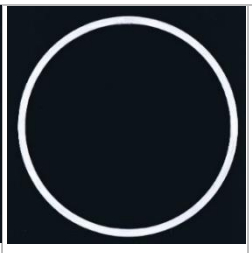
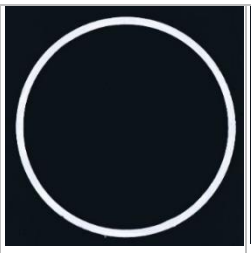
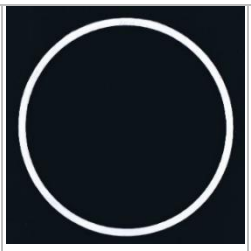
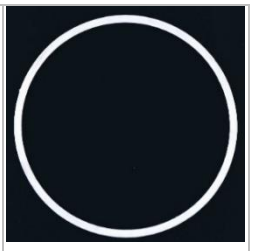
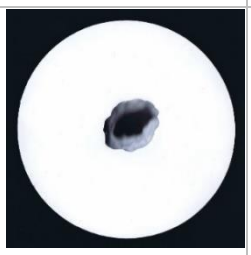
Table 7: Sphere cured depth by time interval

MED-WHT 10					
Cure Interval/Time	**100% (60 Min)**	**200% (120 Min)**	**300% (180 Min)**	**400% (240 Min)**	**500% (300 Min)**
Max Thickness (mm)	3.94	6.82	7.36	9.99	10.72
Min Thickness (mm)	2.65	4.91	6.01	8.05	9.45
Mean Thickness (mm)	3.44	5.56	6.62	9.15	10.06
SD (mm)	0.07(± 1%)	0.19 (± 1.7%)	0.29 (± 2.1%)	0.54 (± 2.9%)	0.41 (± 2%)
PRO-BLK 10					
Cure Interval/Time	**100% (90 Min)**	**200% (180 Min)**	**300% (270 Min)**	**400% (360 Min)**	**500% (450 Min)**
Max Thickness (mm)	2.2	2.54	3.09	3.64	4.15
Min Thickness (mm)	1.90	1.99	2.16	2.83	3.34
Mean Thickness (mm)	2.03	2.16	2.66	3.17	3.74
SD (mm)	0.05(± 1.2%)	0.1(± 2.3%)	0.19 (± 3.5%)	0.18 (± 2.8%)	0.19 (± 2.5%)
MED-AMB 10					
Cure Interval/Time	**100% (60 Min)**				
Max Thickness (mm)	30.56				
Min Thickness (mm)	28.73				
Mean Thickness (mm)	29.55				
SD (mm)	0.58 (± 0.9%)				
Formlabs Resins					
White					

Figure 4 Resins					
Cure Interval/Time	**100% (60 Min)**	**200% (120 Min)**	**300% (180 Min)**	**400% (240 Min)**	**500% (300 Min)**
Max Thickness (mm)	4.15	5.97	6.44	7.4	8.46
Min Thickness (mm)	3.26	4.62	5.88	6.9	7.83
Mean Thickness (mm)	3.72	5.37	6.15	7.14	8.22
SD (mm)	0.21 (± 2.8%)	0.14 (± 1.3%)	0.12 (± 0.9%)	0.12 (± 0.8%)	0.14 (± 0.8%)
Black					
Cure Interval/Time	**100% (60 Min)**	**200% (120 Min)**	**300% (180 Min)**	**400% (240 Min)**	**500% (300 Min)**
Max Thickness (mm)	2.24	2.24	2.33	2.28	2.28
Min Thickness (mm)	1.95	1.94	1.9	1.99	1.95
Mean Thickness (mm)	2.11	2.06	2.06	2.08	2.08
SD (mm)	0.04 (± 0.9%)	0.05 (± 1.2%)	0.05 (± 1.2%)	0.04 (± 0.9%)	0.04 (± 0.9%)
BioMed Amber					
Cure Interval/Time	**100% (30 Min)**				
Max Thickness (mm)	23.8*				
Min Thickness (mm)	19.27*				
Mean Thickness (mm)	22.33*				
SD (mm)	1.28 (± 2.8%)*				

Table 8: Cross-sectional scans

Figure 4 Resins					
Curing Interval:	**100%**	**200%**	**300%**	**400%**	**500%**
Figure 4 MED-WHT 10 *(A)*					
Figure 4 PRO-BLK 10 *(B)*					
Figure 4 MED-AMB 10 0 *(C)*		*	*	*	*
Formlabs Resins					
Curing Interval:	**100%**	**200%**	**300%**	**400%**	**500%**
Formlabs White Resin *(D)*					

Formlabs Black Resin *(E)*					
Formlabs BioMed Amber Resin *(F)*		*	*	*	*

*Was not repeated as 100% interval cured to full depth

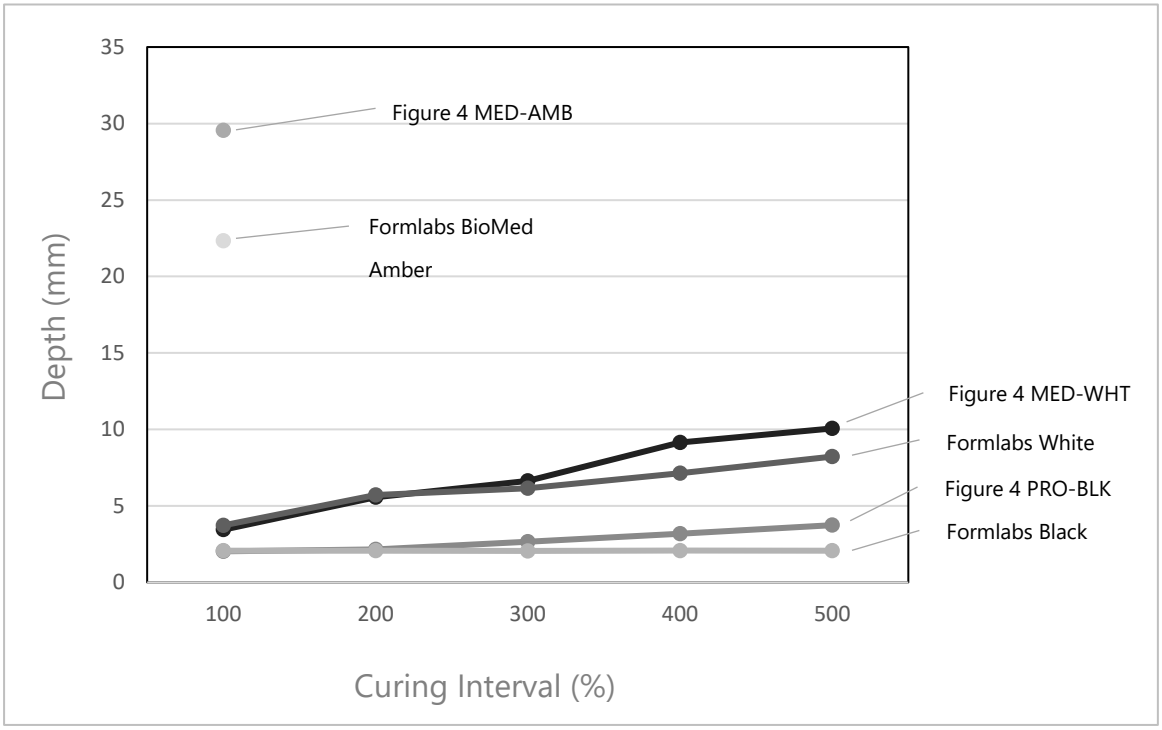


Figure 30: Mean curing depth of all resins

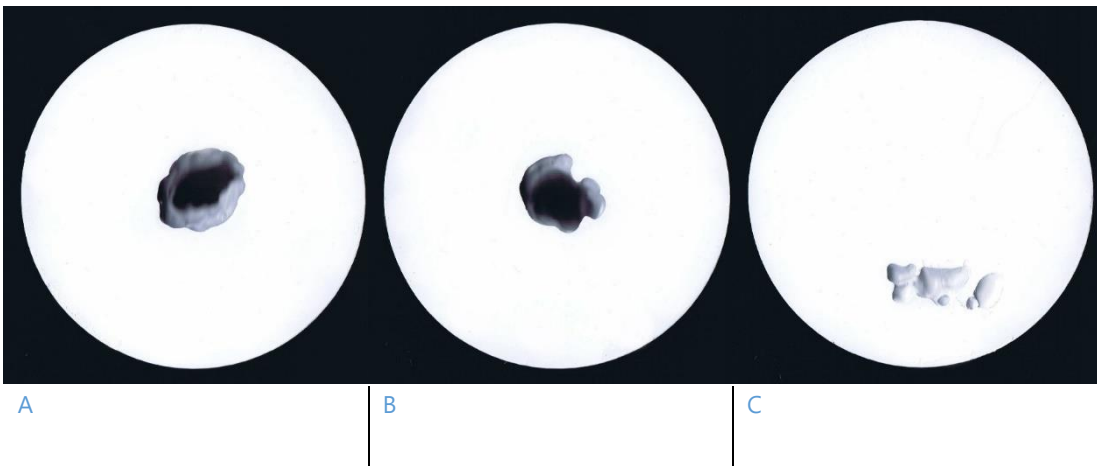


Figure 31: Repeats of biomed amber after cavitation

6.5. Discussion

6.5.1. Depth of curing

Vat-polymerisation 3DP is often utilised in the fields of medicine and dentistry to produce medical devices that are used to directly treat patients. Vat-polymerisation systems use a photosensitive resin that transitions from a liquid to a solid during exposure to UV light. Vat-polymerisation systems use a focussed UV energy source to construct the model, the conversion rate of the resin at this stage is >50% and so requires post-processing to achieve a rate of >90% (Kessler *et al.* 2020). As photosensitive resins are toxic in their liquid state, post-processing is vital to ensure the parts are finished and are safe for use. Post-processing guidance is provided by the resin manufacturers. Manufacturers recommend extending post-curing times for parts that feature large or complex geometries, however there is a general lack of specific

guidance in this respect. This study was performed to assess the effects of extending post-curing times on a selection of photosensitive resins. The results of the current study identified that extending post-curing times increased the cure depth of the resins, but that the effects varied considerably between resin opacities.

In this study, two translucent and four opaque photosensitive resins were post-cured at extended intervals of the prescribed post-curing guidance provided by the manufacturer, to test how cure depth would be affected. Both translucent resins cured to their full depth at 100% of the recommended guidance, whereas none of the opaque materials cured to full depth even at 500%. Of the opaque resins, the two white resins had the deepest recorded cure depths. From nominal depth to 500%, the Figure 4 MED-WHT 10 gained a mean increase of 8.06mm, this was followed by the Formlabs White resin with a mean increase of 6.22mm. The two black resins showed the smallest increase in cure depth, with the Figure 4 PRO-BLK 10 resin increasing by 1.74mm and the Formlabs Black resin showing no discernible increase at all.

The results of this study show that extending post-curing times is highly variable, and is dependent on the opacity of the resin. Table 8 demonstrates how much of a difference opacity makes. After extending post-curing times to 500%, most of the opaque resins were able to cure further, but none cured to full depth. Compared with the translucent resins that both cured to full depth after just 100% of their recommended guidance. As photosensitive resins require exposure to UV light to transition from a liquid to a solid, understandably, opacity has had a considerable effect on the depth of cure. Whilst the method used in this study is unlikely to be repeated by a user, it is designed to replicate uncured resin that may be left inside a large or complex

printed geometry. The geometry used in this experiment is relatively simple and would not be considered complex, or large in relation to the capability of the machines. It could be expected that parts with features such as, thicker walls, channels, threads, and other captive elements would require a post-curing interval past 500% to achieve relative cure depth.

Extending post-curing times showed high variation in cure depth for the opaque resins. For these types of material, users may want to consider introducing limitations for part size and complexity, and to consider breaking designs down into smaller sub-assemblies. Ultimately, the responsibility is on the user to ensure the parts are fully cured and safe for use, by firstly carrying out the prescribed post-processing guidance and then validating its success with regards to the unique geometry they are producing. When possible, users should seek to use translucent resins for producing medical devices that will be used to directly treat patients to increase the cure depth achieved during post-processing.

6.5.2. Potential impact on biocompatibility

Of the materials used in this study, four out of six are marketed as biocompatible. Biocompatible refers to the materials ability to not cause an immunological response to the host at the point of contact within the stated time period e.g. 24-hour skin contact, 12-hour mucosal membrane contact (Remes and Williams 1992; Barrère *et al.* 2008). It is likely that materials marketed with these characteristics will be chosen by some users to produce medical devices for human use. In this study, the Figure 4 MED-WHT 10, Figure 4 PRO-BLK 10, Figure 4 MED-AMB 10 and the Formlabs BioMed Amber are all

certified in accordance with ISO 10993-5 (tests for in vitro cytotoxicity) and 10993-10 (tests for irritation and skin sensitization). In addition, Formlabs BioMed Amber is also certified under ISO 10993-1 (evaluation and testing within a risk management process)(ISO 2001).

The results presented here suggest that caution is required when using opaque resins for biocompatible applications as the penetration of UV light is compromised, potentially leading to semi-cured or uncured resin remaining inside large parts, or those with complex internal geometries. To ensure the safety of end users the amount of cytotoxic remnants inside a printed part must be reduced. Whilst it is known that post-curing under UV light largely mitigates the toxicity of photosensitive printed parts (Oskui *et al.* 2016), other methods have proven successful. Studies performed by Macdonald *et al.* (2016) and Alifui-Segbaya *et al.* (2017) showed that soaking photosensitive resin printed parts in ethanol significantly reduced cytotoxicity levels. Similarly, Inoue and Ikuta showed that heating parts to 225^{o}C successfully reduced the cytotoxicity of photosensitive resin printed parts (Inoue and Ikuta 2013). These methods may be useful for biocompatible devices that require complex or large geometries, and/or must be printed in opaque resins. When extending part exposure to heat, irradiation or solvents, users must be aware of the potential for detrimental side effects to parts, as highlighted by Kim *et al.* (2020), where the flexural modulus of parts began to decrease after extending post-curing times, in some cases. Similarly, Xu *et al.* (2021) found that the flexural strength of photosensitive resin printed parts decreased with the extension of post-washing times. When employing biocompatible photosensitive resins for medical devices, users should seek to use quality certified materials from reputable manufacturers that are appropriate for the devices intended use. If possible, users should use translucent resins, and

perform due diligence to ensure that post-processing has been successful and not detrimental to the mechanical or biocompatible properties of their device.

6.5.3. Visual changes

Visual changes of the samples were noted with regards to shape. An irregularity in the internal circumference was noted across the Figure 4 MED-WHT samples, and also for the 200% interval onwards Figure 4 PRO-BLK samples, where the internal circumferences become noncircular. The internal circumferences of the Formlabs Black and White resins are noticeably more circular than the Figure 4 MED-WHT and PRO-BLK resins. The irregularity of the internal shape was also noted in the variability of the measured diameters. The two opaque Figure 4 resins had higher standard deviations than the Formlabs resins in most instances. A possible explanation for the variability may be due to the difference between the respective curing tanks used. The proprietary curing tank supplied by Formlabs (Formcure) has a platform that turns parts slowly whilst exposed to thirteen 9.1W multi-directional LEDs. The Figure 4 recommended curing box (LC-3DPrint Box) does not have a revolving platform. The LC-3DPrint Box has twelve fluorescent bulbs that differ in wavelength: six are 18W 71 colour and six are 18W 78 colour, with the bulbs alternating consecutively. The two bulb types produce different wavelengths of UV giving a full UV spectrum from 300-550nm. The change in internal circumference might be due to being exposed to different UV wavelengths from different directions on a stationary platform.

The BioMed Amber featured an irregular shaped cavity inside the sphere. No liquid resin was found inside the cavity after sectioning; the process was

repeated a further two times to ensure it was not the result of user error. In the first and second run, cavities formed in the centre of the sphere (Figure 31a, b), in the third run, the cavity was found offset to the centre (Figure 31c). It is proposed that the cavities may be the result of cavitation inside the sphere. As the temperature of the resin increased and it solidified within the captive space, it reached a static pressure below the liquids vapour pressure, creating pockets of vapour that were then captured in the resin as it solidified (Moussatov *et al.* 2003; Franc and Michel 2006). This result is specific to the method used in this study and is not expected to occur under normal printing conditions.

6.5.4. Limitations

A study performed in chapter 5 identified 130 biocompatible photosensitive resins, as the cost and time of printing, filling and post-curing was considerable, only 6 materials were chosen for this experiment. For the same reason, only one run of each interval was tested.

This study was limited to a single geometry model. It is expected that other geometries and sizes will produce different results. The geometry used was selected to show the best results for radial measuring, and to cure evenly when placed in the centre of the respective curing tank.

As the materials used in this study are photosensitive, care was taken to keep samples out of direct light between printing, filling and draining. It is possible that during processes parts were exposed to natural and unnatural light.

6.6. Conclusions

Photosensitive 3DP resins are often used to produce custom devices in the fields of medicine and dentistry. These resins are toxic in their liquid state so post-processing is required to ensure that all liquid resin transitions to a solid. Post-processing guidance supplied with resins typically detail that post-curing times should be increased for larger or more complex parts, however specific detail in this respect is not ordinarily provided.

This study evaluated the effects of extending post-curing times relative to duration in the associated material guidance documentation. The results showed that whilst curing depth increased with extended UV exposure for most resins, there were large differences between resins of different opacities. The opaque resin did not cure fully at five times the recommended guidance, whereas translucent resins cured to full depth at the recommended guidance. Users should exercise caution when using opaque resins in particular to ensure they are fully cured. Users might consider using translucent resins for devices where full curing is important, in particular for medical applications including those that require biocompatibility. There is a need for further research into the efficacy of current guidance regarding post-processing of photosensitive resins used in 3DP. Users should consider developing and validating their post-processing techniques to avoid any potential adverse effects to end users.

Chapter 7: Effects of post-curing duration on the mechanical properties of complex 3D printed geometrical parts

Status: In preparation for submission

7.1. Abstract:

Purpose

This study aims to test the efficacy of post-curing guidance supplied by 3D printing resin manufacturers. Current guidance is supplied generically to all geometries with the caveat that post-curing should be extended for 'large' or 'complex' geometries but does not specify these details.

Design/methodology/approach

Two vat-polymerisation 3D printers (Form3B, Figure 4 Standalone) are used to print 24 test models in 6 biocompatible resins (Pro Black, Med White, Med Amber, Biomed Black, Biomed White, Biomed Amber). The test model replicates a 'complex' geometry by housing ISO 527 test specimens in concentric layers. Two separate intervals of curing are applied (100%, 500%) creating differing curing treatments of the specimens throughout the model. Test models are then disassembled and pull testing is performed on each of the specimens to discover variation in their mechanical properties.

Findings

Statistical analysis showed that extending the curing stage had no significant effect on the mechanical properties, whereas the geometry of the model did have a statistically significant effect. It is also shown that translucent resins can reach a more homogenous state throughout than resins that contained pigments.

Originality/value

The design of this experiment aims to show how generic post-curing technique is inefficient for models that contain internal geometries. Large variations in mechanical properties throughout the model suggest that the material is not fully-cured and is therefore unsafe and unsuitable for handling, especially where biocompatibility is required.

7.2. Introduction:

3D printing technology is now prevalent in many industries, often utilised for its ability to create rapid, complex and cost effective solutions (Gibson *et al.* 2021) -in particular, 3D printing has proven to be a valuable asset to many areas of healthcare. Whilst initially used to make surgical guides and visual aids such as anatomical models for training; fields such as dentistry, orthopaedics, maxillofacial surgery, prosthetics, neurology, oncology and nursing have successfully used 3D printing to produce custom medical devices to directly treat patients (Ko *et al.* 2016; Suska *et al.* 2016; Zhao *et al.* 2017; Bohl *et al.* 2018; Tran *et al.* 2018; Xu *et al.* 2019; Q. Wang *et al.* 2020; Kermavnar *et al.* 2021). To reach the general market, medical devices must adhere to rigorous regulation and standardisation (R.J. Morrison *et al.* 2015; Horst and McDonald 2020). In traditional manufacturing, medical devices must be produced using certified materials and processes in a controlled production facility in accordance with quality management systems such as ISO 13485. Once manufactured, they must be tested to be fit for use in accordance with relevant sections of standards, for example – biocompatibility (ISO 10993/USP VI) (R.J. Morrison *et al.* 2015).

Unlike traditional manufacturing, when 3D printing polymer medical devices for patient use users must rely completely on A., raw materials specifically engineered and certified for a given application (i.e., biocompatible for skin contacting), and B., following manufacturer's instructions on appropriate post-processing techniques to ensure the final parts meet the specified mechanical properties.

Vat-polymerisation 3D printing techniques are frequently favoured for use in medical applications for properties such as isotropy, cleanability, and dimensional accuracy (Chua *et al.* 2017; Kermavnar *et al.* 2021). Vat-polymerisation systems use Ultra-Violet light (UV) to convert the photosensitive resin from a liquid to a semi-cured state (Gibson *et al.* 2021). During printing, the UV light source projects/traces the shape of a layer through the vat membrane onto the print bed (Chua and Leong 2014). Once the layer is cured, the bed retracts along the z-axis permitting the resin to flow back over the membrane (Redwood *et al.* 2017). This process repeats layer by layer until the printed part is complete (Kodama 1981; Alifui-Segbaya *et al.* 2017; Kessler *et al.* 2020). When exposed to UV light, photo-initiators become reactive in the resin and catalyse a process known as photo-crosslinking whereby oligomers and monomers join to create polymer chains that cross-link with other polymer chains giving rise to solidification (Alifui-Segbaya *et al.* 2017; Bagheri and Jin 2019; Gibson *et al.* 2021).

After a typical printing process the resin in the model is in a semi-cured state with the conversion rate from liquid to solid ranging from 35-77%, differing between printing method and material used (J. Ferracane and J. Condon 1990; Kessler *et al.* 2020; Piedra-Cascón *et al.* 2021). As some of the chemical components used in photosensitive resins are toxic in their liquid and semi-

cured states, printed models must be post-processed to ensure they are fully cured, safe for use, and achieve the described mechanical properties (Macdonald *et al.* 2016; Oskui *et al.* 2016; Rogers *et al.* 2021).

During post-processing, parts are removed from the print bed and all unnecessary supports removed (Redwood *et al.* 2017). The parts are then washed to remove any residual liquid resin remaining on the surface of the model. Typically, this is performed with Isopropyl Alcohol (IPA) or tripropylene glycol monomethyl ether. This process is performed manually by hand, or in a programmable washing tank, depending on the printing system and manufacturer's instructions. Parts are air dried, and then placed into a curing tank and exposed to UV light (and in some cases heat) for a prescribed amount of time, the intention being to convert any semi-cured resin within the model to a fully cured state (Chua and Leong 2014; Redwood *et al.* 2017). Studies have identified the presence of toxic leachates in resin printed models, even after post-processing has been performed (Macdonald *et al.* 2016; Oskui *et al.* 2016; Alifui-Segbaya *et al.* 2017; Walpitagama *et al.* 2019; Rogers *et al.* 2021). The same studies noted that with further post-processing, the concentration of harmful leachates was mitigated, but not eradicated.

The instructions given by manufacturers are often generic and apply to all geometries that may be produced on a given printer and it is inferred that post-processing results in a uniformly cured model throughout. In some cases, material manufacturers recommend users extend post-curing times for 'larger' or more 'complex' parts, but do not define what is considered large or complex, nor the amount of time to extend by (Formlabs 2022). As 3D printing is commonly used to produce bespoke parts, it is expected that the size and complexity of models being produced will vary from print to print. This raises

the potential that if a given post-processing procedure was not fully effective, parts of the device could remain in a semi-cured state. This could negatively impact both the mechanical and biocompatible properties of the device.

The purpose of this study was to investigate the suitability of generic post-processing instructions on the mechanical properties of materials in a complex geometry model.

7.3. Method

7.3.1. Experimental design

For each material (6 in total – detailed below) there were two independent variables, Duration of UV curing (100% and 500%), and Layer within the complex model (4 levels: A, B, C, and D). The dependant variables were mechanical properties of samples from the printed models. These properties were Ultimate Tensile Strength (UTS), Young's Modulus (YM), and Elongation at Break (EB). The test specimens were produced in accordance with ISO 527 1BA. Five test specimens were printed per layer of the model, with four concentric layers to form a "complex" test model (Figure 32).

7.3.2. 3D printing

Two vat-polymerisation systems were used: Figure 4 Standalone (3D Systems, USA), Form3B (Formlabs, USA). These systems were chosen as both offer a range of commercially available biocompatible resins, and both have proprietary post-processing systems with specific instructions regarding post-processing methods.

The materials chosen were: Formlabs Biomed Black; Formlabs Biomed White; Formlabs Biomed Amber; Figure 4 PRO-BLK; Figure 4 MED-WHT; Figure 4 MED-AMB. These materials were chosen as they are marketed as ISO certified biocompatible materials.

The Figure 4 prints were sliced using 3D Sprint (3D Systems, USA) with a layer height of 50 microns and the standard quality setting selected. The Formlabs prints were sliced using Preform (Formlabs, USA) also with a layer height of 50 microns. The test models were positioned vertically in the 3D printers with

specimens' perpendicular to the build platform. In the slicer, supports were added from the adhesion raft to the bottom of the model; no supports were in contact with the test specimens.

7.3.3. 3D Printed Test Model

A complex test model (Figure 32) was designed using Solidworks (Dassault Systemes, France) CAD software. The model was pentagonal in plan view, with three concentric equally spaced walls creating four treatment layers (A, B, C, D - outside to inside respectively). The walls were 2mm thick with an 8mm gap to the next parallel wall. Suspended between each set of walls were five ISO 527 1BA test specimens for a total of twenty per model (ISO 2019). The 1BA specimens were chosen as standard sized specimens were unable to fit within the printers build envelope. The specimens were suspended by chamfered supports at each end.

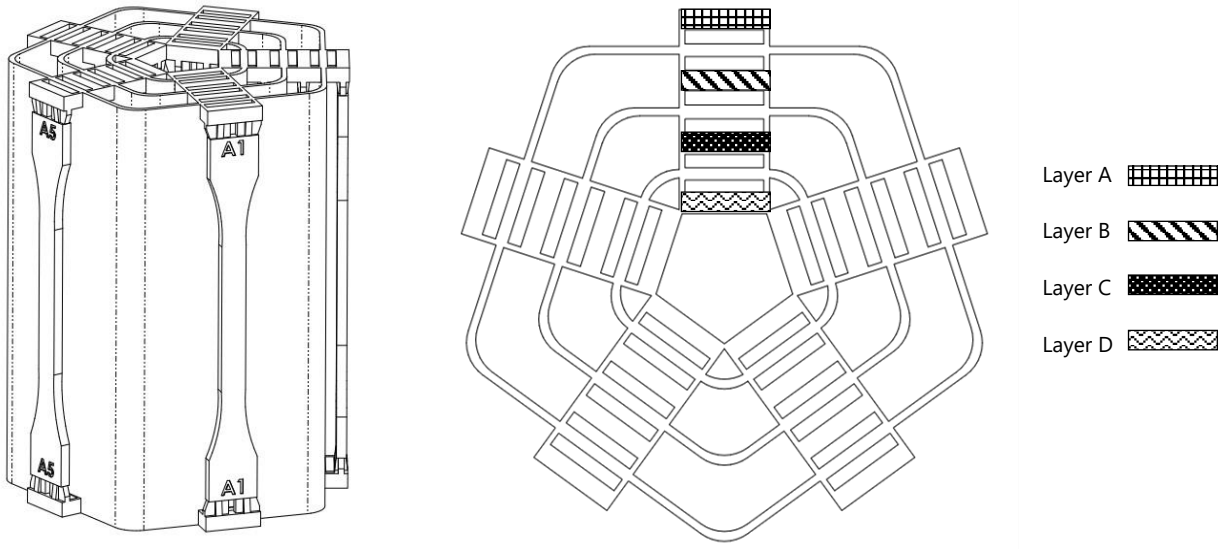


Figure 32: Complex Matrix Mode, Right – Sample layers within the model from outer (A) to inner (D)

7.3.4. Post Processing

All models were post-processed as per the manufacturer's instruction for the individual materials. Support and raft material was trimmed away prior to washing and curing.

The Figure 4 models were washed in two separate tanks by hand. Formlabs models were placed into the Form Wash for the prescribed duration. The hydrometer supplied was calibrated prior to the experiment and used to test the clarity of the IPA before each wash.

Post-curing of Figure 4 models was performed using the LC-3D Print Box (NextDent, Netherlands). Formlabs models were inserted into the Form Cure tank (Formlabs, USA). Details of manufacturer's prescribed times for washing, drying, and curing of the different materials are shown in Table 9.

Table 9: Manufacturer's post-processing requirements

MATERIAL	WASHING TIME (MIN)	AIR DRYING TIME (MIN)	CURING INTERVAL		CURING TEMP (^{O}C)
			100% (MIN)	500% (MIN)	
Med Amber	5	60	60	300	N/A*
Pro Black	10	60	90	450	N/A*
Med White	10	60	60	300	N/A*
Biomed Amber	20	30	30	150	70
Biomed Black	5	30	60	300	70
Biomed White	5	30	60	300	60
*N/A as there are no user programmable temperature controls					

End plates were designed and printed (Figure 33) to restrict UV light exposure to perpendicular with the sides of the model during curing. Aluminium foil was used to line the inside of the end plates to ensure UV would not penetrate.

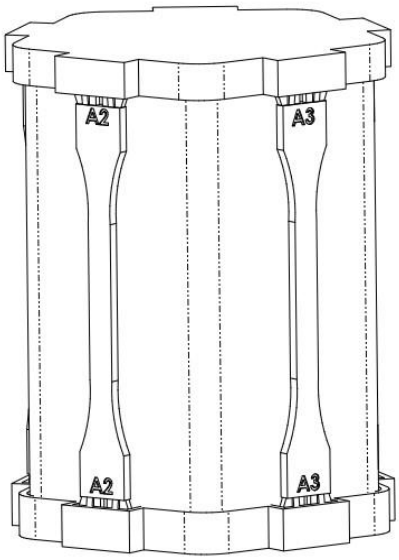


Figure 33: End plates fitted to complex model

7.3.5. Mechanical testing

The specimens were wrapped in aluminium foil and transported inside of a light proof box to the test lab. The specimens were pull tested on a H25KS (Tinius Olsen, USA) with a 1kN load cell and test speed set at 1mm/s, as per ISO 527. The results were recorded using Horizon tensile testing software (Tinius Olsen, USA). An initial test run identified that the use of an extensometer propagated crack sites and added clamp force to the specimens, a non-contact extensometer was not available. All calculations for stress, strain and Youngs modulus used formulae and dimensions given in the ISO 527 standard.

7.4. Results

7.4.1. Statistical Analysis

ANOVA was performed on the effects of Duration and Layer on Young's Modulus (YM), Ultimate Tensile Strength (UTS) and Elongation at Break (EB) (Table 10) for each material. Plots of the averages for the treatments are given in Figure 34, Figure 35 and Figure 36.

Table 10: ANOVA results

	MATERIAL	VARIABLE	ULTIMATE TENSILE STRENGTH	YOUNG'S MODULUS	ELONGATION AT BREAK
			p value		
FIGURE 4	*Med Amber*	Layer	0.067	0.520	0.445
		Duration	0.770	0.627	0.175
		Layer * Duration	0.619	0.026*	0.645
	Med White	Layer	0.017*	0.025*	0.014*
		Duration	0.618	0.719	0.461
		Layer * Duration	<0.001*	<0.001*	<0.001*
	Pro Black	Layer	0.004*	0.007*	0.153
		Duration	0.097	0.221	0.149
		Layer * Duration	<0.001*	<0.001*	0.013*
FORMLABS	*Biomed Amber*	Layer	0.168	0.187	0.005*
		Duration	0.036*	0.191	0.005*
		Layer * Duration	<0.001*	<0.001*	0.933
	Biomed White	Layer	0.021*	0.013*	0.082
		Duration	0.183	0.093	0.171
		Layer * Duration	<0.001*	<0.001*	<0.001*
	Biomed Black	Layer	0.034*	0.017*	0.001*
		Duration	0.732	0.982	0.198
		Layer * Duration	<0.001*	<0.001*	0.207

***** Denotes significance

7.4.2. Ultimate Tensile Strength

For UTS (Figure 34), Layer was statistically significant for all materials except Med Amber (p=0.067). Duration was not statistically significant for any of the materials except for Biomed Amber (p=0.036). For all materials except for Med Amber (p=0.619), there was a significant two-way interaction for layer and duration (p=<0.001). UTS generally exhibited a decline from the outer layer, (A), to the inner layer, (D), for all materials.

Biomed Amber was the only material to demonstrate a noticeable increase in UTS in the innermost layer D due to increasing exposure from 100% to 500% (45.1MPa to 63.5MPa respectively).

7.4.3. Young's Modulus

For YM, (Figure 35) Layer was statistically significant for all materials except for the two translucent materials, Med Amber (p=0.520), and Biomed Amber (p=0.187). Duration was not found to be statistically significant in any material. All materials showed a statistically significant two-way interaction for layer and duration.

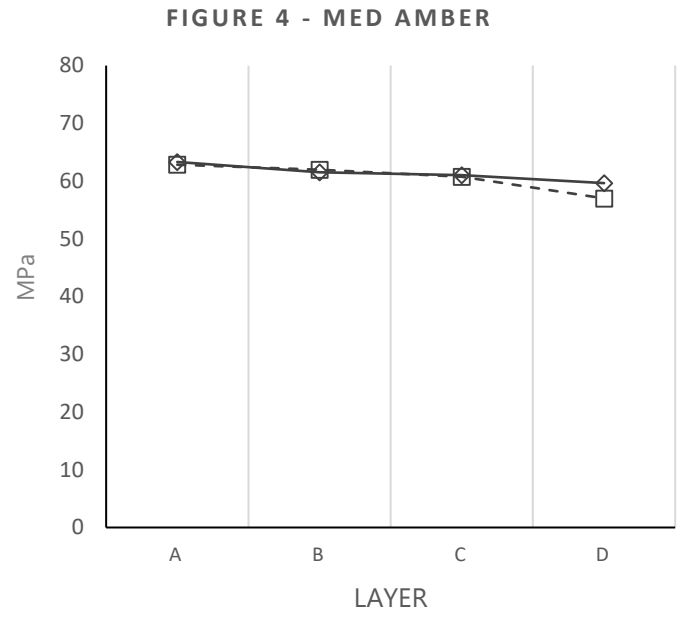
Again, the only notable increase in YM because of increased duration can be seen in Biomed Amber, (671.7MPa to 879.8MPa respectively).

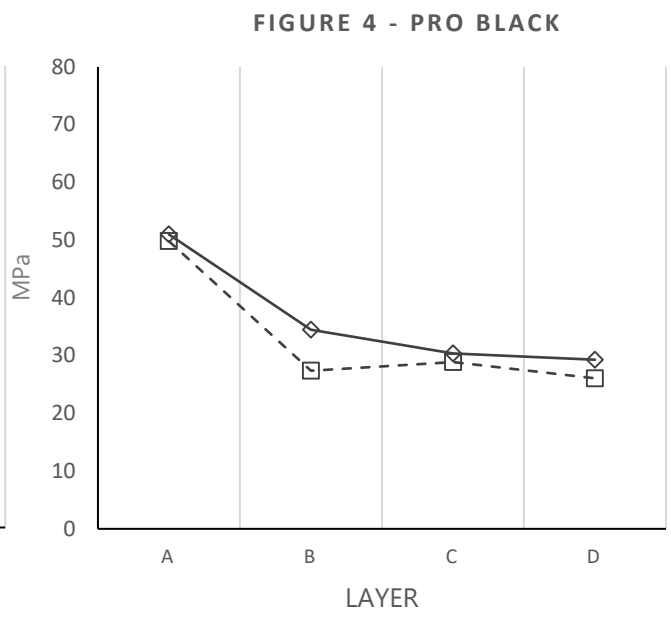
7.4.4. Elongation at Break

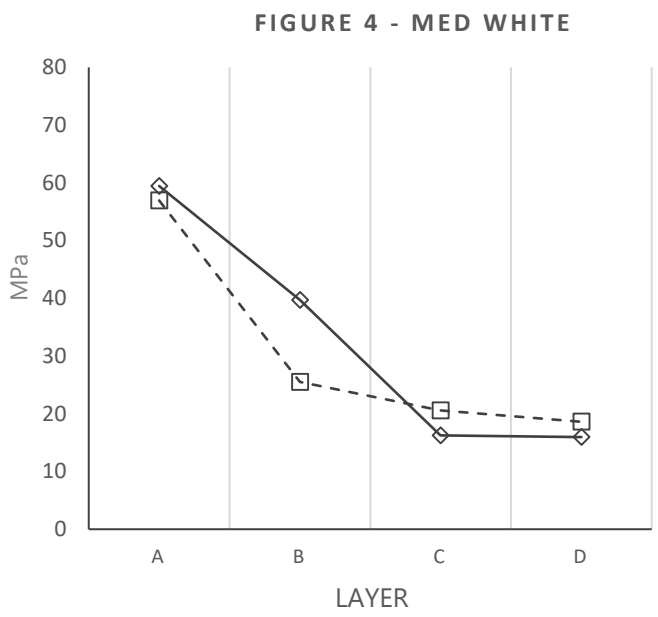
For EB (Figure 36), Layer was statistically significant in Med White (p=0.014), Biomed Amber (p=0.005), and Biomed Black (p=0.001). Duration was only found to be statistically significant for Biomed Amber (p=0.005). At the two-way interaction, significance was found in Med White (p=<0.001), Pro Black (p=0.013), and Biomed White (p=<0.001).

For all materials except Med Amber, an increase in EB was seen from layer A to D. The most notable increase between individual layers was seen in the 100% treatment of Pro Black from layer A to layer B (26.7% to 108.7% respectively).

FIGURE 4







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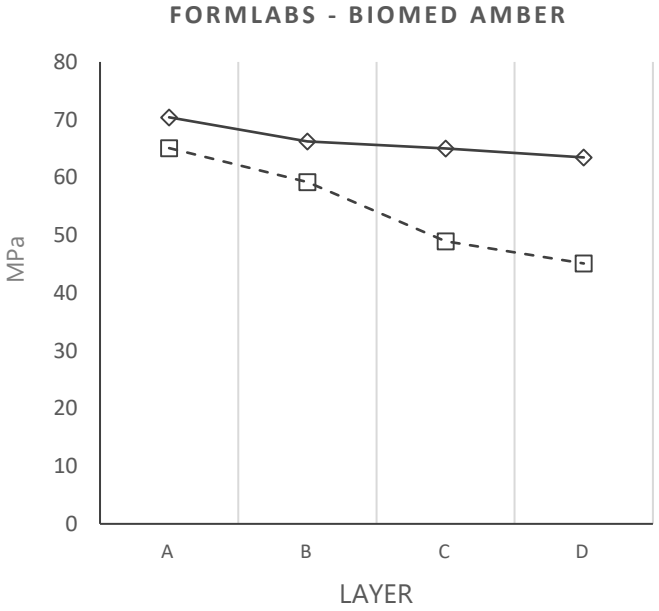
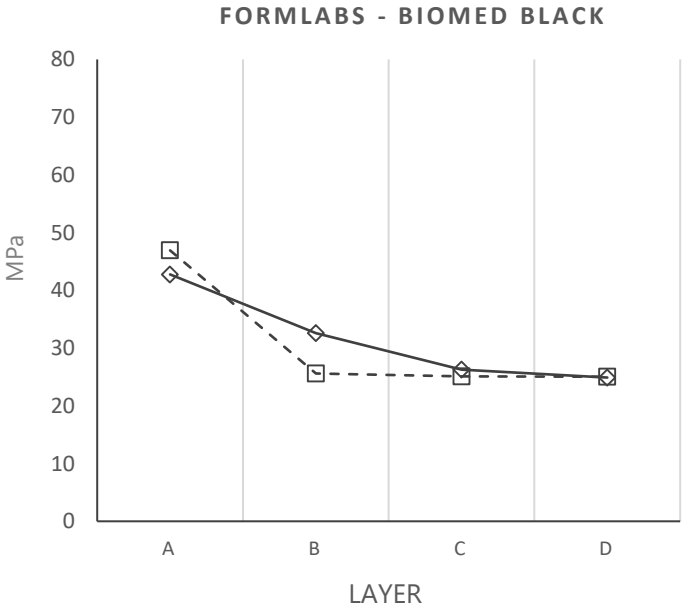




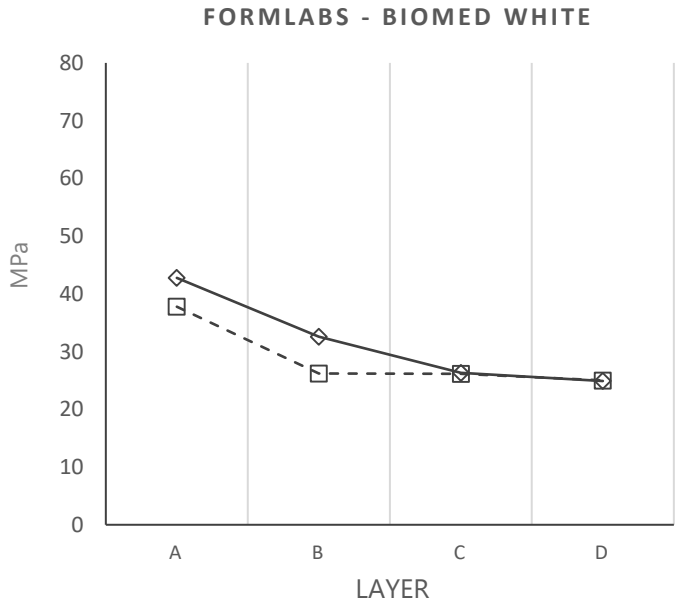
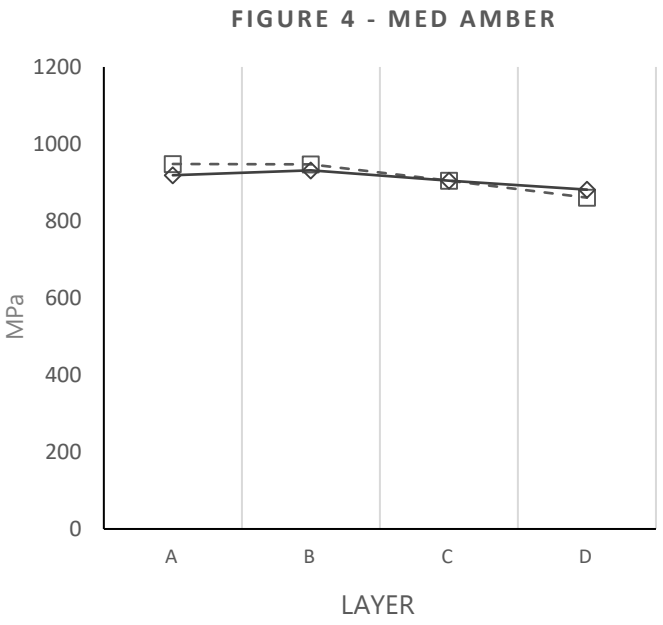
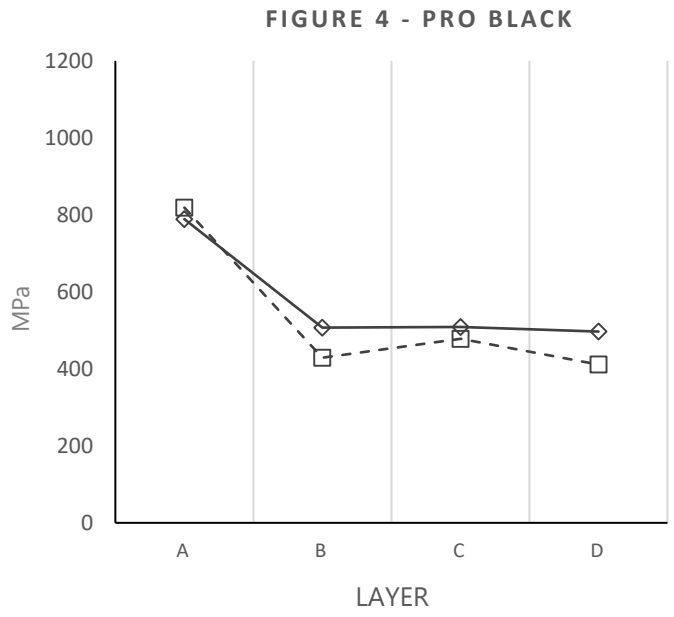
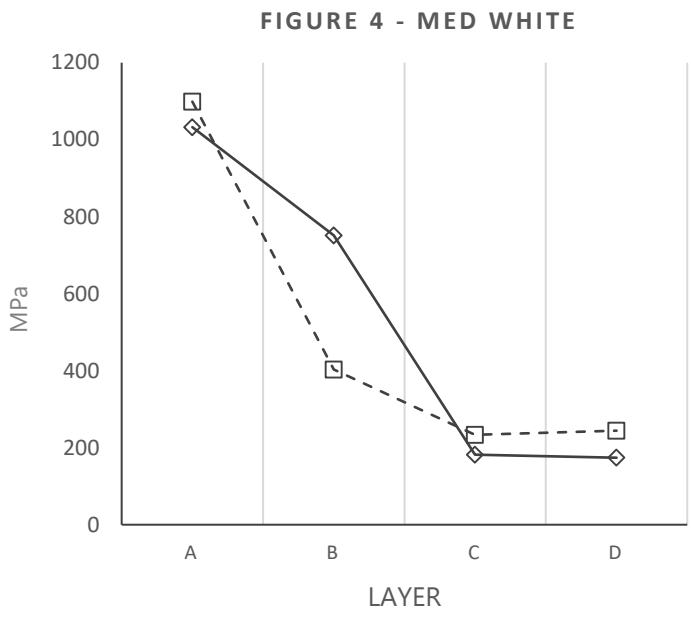


Figure 34: Ultimate Tensile Strength of Layers A, B, C, D (Figure 4: Med Amber [A], Pro Black [B], Med White [C]) (Formlabs: Biomed Amber [D], Biomed White [E], Biomed Black [F]) at 100% and 500% curing intervals.

FIGURE 4







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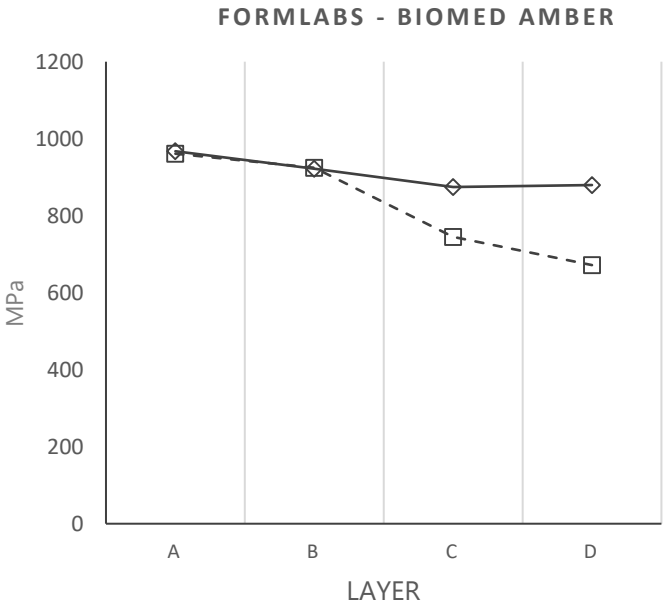
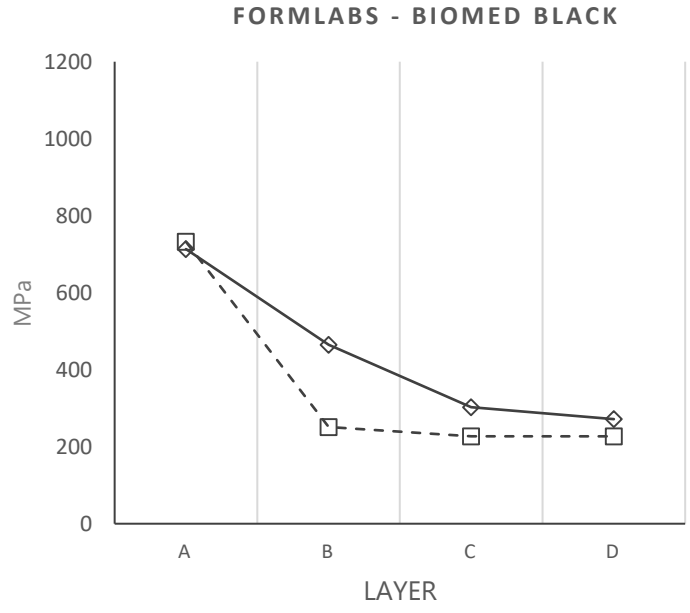




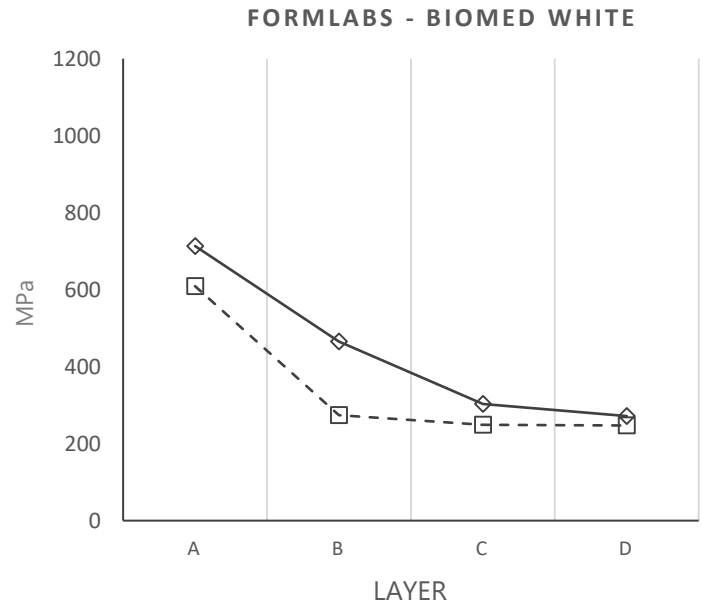


Figure 35: Youngs Modulus of Layers A, B, C, D (Figure 4: Med Amber [A], Pro Black [B], Med White [C]) (Formlabs: Biomed Amber [D], Biomed White [E], Biomed Black [F]) at 100% and 500% curing intervals.

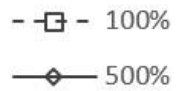
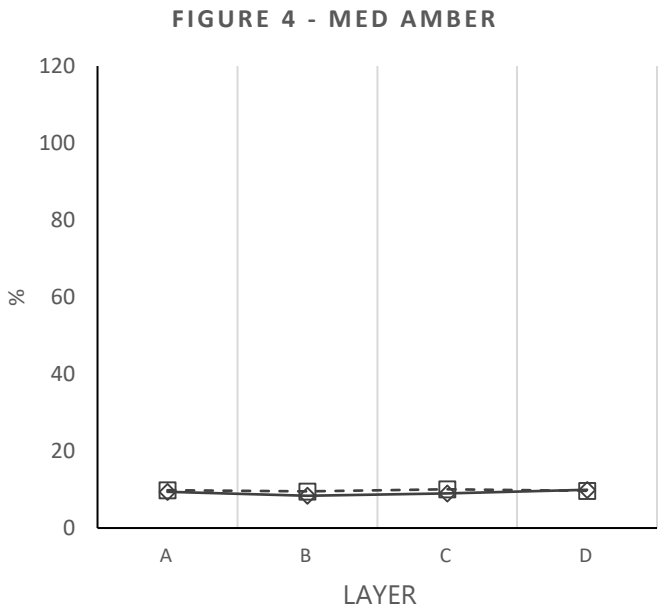
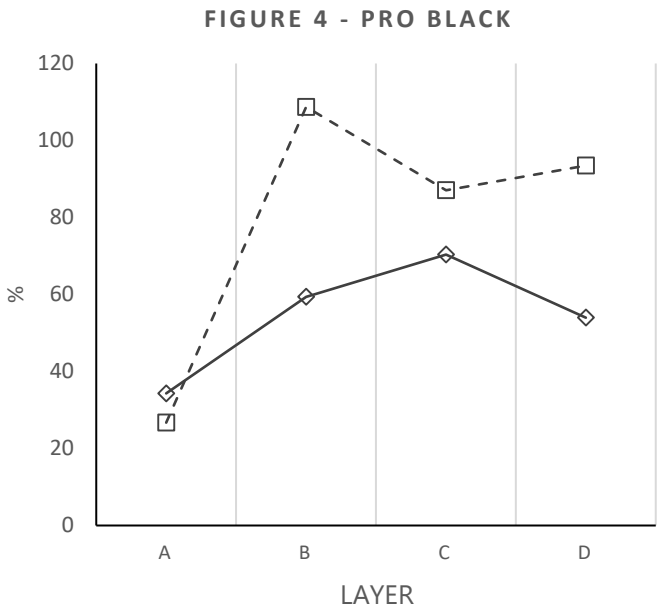
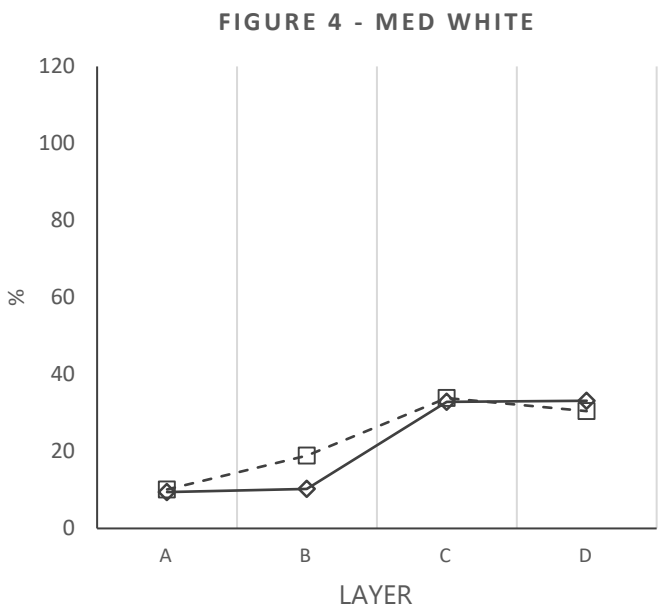


FIGURE 4







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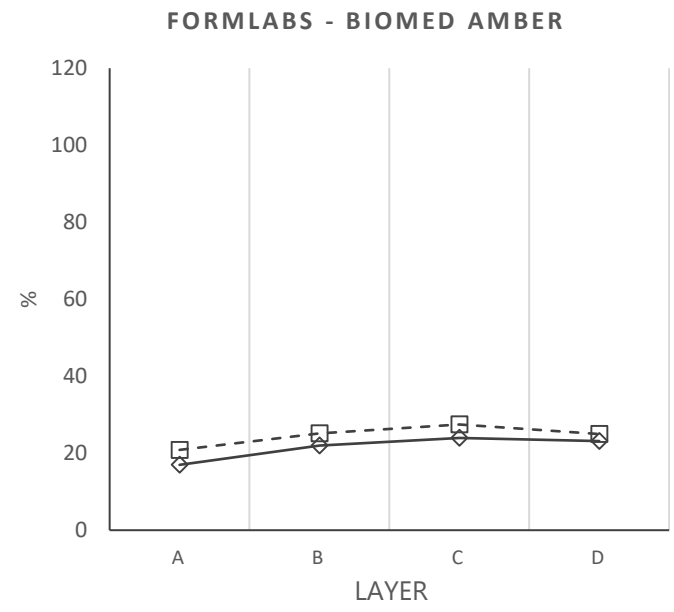
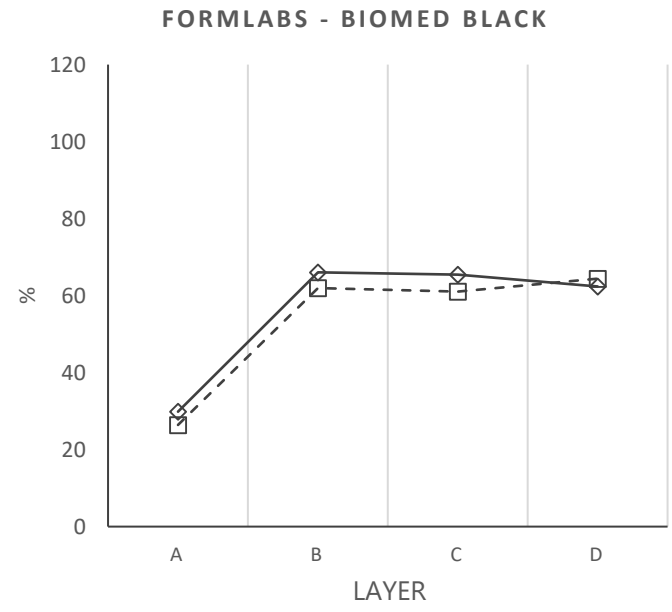




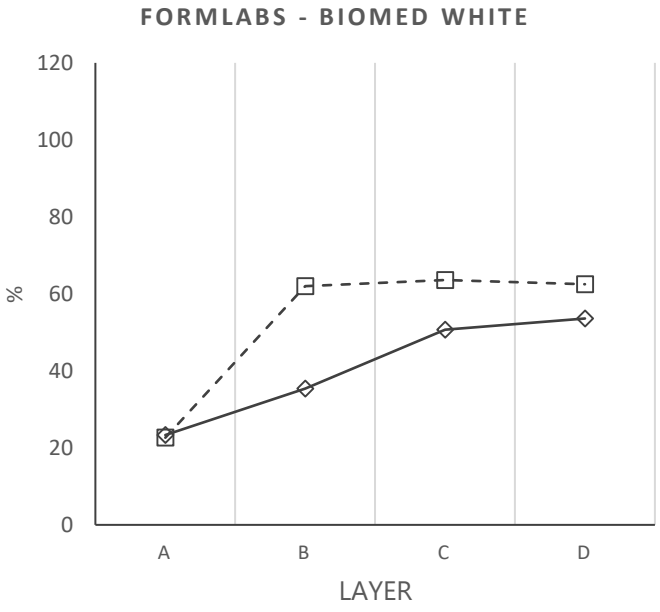
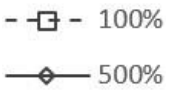


Figure 36: Elongation at break of Layers A, B, C, D (Figure 4: Med Amber [A], Pro Black [B], Med White [C]) (Formlabs: Biomed Amber [D], Biomed White [E], Biomed Black [F]) at 100% and 500% curing intervals



7.5. Discussion

7.5.1. Background

The rise in development and application of 3D printing systems and the ever-reducing cost associated both in capital and materials has reduced the barrier to entry from hobbyist use through to high-end industrial use in manufacturing (Mota 2011; Anderson 2012). The application of 3DP in medicine has been a growing area of interest over the last decade for bespoke/personalised devices (Kermavnar *et al.* 2021). The COVID 19 pandemic highlighted the potential for 3DP to replace traditional manufacturing methods, especially in circumstances where there are supply chain challenges (Choong *et al.* 2020). The accessibility of 3DP systems and materials that are marketed as biocompatible has allowed the production of medical devices by researchers, health care professionals, and novices, outside of traditional manufacturing and regulatory settings (Trenfield *et al.* 2019). This has the potential to negatively impact on the quality of 3DP medical devices as it is inferred, and often assumed, that the instructions provided by 3DP manufacturers are a de facto assurance of quality. Generic printing and post processing instructions are applicable to any model that can be printed within the parameters of the respective 3D printer, regardless of size or complexity of geometry.

7.5.2. Effects of geometry

The rationale for the design of the complex test model was to approximate a 'complex' model, with the presence of internal features. The radially spaced test specimens and internal walls were intended to evaluate any impact on mechanical properties as the inner specimens were further from the light sources. Results for the UTS and YM generally showed a decline in value from the outer layer "A" through to the inner layer "D", however it appears there is

a trend in Figure 34 and Figure 35, whereby the reduction in mechanical properties is greater in materials with pigmentation (Pro Black, Med White, Biomed Black, Biomed White) than in the translucent materials (Med Amber, Biomed Amber). This would suggest that the pigmentation is possibly absorbing and/or reflecting the UV light, and as a result the inner layers were exposed to less energy, thereby reducing overall curing (Tumbleston *et al.* 2015; Ahn *et al.* 2020).

The sharp reduction seen in mechanical properties of the pigmented resins between layers "A" and "B" are of particular note. The geometry separating layers "A" and "B" was a single 2mm thick wall, and the results suggest that the UV light was largely unable to penetrate past the wall to the second specimen layer. This result is cause for some concern as to the ability of complex parts to fully cure internally from the recommended UV exposure.

7.5.3. Extending curing duration

As material manufacturers recommend extending post-curing times for 'large' or 'complex' models, this experiment tested two intervals of post-curing (3DSystems 2020c). As no guidance is provided as to how much to extend the exposure time by, 500% of the recommended time was chosen as an arbitrary 'worst case' interval to apply to the test model. For the translucent materials (Med Amber and Biomed Amber), similar mechanical properties were achieved at both time intervals, suggesting that the recommended 100% interval is sufficient to fully cure these materials. Biomed Amber showed modest increases in UTS and YM, with a slight reduction in EB for the outer layer "A", suggesting that the material had become slightly brittle after exposure to the 500% interval.

Results for the pigmented resins (Pro Black, Med White, Biomed Black, Biomed White) showed very little increase in mechanical properties for the inner layers

at 500% of recommended curing times, and none of the materials demonstrated homogenous properties throughout even after this excessive exposure length. While it cannot be definitively stated that further exposure would eventually be sufficient in curing layers "A" through "D" to similar states, the practicalities of curing any parts for durations beyond 500% makes the point somewhat moot.

7.5.4. Potential impact on Biocompatibility

Several studies have identified leachates of uncured resin from printed models after post-processing has been completed (Macdonald *et al.* 2016; Oskui *et al.* 2016; Alifui-Segbaya *et al.* 2017; Walpitagama *et al.* 2019; Rogers *et al.* 2021). Those studies noted that whilst further post-processing reduced the concentration of these leachates, it did not eradicate them. While biocompatibility was not directly evaluated in this study, the reduced mechanical properties shown here are cause for concern as it heavily implies the presence of semi-cured resins, even after significantly increased exposure time. As stated in all of the material safety data sheets for materials used in this study, uncured resin may cause several toxicological and immunological responses.

7.5.5. Limitations

The printer technology used for this experiment was limited by availability. The materials chosen were dictated by the technology choice due to the system requirements for proprietary resins. Only three materials from each range were tested due to time and cost constraints.

The test model designed was intended to collect the necessary data and was the only test model used. Other designs for test models may vary by results.

7.5.6. Future Research

Using the data collected in this experiment, future work may consist of applying the data to establish the limitations of curing for each of the materials. Using the dimensions of the test model, gauges for maximum and minimum thicknesses may be used to signal whether a prospective geometry is capable of curing with the intended material.

7.6. Conclusions

- The findings of this study reinforce that caution must be taken when post-curing parts printed on vat-polymerisation 3D printers, as generic instructions may not result in sufficient curing of the entire part throughout.
- Translucent materials appear to perform best when creating large parts or those with complex internal geometries.
- Extending post-curing times by 500% of the manufacturer's instructions may not necessarily result in homogenous curing of parts when using resins with pigmentation.
- The presence of semi-cured material internally of vat-polymerised 3D printed parts may negatively impact the biocompatibility of the finished part.

Chapter 8: Discussion

8.1. Overview

The aim of this thesis was to investigate the factors affecting biocompatible 3D printing photosensitive resins, with respect to the current applications and challenges of the technology within a medical setting. This chapter summarises and discusses the findings of the research, and identifies key points that health care professionals and other users should consider when using these materials.

8.2. Chapter 3 – 3D printing response to COVID-19 PPE shortage

8.2.1. Background to the study

During the COVID-19 pandemic there was a shortage of PPE and other much needed medical devices. The shortage was the result of high demand for integral equipment, and the restriction of existing supply chains once government lockdowns were issued. Initially, 3D printing was used on a small scale to manufacture critical ventilator components, most notably in Italy during the first wave of COVID infections (Meyerowitz-Katz and Merone 2020). After this gained notoriety across the world there were a number of local responses by the 3D printing community to manufacture other medical devices using unofficial or open-source designs. This movement was largely unchoreographed, and lead by open-source file sharing across amateur makers, research institutions and professional manufacturers. The rapid mobilisation of decentralised manufacturing using 3D printing during the COVID-19 pandemic was the first of its size and demonstrated a mix of

successful and unsuccessful applications of the technology, while highlighting the inherent deficiencies in an unregulated supply chain.

8.2.2. Summary of findings

The study performed in chapter 3 reviewed the outcomes of a decentralised supply chain in order to assess what can be learned and applied to optimise future potential responses. The findings of the study showed that the movement was generally successful in supporting health care systems during the pandemic. However, due to the emergency nature of the situation, many regulatory requirements were disregarded and overlooked, and these were defined by six key lessons learned.

1. Volume manufacturing using 3D printing at required quality levels was a challenge during the pandemic
2. Infection prevention and control practices need to be respected or printed solutions will not be used in health care settings
3. Emergency 3D printed devices need to consider mechanical strength characteristics
4. There is a need for guidance on good manufacturing practices for 3D printed devices
5. Makers may be inadvertent medical device manufacturers and responsible for product liability and IP infringement
6. It is crucial to involve clinical stakeholders if making or designing solutions

8.2.3. Relevance for practice

As detailed by Choong *et al.* (2020), it is important to identify and critique the issues seen during the 3D printing response to COVID-19 in order to build on better frameworks for future responses. The issues identified in chapter 3 can be grouped under standardisation, communication, and traceability.

Regarding standardisation, it is necessary that it is applied across all aspects of the supply chain. It is vital that the final device is consistent, especially when

there are multiple contributors involved in manufacturing it (Kumar and Pumera 2021).

As 3D printing has a multitude of customisable options that ultimately effect the output, an envelope of controlled inputs must be established before manufacturing commences. This may entail:

- One design file being created with feedback from end users
- A set of slicing parameters being established e.g. layer height, infill density, wall count, orientation etc.
- Specifying the type of material to be used

By introducing standardisation the issues seen with parts being rejected by end users due to variation in the overall quality and viability will be reduced.

Communication between stakeholders should be improved. A system of feedback should be established either locally or globally dependant on the need of the situation. Communication could be set up via the same open-source file sharing sites often utilised by the 3D printing community. Most importantly this should be used to communicate volume needs, feedback concerning defects, part assembly, and information for stakeholders regarding infection prevention control aspects such as handling, and drop off points. Efforts by 3D printing company Prusa3D (Prusa3D, USA) attempted similar strategies by publishing guides for contributors to follow alongside iterations of their face shield visors (Prusa3D 2020). This was one of few detailed initiatives seen during the response.

Finally, full traceability should be implemented. This would require contributors to register themselves and their printer. For example, a serial number could be attached to batches so that defects or faulty parts can be traced back to the contributor/maker.

It is important to address these inefficiencies and establish a framework to be used for future situations. By centralising the 3D printing supply chain in these ways, the overall success of the response could be improved.

8.3. Chapter 4 – 3D printing in palliative care

8.3.1. Background to the study

As a production method 3D printing is often favoured for its ability to create rapid bespoke solutions. Some fields of medicine tend to utilise 3D printing more than others. These fields are often associated with patient specific devices, or that require a device that is not commercially available on the market. Palliative care is a discipline of medicine is an example of one of these and from which we can learn regarding potential future uses and needs of 3D printing to directly treat patients.

Palliative care is defined by the need to improve the quality of life for the patient, given with or without curative intent (IAHCP 2019). Interventions in this clinical discipline can require bespoke solutions with a fast turnaround time. As such, 3D printing could be an ideal production method for some of the solutions required. A systematic review was performed on the literature to profile the types of devices currently being designed and manufactures, whilst also considering the problems addressed by 3D printing, and the 3D printing technologies used.

8.3.1. Summary of findings

The systematic review identified 30 studies detailing 36 3D printed devices used to provide palliative care. The majority of studies were published between 2016 and 2020, prior to 2016 only a few publications were found.

The most common fields of medicine were oncology based, making up 31/36 of the results. Other fields included neurology, chemotherapy, pain palliation and enteral feeding.

The most common reasons for utilising 3D printing were that the devices did not already exist, or that using traditional methods were inaccurate, slow, expensive or lacked the option for customisation.

8.3.2. Relevance for practice

Two key observations can be made from the identified studies. Firstly, the devices were often sanctioned because a solution did not already exist on the commercial market. Many of these devices were similar in function across the studies, but differed by their being patient-specific aspects. Secondly, it is apparent that the choice of 3D printing method was often made due to availability rather than the suitability of the technology.

8.3.2.1. Collaboration in medical research

Many of the devices produced in the identified studies were made because a solution did not exist on the commercial market. Often, this was because the device itself was patient specific and would not be fit to serve elsewhere. However, many of these devices had very similar applications. Whilst the exact device could not be reused, the process could be shared to an online repository to help other HCP's who require similar bespoke devices to learn from existing trials. This would be preliminary to publication, meaning collaboration could begin earlier. This would help to inform the choice of technology, material used, post-processing/finishing requirements, previous iterations, and patient outcomes.

8.3.2.2. Knowledge of 3D printing technology

In the studies identified by the systematic review, the technologies used were not always the correct choice for those applications. This suggested that the choice of technology was made by the availability to the HCP, rather than the suitability of the technology to the required device.

The most commonly used technology was FDM. Generally, FDM would not be used to produce medical devices due to its poor surface finish, issues surrounding sterilisability, and lack of available biocompatible materials. FDM would usually be chosen for larger single use devices, such as jigs or fixtures. Methods such as SLA, DLP and EBM would be expected as the better choice for producing devices that required sterilisability, biocompatibility and smooth surface finishes.

While the barrier to entry to 3D printing has improved significantly since the release of key patents in the early 2000's, investment into specific technologies for individual needs may not be feasible in some cases. It is also possible that knowledge of the technology is limited, and suboptimal methods of 3D printing are being utilised by HCP's as they are unaware of other machine capabilities.

HCP's should seek consultation prior to manufacturing to ensure the optimal 3D printing method is being used, and that the required mechanical and biocompatible properties are achieved. If the technology needed is not available to them, out sourcing should be considered.

8.4. Chapter 5 – Review of biocompatible materials

8.4.1. Background to the study

The increase in the use of 3D printing in healthcare has created a need for biocompatible materials with specific properties such as biocompatibility. There are a large number of these commercially available to the general public which can be easily purchased online, most of which are photosensitive resins developed for vat-polymerisation systems. The aim of chapter 5 was to review the information from the grey literature concerning certification and intended uses in terms of quantity and quality of the information supplied.

8.4.2. Summary of findings

The study identified 130 materials which met the search criteria. The information retrieved varied in quality, quantity and in the terminology used. Some materials stated up to seven specific certifications alongside detailed post-processing information and instructions for the intended use of the material, whereas in some cases little to no detail was provided. The terminology used across different material suppliers in the grey literature varied, with words such as ‘capable’, ‘compliant’, ‘meets’, and ‘satisfies’ being used to refer to certifications the material had passed. It was summarised that the use of terminology and the formulation of how materials are marketed may be misleading to users, and if unscrutinised could shift responsibility to the user.

8.4.1. Relevance for practice

The information provided by material manufacturers for biocompatible 3D printing resins varies significantly, and is often ambiguous, vague, or completely lacking. Standardisation should be implemented for the overall quality and quantity of information regarding post-processing, the

terminology used to cite certifications, and clarification of what certifications entail. This information is integral to achieve the intended material properties, for the material to be employed correctly, and for users to be aware of what is required of them in relation to these points.

Firstly, the information that is provided with materials should include:

- Detailed post-processing instructions including techniques and times for washing, techniques and times for curing, and recommended brands of curing tank that are compatible
- Clear upfront statements concerning the importance of testing post-processed devices to determine if the mechanical and biocompatible properties have been achieved
- The certifications passed when the material is in its finished state
- Intended uses for the material relevant to the certifications passed

The terminology used to market biocompatible materials should be clear to users. Currently, phrases such as ‘meets’, ‘satisfies’, and ‘complies’ are ambiguous and could be interpreted as synonyms for ‘passed’. The language used for the passing of certifications should be standardised to ‘passed’, or ‘not passed’. This would clearly indicate to users to what extent they should seek to test the biocompatibility or mechanical properties of their printed devices.

8.5. Chapter 6 & 7 – Post-processing large and complex geometry models

8.5.1. Background to the study

As identified in chapter 5 and discussed in section 8.4, there is significant variation in the quality and quantity of information provided with biocompatible 3D printing photosensitive resins. It was also identified in section 2.4 that these materials require very specific post-processing treatment to achieve a state where they meet the biocompatible properties stated by suppliers.

Some 3D printing biocompatible resin suppliers will provide detailed information concerning the technique that should be used when post-processing their materials (3DSystems 2020c; Formlabs 2022). This information comes with recommendations for users that 'larger or more complex geometries' may require further post-processing. However, they do not provide detail of these parameters.

Two experiments were conducted (chapter 6 & 7) to test the effects of extending post-curing on test models that simulated 'larger' and 'complex' geometries. Opaque pigmented and translucent pigmented materials were chosen for the experiments to investigate any differences in their requirements.

8.5.2. Summary of findings

The high level results of the first experiment that tested 'larger' geometries identified that materials with opaque pigmentation did not cure to full depth, whereas the translucent materials did. Similarly, in the second experiment that tested 'complex' geometries, the materials with opaque pigmentations were unable to reach similar mechanical properties throughout, but again, the translucent materials were.

8.5.3. Relevance for practice

The results of the experiments identified two important outcomes. Firstly, the opaque pigmented materials tested were much less capable of curing completely through than the translucent pigmented materials. Secondly, generic instructions for post-processing in these instances would be ineffective when the technology is often utilised to produce unique batch-of-one models. These two points must be reviewed within the technology. Suggestions for possible actions are made in the following two sections.

8.5.3.1. Recommendations for post-processing

3D printing is often utilised for its ability to create unique structures of varying sizes and complexities (Zhang and Xiao 2018). This should be expected, and post-processing information should be given in such a way that it can be quantified by the dimensions of the required model.

Material manufacturers often reference the use of 'test coupons' used to determine the given post-processing instructions (3DSystems 2020c). The dimensions of these test coupons are not detailed. To help inform users of the post-processing requirements of their specific model, manufacturers could provide details of test coupon dimensions, as well as perform curing depth tests on a series of scaled up thicknesses. Each thickness would then specify the amount of time taken to achieve the optimal material properties. Whilst the results shown in chapter 6 suggest that these intervals would be lengthy, users would have a much clearer idea of the post-processing requirements of their models.

8.5.3.2. Recommendations for opaque pigments

A similar practice may be applied to opaque pigmented materials. As seen in chapter 6 and 7, at a certain depth opaque pigmented materials plateau and

are unable to cure further at a feasible rate. Material manufacturers may suggest maximum thicknesses for these materials, and recommend that users consider printing the model in smaller sub-assemblies that are first post-processed, then post-assembled. This would allow users to still use opaque pigmented materials for applications that require them, whilst still being able to rely on post-processing being successful.

8.6. Regulatory aspects

3D printing itself is still considered to be in its infancy and is growing at such a rate that defining a regulation before the technology evolves is difficult (Pierrakakis *et al.* 2014). This is further convoluted by the term '3D printing' being an umbrella term encompassing several technologies (Gibson *et al.* 2021). Whilst these technologies share many similarities in their process, the various inputs and requirements of those systems are significantly different, and so creating regulations that consider all technologies within 3D printing is arduous (Pilipović *et al.* 2020). This has led to the slow development of an indistinct regulatory framework that is unclear, misinterpreted, or are altogether disregarded (Chua *et al.* 2017; Ricles *et al.* 2018).

Whilst medical device manufacturing is highly regulated, during the COVID response typical standards for testing and validation were overlooked due to the necessity required from the situation. During this time, interpretations of regulations were made by contributors, whereby certified design files such as those provided by 3DSystems, Prusa3D and Formlabs were published free for download (3DSystems 2020b; Formlabs 2020a; Prusa3D 2020). The assumption was made by some contributors that because these designs had been tested and certified by reputable sources, that replicating the designs on their own machines, with their own input parameters also equated to a certified device (Choong *et al.* 2020). However, this was not the case and may have contributed

to some of the issues identified in chapter 3 concerning 'lessons learned'. In this example, 'certified for 3D printing' was misunderstood, but actively disregarded due to the urgent need for PPE.

The difficulty in interpreting regulations is also seen in chapters 5 through 7. The information supplied with biocompatible materials provides specific post-processing instructions with recommendations to extend curing times for large or more complex model geometries. An interpretation of this statement was replicated by the methods used in chapters 6 and 7, and was shown to be mostly ineffective.

Defining regulations in 3D printing is complicated due to what the term '3D printing' encompasses. In this sense, it may be better for regulatory bodies to acknowledge 3D printing technologies individually. This could mean creating standardised profiles specific to each method that provide input settings for users to follow, these could be provided with *de facto* dimensional tolerances that must be achieved to be within regulation.

8.7. Limitations

8.7.1. Palliative care systematic review

There are many more studies concerning 3D printed palliative care devices that may not have been identified by the search string used. It is also possible that the definition of 'palliative care' used to filter inclusion/exclusion may differ from other definitions.

8.7.2. Review of biocompatible 3D printing resins

This review was performed on the grey literature using Search Engine Operatives (SEO's). It is possible that the operatives used to identify

biocompatible materials did not collect all relevant information. It is also highly likely that repeating this search will collect different results due to the changing of SEO's and release of new materials.

8.7.3. Post-processing to address large and complex model geometries

The 3D printers used in the two experiments testing the post-processing of large and more complex model geometries were chosen due to their availability to the author. This is also the case for the materials used as the 3D printers used require proprietary materials. It is possible that the outcomes of the experiment would vary using different 3D printers/materials.

The test models designed for both experiments were novel. They were designed to be quantifiable, however there may be more optimal test model designs.

The intervals chosen for post-curing were arbitrary extensions of the given recommendations by material manufacturers. Longer periods of testing were ruled out due to time/cost constraints. As other intervals were not tested, it cannot be said as to whether further post-curing would have different results.

8.8. Future research

Building on the findings of chapters 3 and 4, future research may look to improve the education of 3D printing at the point-of-care and be used to establish standards and frameworks for users to follow. This may include:

- Increasing the education of 3D printing at the point-of-care via consultation to help users establish a better understanding of existing technologies, their application and the optimum method of printing for specific devices
- Providing IPC control systems for users to follow when 3D printing at the point-of-care that can be used by contributors in emergency situations, such as pandemics
- Establish standards frameworks for contributors to follow when regulations are unavailable
- Development of standards for the quantity/quality of information that is to be supplied with 3D printing biocompatible materials

In particular, future research should build on the findings of chapters' 5, 6 and 7 to further understand the post-curing limitations of commercially available biocompatible resins. This could entail:

- Establishing profiles for maximum thicknesses and geometries capable of successfully post-curing opaque pigmented materials
- Providing the dimensions of 'test-coupons' used to design post-processing instructions to help inform users
- Recommending the use of sub-assemblies for parts that feature large or more complex geometries to ensure post-curing is successful
- Recommending the use of translucent/transparent materials for biocompatible applications

8.9. Future work: Digitalisation of post-processing

Future work may include digitalising post-processing information for users. This could be built into the slicing programs of proprietary printers. Prior to slicing, the program would run an analysis of the users uploaded geometry and identify areas that may not be capable of post-curing successfully, or areas that may harbour liquid resins and therefore require further post-washing. In order to do this, the mesh of the 3D file would firstly have to be converted from a tri-mesh, to a quad-mesh for the program to understand the model as a physical artefact. A multiphysics based engine such as COMSOL (COMSOL, Sweden) may be used to simulate UV curing on the selected geometry to ascertain the potential UV and heat penetration capabilities of the chosen model. The program would then be able to make recommendations to the user such as:

i. The geometry and chosen material will be successful in post-processing when following the manufacturer's instructions
ii. The geometry will be unable to cure to full depth using the selected material, it is recommended that post-curing be increased by 'X' amount of hours
iii. The geometry will be unable to cure to full depth and extending post-curing will require an unfeasible amount of time and possibly cause damage to the outer surfaces of the model. Therefore, please consider re-designing the model as smaller sub-assemblies and post-processing them individually before final assembly

This feature could be available for all materials, but be a requirement for biocompatible materials. If a biocompatible material is chosen in the slicing software, and the analysis shows the chosen geometry is incapable of successfully post-curing, the user would be unable to export the g-code file to

the printer. The user would then have to digitally sign, and accept the responsibility of production in order to export the file. This would ensure that users at the point-of-care are fully aware of the potential for the material to not achieve its optimal biocompatible and mechanical properties, and to seek alternative methods for their device.

Chapter 9: Conclusions

- Many regulatory aspects were overlooked during the decentralised 3D printing response during COVID-19
- Standardisation, communication and traceability must be improved upon in similar future situations
- 3D printing has become increasingly popular to manufacture patient-specific devices for the field of palliative care in recent years
- Often, suboptimal 3D printing methods are used for devices, seeking consultation would help to inform this
- Communication could be improved to help facilitate collaboration between HCP's that are working on similar bespoke devices
- There is considerable variation within the quantity/quality of information provided with biocompatible photosensitive resins concerning certifications, intended uses and post-processing information
- Standardisation should be implemented that requires material manufacturers to provide a minimum amount of information, and to only use specific unambiguous terminology within the grey literature
- Opaque pigmented and translucent materials presented significantly different results when post-processed using intervals of the given instructions
- Opaque pigments should only be used for smaller assemblies, or should be removed from the biocompatible commercial market
- Post-processing instructions should provide a series of quantifiable gauge sizes for users to establish post-processing requirements relative to their unique model

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Appendix I: Supplemental table reviewed studies of 3DP in palliative care.

Study **Field of application** Device type and indication	**Problem solved by 3DP**	**Device Production**		**Device testing/use**		
		Imaging technique Software	**3DP technology** 3D printer (manufacturer) Material *Additional procedures (if applicable)*	**Participants** Number, sex, age Medical status	**Methods**	**Outcomes**
(Kim *et al.* 2017) Gastrointestinal oncology (gastroduodenal) Anatomical phantom for testing of gastroduodenal stents for treatment of malignant strictures	Ethical unacceptability of investigating the mechanism and significance of stent abutment in the duodenal wall of live patients.	**CT** MeshLab Meshmixer	**MJ** Objet500 Connex3 (Stratasys) Tango family	Retrospective analysis ♂, 62 years Advanced gastric cancer	Measurement of elapsed times at passage of water (300 ml, 4 s), and soft and solid food materials (3 types; 300 ml); partially and fully covered self-expanding metallic stent; 2 locations of distal stent ends; 10 repetitions.	Proof of concept: Stent abutment can cause prolonged passage of soft and solid diets through the stent, impaction of solid diets into stent.
(Yang *et al.* 2018) Gastrointestinal oncology (bile duct) Patient-specific anatomical model of tumor and bile duct visualization to aid surgical planning for ERCP biliary stent placement	Difficulty determining target bile duct with traditional imaging techniques in complex HCC.	**CT/MR** Mimics 17.0	**MJ** ProJet 4500 (3D Systems) VisiJet C4 Spectrum Core	Retrospective analysis 6♀, 9♂, 65.4 ± 14.9 years Inoperable hilar cholangiocarcinoma	Target bile duct and Bismuth-Corlette (BC) classification on the basis of 3D models; comparison with those in ERCP.	86.7% concordance rate of target bile duct, 93.3% concordance rate of BC type classification with 3D model compared to ERCP.
(Heunis *et al.* 2019) Orthopaedic oncology (pelvis) Patient-specific anatomical model of the pelvis for surgical planning to minimize acetabular bone loss and maximally preserve native hip function and stability	Difficulty of safe tumor resection with negative oncological margins, acceptable postoperative function, preservation of critical neurovascular structures and minimal perioperative morbidity, mortality and recurrence within tightly confined, complex anatomical areas.	**CT** N/A	**N/A** N/A N/A Manufactured by Onkos Surgical	♂, 21 years Metastatic osteoblastic osteosarcoma	Clinical follow-up.	Successful joint-preserving posterior acetabular resection of metastatic osteosarcoma with tumor-free margins and preserved hip stability. Improved quality of life, patient returned to athletic and academic pursuits.

(Pham *et al.* 2018) Radiation oncology (brain) Patient-specific anatomical model of the head and head-and-neck rest to serve as a volume and position mould for radiotherapy immobilization mask in whole brain radiotherapy	The need for an additional simulation CT-scan in preparation for radiotherapy with traditional methods, which increases the number of patient visits, interventions and waiting times.	**CT** CATIA	Mould: **FFF** BigBuilder Dual-Feed (Builder 3D Printers BV) PLA *Immobilization mask:* *Thermoplast (Aquaplast RT) moulded onto model head*	Retrospective analysis 9♀, 2♂, 60 ± 11 years (range 47-85) Brain metastases	CT scan of immobilization mask and comparison of volume to patient CT scan in Eclipse. Calculation of simulated radiation dose and comparison.	98.1% similarity between patient head surface geometry and 3D model (model volume 1.6% smaller due to segmentation smoothing), reproduction accuracy for head position within institutional constraints. Minimal differences in dosimetry during whole brain radiotherapy. Lower cost compared to simulation CT-scan, potential for reducing patient visits and waiting times.
(Templin *et al.* 2020) Gastrointestinal oncology (pancreas) Patient-specific anatomical model for pylorus-preserving pancreatic head resection and reconstruction planning in locally advanced adenocarcinoma	Difficulty establishing detailed anatomy from 2D CT images, especially in complex and unconventional cases.	**CT-angiography** N/A	**N/A** N/A N/A (multimaterial)	♂, 71 years Locally advanced adenocarcinoma of the papilla vateri; metastatic squamous-cell carcinoma of the lung (4 years stable); previous right hemicolectomy and patch plasty of the celiac trunk and superior mesenteric artery; primary adrenal insufficiency; Bühler anastomosis	/	Successful tumor resection. Bühler anastomosis only detected in 3D reconstruction; perioperative anatomy visualization using 3DP has the potential to increase patient safety.
(Lin *et al.* 2019) Gastrointestinal oncology (oesophagus) Self-expanding plastic oesophageal stent to alleviate the symptoms of irresectable oesophageal malignancies	Traditional manufacturing methods do not enable time-efficient production of parts with custom geometry and structure.	**/** Multiphysics™	**FFF** Ultimaker 2 (Ultimaker) PLA/TPU composite (0:100, 5:95, 10:90, 15:85)	/	In silico, in vitro and ex vivo evaluation: Finite element analysis, testing of self-expanding properties, compression forces, self-expansion and anti-migration forces (porcine oesophagus), 16-week hydrolytic degradation rate (phosphate buffered saline, simulated gastric fluid), biocompatibility test (human primary oesophageal epithelial cells).	Proof of concept: Significantly higher anti-migration force compared to existing stents, reduced migration distance, adjustable self-expansion force.

(Fouladian *et al.* 2020) Gastrointestinal oncology (oesophagus) Patient-specific oesophageal endoluminal drug-eluting stent for sustained local delivery of 5-FU to achieve short-term reduction of tumor size in patients with oesophageal cancer	Wide morphological and clinical variability of gastrointestinal tumours can affect the performance of non-customisable drug-eluting stents.	**/** SolidWorks Cura	**FFF (dual extrusion)** Ultimaker S5 (Ultimaker) PU	/	Material, mechanical and in vitro evaluation: Analysis of 5-FU distribution (photoacoustic Fourier-transform infrared spectroscopy), topography (scanning electron microscopy), mechanical properties (local compressive force, recovery rate), thermal analysis, drug content (high-performance liquid chromatography), in vitro drug release over 110 days, 5-FU stability following stent sterilization (UV, gamma irradiation) and accelerated storage (different temperatures and humidities)	Proof of concept: Confirmed homogeneous dispersion of 5-FU throughout the PU matrix, sustained release profile over 110 days, permeability from stent through oesophageal tissues, negligible degradation during thermal processing, minimal degradation during sterilization, reasonable stability over 3 months of accelerated storage.
(Ha *et al.* 2021) Gastrointestinal oncology (oesophagus) Tissue-specific EdECM hydrogel-loaded oesophageal stent to alleviate symptoms of radiation esophagitis	Limited precision and architectural control in hydrogel-loaded stent fabrication using traditional technologies (e.g. braiding, knitting, laser-cutting, segmentation).	**/** N/A	**FFF (spindle)** 2RPS (custom) PCL	/	Material, mechanical, in vitro evaluation, and in vivo animal study: Stent surface morphology (SEM) and topography (AFM) analysis, static compression test to evaluate radial forces, cyclic 3-point bending to test flexibility and mechanical stability; rheological assessment of EdECM hydrogel, viability assessment of human oesophageal Het-1A cells in EdECM; radiation esophagitis rat model for evaluation of therapeutic effects.	Proof of concept: Therapeutic effects confirmed on animal model: resolved inflammatory response, facilitated tissue regeneration. Promising clinical approach to local delivering of therapeutic cells/drugs to manage disease.
(Boyer *et al.* 2019) Gastrointestinal oncology (bile duct) Patient-specific biliary stent with stem cell-collagen-cholangiocyte coating to provide relief from malignant and benign bile-duct obstructions	Progressive loss of biliary stent patency over time due to biofilm and biliary 'sludge' formation.	**/** TinkerCAD ImageJ Makerbot	<u>Stent:</u> **FFF** Replicator (Makerbot) PVA (Aquasolve) <u>Collagen injection moulding chamber:</u> **SLA** Form 2 (Formlabs) Flexible Resin *Stem cell collagen injection moulding, stent maturation, cholangiocyte seeding*	/	Material and in vitro evaluation: Stent surface morphology (X-ray), human placental mesenchymal stem cell and cholangiocyte viability assessment (high-resolution Cryo-SEM, phase microscopy, flow cytometry, immunofluorescent imaging)	Proof of concept: Successful incorporation of cholangiocytes to improve stent patency by reducing the entrance and adherence of harmful bacteria.

(Jang *et al.* 2020) Gastrointestinal oncology (bile duct) Self-expanding, drug-eluting biliary stent for palliative treatment of biliary obstruction in unresectable hilar malignancies	Limited architectural, dosage precision, drug distribution and release control in drug-loaded stent fabrication using traditional technologies.	**/** N/A	**FFF** N/A PCL/PTX	/	Material, mechanical, and in vitro evaluation: Surface morphology (optical microscope, FE-SEM), radial and axial forces, chemical and thermal structure, degradable behaviour and drug release (porcine bile solution, 8 weeks), inhibitory effect on tumor growth (human biliary tract cancer cells, nude mice).	Proof of concept: Confirmed uniform drug distribution and steady release in vitro, no changes in weight and shape over time, inhibitory effect on tumor cell proliferation in small animals.
(Chiang *et al.* 2005) Pulmonary oncology Stent master for silicone moulds to rapidly produce customised airway stents for treatment of life-threatening tracheobronchial obstructions in patients with respiratory cancer	Long manufacturing times and high costs of conventional manufacturing methods, short durability of silicone moulds.	**/** N/A	**SLA** N/A N/A	/	Testing of airway stent customisation protocol: estimation of time required to deliver customised stent to the patient.	Proof of concept: Possibility of providing relief to patients within a day or over the weekend, at a relatively low cost.
(Lim *et al.* 2004) Pulmonary oncology Customised tracheobronchial stent to provide relief in respiratory tract obstruction by tumours or other lesions	Need for rapid airway-stent customisation in unusual airway morphology or unresectable, stiffer than normal lesions to suit the airway geometrical and distending strength requirements for effective palliation.	**/** N/A	<u>Stent master:</u> **SLA** N/A N/A <u>*Mould and final stent:*</u> *Casting of silicone to create stent mould, vacuum casting of PU-based resin for final stent*	/	Mechanical testing: distending strength, collapsibility; comparison to Dumon stent.	Proof of concept: Distending strength comparable to, collapsibility 17% larger than Dumon stent. The stent could be delivered to the patient in 24 h.
(Lim *et al.* 2004) Gastrointestinal oncology (colon) Customised colorectal stent to provide relief in occlusion by colorectal cancer	22-23% mortality rate of surgical procedure to create temporary stoma before resection of the stricture. Existing colonic stents are costly and nonreusable.	**/** N/A	<u>Stent master:</u> **SLS** N/A N/A <u>*Mould and final stent:*</u> *Casting of RTV9 silicone to create stent mould, vacuum casting of PU-based resin for final stent*	/	Mechanical testing: distending strength, collapsibility.	Proof of concept: Superior collapsibility ratio to conventional polymer stents, surpassed required collapsibility required for effective irrigation of the bowel. Comparable strength to metal colonic stents (e.g. ChooStent).

(Ali *et al.* 2014) Gastrointestinal oncology (oesophagus) Master for vacuum casting of semi-rigid and rigid auxetic oesophageal stents for palliative treatment of oesophageal cancer and prevention of dysphagia	N/A	/ Inventor	Stent master: **FFF** N/A ABS *Stent:* *Vacuum casting of PU resin (PX 212, VC-3300)*	/	Surface characterization (SEM), mechanical characterization (tensile and expansion testing), finite element analysis	Proof of concept: Radial expansion 0.5-5.73 mm, longitudinal extension 0.15-1.83 mm at applied pressures 0.5–2.7 bar from balloon catheter. Possibly good conformation to oesophageal wall due to non-linear anisotropic mechanical response.
(F. Wang *et al.* 2020) Radiation oncology (brachytherapy rectum) Patient-specific non-coplanar navigation guide for RIS implantation in palliative treatment of locally recurrent rectal cancer	Efficiency and accuracy of RIS implantation using traditional approaches relies on operators' experience, and misplacement can lead to unsatisfactory outcomes.	**CT** N/A	**N/A** N/A Photopolymer resin	28♀, 38♂, median 56 years (range 32-79) Recurrent sacral-invasive, lateral-invasive, or localized rectal cancer; post chemotherapy, EBRT, or surgical resection	Post-operative dose evaluation (CT); Clinical evaluation at follow-up (2.5-35.9 months): blood test, tumor markers test, abdominal and chest CT, pelvic MR imaging, tumor response (RECIST guideline version 1.1), pain assessment (Numeric Rating Scale), side-effect evaluation (toxicity criteria of the Radiation Therapy Oncology Group), overall survival time.	Confirmed effectiveness and safety of salvage treatment strategy: 85.1% pain relief, 9.1% severe side effects, median overall survival time 14.7 months, median local control time 12.2 months.
(Jiang *et al.* 2018) Radiation oncology (brachytherapy head and neck) Non-coplanar navigation guide for RIS implantation in palliative treatment of recurrent malignant head and neck tumours	Limited accuracy of RIS implantation using traditional approaches.	**CT** N/A	**N/A** N/A Photopolymer resin	14♀, 28♂, median 61 years (range 29-79) Recurrent or metastatic head/neck tumor: naso-/hypo-/oropharyngeal, oral, laryngeal, salivary-gland, thyroid, oesophageal, cervical, lung, breast, or colon cancer, soft-tissue sarcoma, lymph-node metastasis of unknown aetiology	Post-operative dose evaluation (CT); Clinical evaluation of side effects at follow-up (4-14 months): skin puncture: bleeding, pain, infection, non-union of puncture point, metastasis due to RIS implantation; radiation (toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer): skin injury, mucosal response, spinal-cord injury, peripheral-nerve injury, xerostomia, blood toxicity; nerve injury (Common Terminology Criteria for Adverse Events v4.0); seed migration.	Successful RIS implantation with good accuracy of positioning. 3 cases of grade 1 acute skin reaction, no cases of grade >3 reactions. No blood toxicity, no spinal cord injury, 1 case of grade 3 nerve response.

(Wang *et al.* 2018) Radiation oncology (brachytherapy various) Patient-specific navigation guide for CT-guided RIS implantation in treatment of advanced malignant tumours	Limited accuracy of RIS implantation, and associated unwanted effects using traditional approaches.	**CT** N/A	**N/A** N/A Medical resin	18♀, 24♂, 58.9 ± 14.1 years (range 25-91)	Patients' quality-of-life assessment: EORTC QLQ-C30 (4-point scale: 1 - not at all, 4 - very much): function (physical, role, cognitive, emotional, social), symptoms (fatigue, pain, nausea/vomiting), single measurement items, global quality of life; administered prior to surgery, at 24 h, 1 and 3 months after surgery.	Average EORTCQLQ-C30 score after seed implantation higher at 1-month follow-up compared to 24-hour and 3-month follow-up.
(Huang *et al.* 2018) Radiation oncology (brachytherapy pancreas) Coplanar navigation guide for RIS implantation in treatment of pancreatic cancer	Limited accuracy and considerable complexity of RIS implantation using traditional approaches; impossible real-time adjustment of puncture direction with non-coplanar guides.	**/** N/A	**N/A** N/A PMMA	Experimental group: 6♀, 6♂, median 65.5 years (range 48-81) Control group: 7♀, 6♂, median 63.8 years (range 47-84) Unresectable pancreatic carcinoma	Between-group comparison of post-operative dose (CT), implementation success rate and complications.	Successful RIS implantation without major complications; 1 self-limiting, clinically insignificant local hematoma due to mesentery vessel injury. Dosimetry values significantly higher in experimental compared to control group.
(Ji *et al.* 2020) Radiation oncology (brachytherapy rectum) Patient-specific non-coplanar navigation guide for RIS implantation in palliative treatment of primary or metastatic thoracic tumours	Discrepancy between the postoperative target dose and preoperative plan in freehand RIS implantation.	**CT** N/A	**N/A** N/A Medical curing resin	32♀, 60♂, median 62 years (range 17-88) Primary or metastatic solid, unresectable malignant tumor of the lung, chest wall, or mediastinum	Clinical examination and assessment of toxicity effects (radiation pneumonia, esophagitis, skin reaction, myelitis, cardiotoxicity) at follow-up (median 10.7 months). Overall survival and local control duration and rate at 1 and 3 years.	Toxicity effects: 3 grade ≥2 radiation pneumonia, 2 grade ≥2 radiation esophagitis, 1 oesophageal fistula, 2 tracheal fistulae, 1 chest-wall pain, 3 haemoptysis, 5 grade 2 radiation skin reaction; no defined radiation myelitis or cardiotoxicity. 34 cases of pneumothorax. Overall survival: median 15 months; 59.7% (1 year), 22.2% (3 years). Local control: median 16.4 months; 64.9% (1 year), 32.8% (3 years); significantly better for metastatic than primary cancer.

(Palin *et al.* 2019) Maxillofacial oncology Definitive cast for manual fabrication of the mould to produce a patient-specific self-retentive interim obturator for palliative palate reconstruction after partial maxillectomy due to cancer	Inability to fabricate the obturator using impression trays due to limited maximal incisal opening.	**CT** Mimics SpaceClaim	<u>Definitive cast:</u> **MJ** Objet260 Connex 3 (Stratasys) ABS (RGB 515 Digital ABS) *<u>Duplicate definitive cast:</u>* *PolyPour mould, type III dental stone cast* *<u>Obturator:</u>* *Wax positive mould, 3-piece dental stone negative mould, packing of platinum silicone elastomer (A-RTV-40), colouring, trimming, contouring*	♀, 55 years Post unilateral maxillary resection due to T4aN0M0 invasive squamous cell carcinoma with bone and perineural invasion, failed free-flap reconstruction, severe trismus	Visual inspection of fit, patient feedback regarding comfort	Restored functional quality of life: improved speech and mastication, prevented nasal regurgitation. Eliminated need for impression materials.
(Jiao *et al.* 2014) Maxillofacial oncology Definitive cast for manual fabrication of the mould to produce a patient-specific obturator for palliative palate reconstruction after partial maxillectomy due to cancer	Labour-intensive, time-consuming fabrication of one-piece obturators using traditional techniques because of access limitations due to soft tissue fibrosis and trismus after maxillectomy and radiation.	**CT** Mimics Geomagics Studio 12	<u>Definitive cast:</u> **MJ** ProJet HD 3500 (3D Systems) N/A	4♀, 7♂, 44 ± 16 years (range 25-68) Post partial maxillectomy due to squamous cell, mucoepidermoid or adenoid cystic carcinoma, myofibroblast or fibromyxoid sarcoma	Assessment of obturator retention, marginal fit and occlusion, and excessive tissue displacement. Patient feedback at 1-week follow-up (Obturator Functioning Scale of the Memorial Sloan-Kettering Cancer Center): problems with eating, speech difficulties, dry mouth, poor aesthetics, upper lip paraesthesia, difficulty inserting the obturator, avoidance of routine social interactions); 3-point scale: 1 - not at all/a little, 3 - very much/extremely.	Maximum support, stability and retention; 1 case of leakage drinking liquid, no leakage while swallowing; 2 cases of somewhat nasal voice; 3 cases of clasps noticeable on anterior teeth; 3 cases of extreme numbness; 3 cases of dry mouth. Overall, regained functions of mastication, pronunciation and swallowing, improved psychological and social wellbeing.
(Ciocca *et al.* 2009) Maxillofacial oncology (facial epithesis) Patient-specific working model and mould for facial prosthesis to restore the cosmetic appearance of patients with facial defect after ablative tumor surgery	High cost of customised products, and difficulty producing geometrically complex parts with traditional technologies.	**3D Scanner HD "Ear & Nose Digital Library"** ScanStudio RapidForm	<u>Working model and mould:</u> **FFF** Dimension (Stratasys) ABS P400 *<u>Final epithesis:</u>* *Silicone casting, colouring*	♀, 73 years Recurrent squamous-cell carcinoma, infiltrating facial bone	N/A	Possible improvement of patients' quality of life and comfort, semi-functionally and aesthetically.

(Ciocca *et al.* 2010) Maxillofacial oncology (nasal epithesis) Mould for patient-specific nasal prosthesis to restore the cosmetic appearance of patients with facial defect after ablative tumor surgery	High cost and difficulty producing geometrically complex parts with traditional technologies, especially in the absence of symmetric body part to mirror.	**3D Scanner HD "Ear & Nose Digital Library"** ScanStudio RapidForm	<u>Mould:</u> **FFF** N/A (Stratasys) ABS P400 *<u>Final epithesis:</u>* *Silicone casting, colouring*	♂, 67 years Post ablative surgery of the nose due to recurrent squamous-cell carcinoma, failed plastic reconstruction	Analysis of production cost and time, comparison with traditional techniques.	Reduced time and cost of the procedure compared to traditional techniques.
(Pruksakorn *et al.* 2015) Orthopaedic oncology (upper extremity) Patient-specific endoprosthesis for palliative upper-extremity reconstruction after bone-metastasis resection	Challenging production, time- and cost-inefficiency of traditional methods for producing patient-specific endoprostheses for reconstruction after extensive bone resection.	**CT** Mimics	**Selective Laser Lithography*** N/A (MTEC) PMMA	16 patients Humeral, ulnar metastases of multiple myeloma, prostate, breast, lung adenocarcinoma, thyroid follicular-cell carcinoma, cholangiocarcinoma, or osteosarcoma	Functional outcome evaluation: MTSS (5-point scale), Mankin score (poor-good); elbow and forearm range of motion assessment; Endoprosthesis failure evaluation: prosthesis fracture, prosthesis-bone interface failure, prosthesis and fixative device failure at follow-up (38-1324 days).	Production of affected-bone replicas within 48 h. Successful reconstruction with good shoulder stability, low rate of complication, and no cases of poor outcome or endoprosthesis failure. 3 of 13 cases of soft tissue failure in first 6 months. Mean MTSS 55%, higher for emotional acceptance and associated pain compared to functional activities, lifting ability, and hand positioning; Mankin score: 64% good, 36% fair.
(Efetov *et al.* 2020) Orthopaedic oncology (pelvis) Patient-specific pubic bone endoprosthesis for pelvic ring reconstruction after exenteration for anal cancer recurrence	Poor physical well-being and postoperative quality of life after complete pelvic exenteration without pubic symphysis reconstruction when osteosynthesis is not possible.	**CT/MR** Mimics 21.0	**DMLM** Concept Laser M2 cusing (GE Additive) Rematitan (90% titanium, 6% aluminium, 4% vanadium) Designed by TIOS, Ltd. (Moscow, Russia)	♀, 52 years Recurrent anal squamous cell carcinoma with vagina, bladder, and pubic bone invasion, locoregional failure after chemotherapy	SF-36: qualitative assessment of patients' perceptions of their physical functioning, physical and emotional limitations, social functioning, bodily pain, general and mental health.	Successful endoprosthesis implantation 5 weeks after initial pelvic exenteration (R0 resection), without severe complications. Patient started to walk 9 days and resumed normal activities 6 weeks after surgery. No recurrence or implant rejection at 6-month follow-up. SF-36v2: 62% with positive dynamics in physical health status.

(F. Han *et al.* 2019) Orthopaedic oncology (pelvis) Patient-specific osteotomy guide and hemi-pelvic endoprosthesis for metastatic acetabular carcinoma resection and pelvic reconstruction	High incidence of prosthetic mismatch and loosening in pelvic reconstruction surgery with conventional modular prostheses.	**CT** Mimics 17.0 Magics 18.0	Pelvic model: **SLA** iSLA-450 (Shining 3D) N/A Osteotomy guide: **SLS** Formiga P110 (EOS) N/A Endoprosthesis: **EBM** Arcam A1 (Arcam Corporation) Ti6Al4V	♀, 62 years Destructive metastatic acetabulum carcinoma, right renal clear-cell carcinoma	Clinical assessment preoperatively and at 12-month follow-up: MSTS score: rating (0-5 scale) of pain, function, emotional acceptance, use of external support, walking ability, gait alteration; Harris Hip Score: rating (1-4 scale) of pain, support, walking distance, limp, activities, sitting, stair climbing, public transportation; RoM; SF-36: qualitative assessment of patients' perceptions of their physical functioning, physical and emotional limitations, social functioning, bodily pain, general and mental health.	Accurate tumor resection and pelvic reconstruction without prosthetic loosening or migration, periprosthetic fractures, or infection; walking 1 km with assistance at 6 months, independent at daily activities at 12-month follow-up. Improved MSTS result (from 7 to 16), SF-36 (from 52.7 to 108.2), and Harris score (from 19 to 52).
(Karyakin *et al.* 2017) Orthopaedic oncology (upper limb) Patient-specific mould for bone-substitute endoprosthesis to reconstruct upper-limb long bones after tumor resection	Limited possibilities of traditional methods to produce custom shape, size and complexity of endoprostheses in large limb-segment lesions.	**CT** N/A	Mould: **FFF** Replicator 2 (MakerBot) N/A *Endoprosthesis:* *Casting of bone substitute material (PMMA or Rekost) with allograft chips*	12♀, 10♂, 50.9 ± 7.2 years (range 41-62) Lesion at the humerus, ulna or radius due to enchondroma, osteoblastoclastoma, non-osteogenic fibrosis, solitary bone cysts, osteogenic sarcoma, metastasis of mammary or prostate gland and lung cancer.	Clinical assessment preoperatively and at 12-month follow-up: SF-36: qualitative assessment of patients' perceptions of their physical functioning, physical and emotional limitations, social functioning, bodily pain, general and mental health; MSTS score: rating (0-5 scale) of pain, function, emotional acceptance, use of external support, walking ability, gait alteration; VAS: pain assessment.	Significant postoperative pain reduction and improved function of the upper limb. Benign cases: SF-36: 71.4 ± 6.6, VAS: 2.5 ± 1.5, MSTS: 65.1% ± 8.3%; malignant cases: SF-36: 39.2 ± 4.3, VAS: 4.8 ± 1.4, MSTS: 41.8% ± 5.2%. No statistically significant differences depending on material used. No radiographic evidence of implant migration, 4 cases of marginal osseointegration with Rekost.
(O'Sullivan *et al.* 2018) Enteral feeding Bespoke sealing device for emergency repair of leaking PEG tubes in patients ineligible for surgical replacement procedure	Disrupted enteral feeding in patient ineligible for surgical PEG-tube replacement, significant risks associated with non-operative methods of replacement, no existing repair kits	**/** SolidWorks	**MJ** Connex500 (Stratasys) MED610	♂, 15 years Advanced cystic fibrosis	Application of sealing device, check for leaks at tube flushing.	PEG-tube function restored within 24 h from first contact between medical staff and designers. PEG tube ready for use immediately after application of sealing device, patient recommenced on feeding regime.

(Wu and Chen 2018) Neurology (ALS) Patient-specific interface for a generic mask for noninvasive ventilator support in chronic medical conditions with weakness of respiratory muscles	Generic masks in standard sizes are often uncomfortable, ill-fitting, and leaky, which causes patients to discontinue using them.	**MR** (patient's face) Mimics **Vivid 9i (Konica Minolta)** (modified oronasal mask Veraseal 2) Visualization toolkit library Blender 2.78	Rigid interface, mould for silicone interface: **SLA** Form 2 (Formlabs) Standard clear resin *Silicone interface:* *Casting of Dragonskin10 (Smooth-On)*	♂, age N/A Variant ALS, unique facial contours (high nose bridge, lower-jaw overbite), prescription glasses	1-night trials with 10 modified masks and 2 standard masks; two 7-night trials with favourite mask. Custom questionnaire for patient evaluation of comfort, leakage, preference, recommendation, tolerance (Likert-type 1-5 scale questions), open-ended questions.	Scores for favourite masks over 7-night trials: comfort: 4, 4; leakage: 3, 2; preference: 4, 3; recommendation: 4, 3; tolerance: 4, 3. Compared to standard mask, 8 of 10 custom masks were rated higher in all aspects. Common complaints: masks were unable to accommodate his sleep movement and jaw movement.
(Ahangar *et al.* 2018) Oncology – Chemotherapy (spine) Nanoporous scaffold for local chemotherapeutic delivery in spine metastases of prostate cancer	Severe side effects of high systemic doses of chemotherapeutics; large defects after surgical removal of spine metastases that cannot spontaneously heal and require bone grafting.	**/** SketchUp Simplify 3D	**FFF** Creator Pro (Flashforge Corp.) TPU/PVA (PORO-LAY series: Lay FOMM 60, 40; Gel Lay) *Doxorubicin loading on scaffolds*	/	Assessment of doxorubicin release from scaffolds over 7 days (fluorescence detection); tumor-cell metabolic activity and proliferation assessment; scaffold porosity evaluation (SEM).	Proof of concept: 60-75% of doxorubicin loaded onto scaffolds was released over 7 days, significantly reducing metabolic activity and proliferation of prostate cancer cells and spine metastases cells.
(Menikou *et al.* 2017) Oncology – Pain palliation (bone) Portable MRI-guided robotic system for pain palliation in bone cancer using thermal ablation with focused ultrasound	N/A	**/** N/A	**FFF** FDM400 (Stratasys) ABS	/	Evaluation of robot functionality (gel phantoms), and MRI safety and compatibility.	Proof of concept: Verified MRI safety and compatibility, and the capacity for creating discrete and multiple overlapping lesions in a gel phantom.

5-FU – 5-fluorouracil, ABS – Acrylonitrile Butadiene Styrene, AFM – Atomic Force Microscopy, BJ – Binder Jetting, CT – Computed Tomography, DMLM – Direct Metal Laser Melting, EBRT – External Beam Radiotherapy, EdECM – Esophagus-derived decellularized Extracellular Matrix, EORTC QLQ-C30 – European Organization for Research on Treatment of Cancer Quality of Life Questionnaire, ERCP – Endoscopic Retrograde Cholangiopancreatography, FE-SEM – Field Emission-Scanning Electron Microscopy, FFF – Fused Filament Fabrication (also FDM – Fused Deposition Modelling), MJ – Material Jetting, MR – Magnetic Resonance, MSTS – Musculoskeletal Tumor Society, MTSS – Musculoskeletal Tumor Society Score, PCL – Polycaprolactone, PEG – Percutaneous Endoscopic Gastrostomy, PLA – Polylactic acid, PMMA – Polymethyl Methacrylate, PTX – Paclitaxel, PU – Polyurethane, PVA – Polyvinyl Alcohol, RIS – radioactive ^{125}I seed, RoM – Range of Motion, SEM – Scanning Electron Microscopy, SF-36 – 36-Item Short Form Survey, SLA – Stereolithography, SLS – Selective Laser Sintering, TESS – Toronto Extremity Salvage Score, TPU – Thermoplastic Polyurethane. **The authors are unfamiliar with the stated technolog*

Appendix II: Three-Dimensional Printed Devices for Health Care in Response to the Coronavirus Disease 2019: Lessons Learned to Date – *Published format*

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COMMENTARY

Three-Dimensional Printed Devices for Health Care in Response to the Coronavirus Disease 2019: Lessons Learned to Date

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Abstract

During the first surge of the coronavirus disease 2019 (COVID-19) there was a tremendous global response from three-dimensional (3D) printing communities and individuals to support local health care systems and staff. The responses involved a range of 3D printer users from amateur makers to conglomerate manufacturers creating personal protective equipment (PPE) and other supplies of which there were shortages. These new supply chains resulted from the democratization of 3D printing, open source file sharing, mass production of desktop machines, and the relatively cheap cost of 3D printers. The democratized state of 3D printing facilitated an altruistic movement of makers with ranging experience, to work alongside traditional manufacturers to make medical supplies. With the critical nature of the shortages and the sharp increase in COVID-19 infections, many standards and regulations were bypassed, and good manufacturing processes disregarded, in cases. The outcomes from this article is a set of six lessons learned from the authors perspective regarding the use of 3D printing during the initial phase of the COVID-19 pandemic. We note challenges experienced around volume manufacturing, infection control requirements of produced parts and the cleanability of devices, mechanical strength considerations, good manufacturing practices, product and intellectual property (IP) liability, and the role of involving clinical stakeholders.

Keywords: design, medical applications, remote manufacturing, 3D printing

Background

THE FIRST CASES of coronavirus disease 2019 (COVID-19) were reported by officials in Wuhan City, China, in December 2019.[1] By January 2020, the first cases of COVID-19 were confirmed in Europe and the United States. Italy, Spain, and Germany saw dramatic rises in cases until April 2020, and were then surpassed by rates in the United States, Brazil, and India. By September 2020, the virus spread to 188 countries globally and infected upward of 31,000,000 people, of which >900,000 people are estimated to have died.[2] As the pandemic spread, health care systems ran out of PPE and other medical supplies.[3] With quarantine restrictions in place many manufacturers also struggled to meet demands due to the closure of manufacturing lines and/or submanufacturers/suppliers.[4] Furthermore, as governments issued lockdowns, and in some cases trade embargos on the export of associated equipment, many supply chains froze internationally.

The initial response was largely on the basis that 3D printed devices would be a last resort and were better than nothing.[5,6] However, as the infection rate soared, last resort products became more commonplace in some areas.[7–9] There was a notable trend regarding communities/individual makers producing 3D printing face visors, face masks, and respiratory equipment, among various other health care devices.[3,10] Although there were deeply commendable individual and community efforts during this time of emergency, our experience was that a great many erroneous assumptions were made, such as the extent of shortages of specific products locally and in supply chains. Solutions were produced that had design/production challenges that limited their actual use in the health care settings. Issues such as sterility,

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consistency, scalability, and product liability were widely overlooked.

Stringent standards and regulations are in place for medical device manufacturing to protect all members of the supply chain, particularly the end user/patient. With the emergency nature of the pandemic and the risk to frontline workers from extreme shortages of supplies, many, if not all, regulatory requirements were ignored by many to deliver solutions (knowingly or otherwise).

The 3D printing community internationally responded rapidly during the first wave of COVID-19. Some responses were more fruitful than others. It is appropriate to now reflect on the responses and consider aspects that affected the utility and success of these efforts, which should be considered through research activities for future emergencies of this nature. This could help ensure that such efforts in the future are optimized and the opportunities for utilizing 3D printing fully exercised. The purpose of this commentary is to detail six lessons learned by the current authors on this topic.

Lessons Learned

Volume manufacturing using 3D printing at required quality levels was a challenge during the pandemic

As the production throughput of 3D printing is low in comparison with traditional manufacturing, many machines must be utilized for the output rate to sufficiently meet moderate demands. Quality control of 3D printed relative to traditionally manufactured devices remains a challenge.[11,12] Many nonprofessional maker groups came together to scale up production of some designs, notably visor head bands.[3,9] The very nature of multiple disparate makers producing a single design brings with it the potential for large variability in printer technologies, settings, materials, and quality. For example, our experience in Ireland was that many groups donated 3D printed visor headbands to health care facilities, with significant variability in overall quality. As a proportion of these donated units were unsuitable for use, some facilities disregarded 3D printed solutions *en masse*. The lesson learned is that for volume manufacturing across various makers, there is a need to produce such devices to a minimum acceptable standard, even during emergencies such as a pandemic.

Infection prevention and control practices need to be respected or printed solutions will not be used in health care settings

Health care facilities work under stringent infection protection and control (IPC) considerations. 3D printed components to be used in health care must consider infection/sterilization-related aspects as they may affect their use.[13] These increased significantly during the pandemic. IPC teams require that solutions are clean (not necessarily sterile) before they can be used in a health care facility. Furthermore, reusable devices must be cleanable using conventional methods such as with isopropanol wipes.

The printing technology used can also affect IPC risk. Technologies such as fused deposition modelling (FDM) often have small crevices/spaces between print layers, and in such cases, there may be a risk that surfaces cannot be thoroughly cleaned.[14] For single-use applications in some health care settings this may not be as much a concern as for repeated use in settings where devices require cleaning before reuse.

In our experience, there were cases in which large volumes of devices were produced without any/sufficient IPC team input. Where the IPC team only evaluate devices post-manufacturing through 3D printing there is a significant risk the entire batch will be rejected if a concern emerges. This can lead to negative opinions and low adoption of 3D printed devices in those health care settings.

Emergency 3D printed devices need to consider mechanical strength characteristics

A response during the early stages of the pandemic when supply chains froze was to 3D print devices locally as an alternative production method.[3] There is significant variability in the mechanical characteristics of 3D printed components depending on the 3D printing technology used. Many of the designs available on open source websites were intended for production on specific systems, but may have been printed using alternatives or lower-end 3D printing technologies. A potential concern is that some devices were printed without sufficient consideration for their mechanical strength and performance, which may give rise to product failure and injury during use.[3,4]

There is a need for guidance on good manufacturing practices for 3D printed devices

Maintaining good manufacturing practice (GMP) in medical device supply chains is central to product safety. This includes protocols regarding sterility, quality control, part validation, and verification. Traceability of parts is also important if devices need to be recalled on safety grounds.[15] Products created and supplied to health care facilities using 3D printing should be subject to appropriate manufacturing standards. Although it is appreciated that in the crisis phase of a pandemic that some supplies are better than none, the devices must still meet minimum safety standards. It is important that GMP guidance for 3D printed emergency medical devices are established, but in particular in response to pandemics, to ensure they are as safe as is reasonably feasible, and above all, safe for clinical use.

Makers may be inadvertent medical device manufacturers and responsible for product liability and IP infringement

The emergency response during COVID-19 was a passionate response of many. Several device designs were shared internationally, some with caveats that they were to be used as a last resort, and others with liability warnings.[4] Makers may have made assumptions that because designs were made available online that they were ''approved'' in accordance with requisite regulations and standards. In some cases, makers became medical device manufacturers unknowingly, and in so doing, became potentially responsible for product liability.[15] In addition, assumptions may also have been made by some makers that they could reverse engineer and reproduce commercial designs without consideration for IP infringement. Inadvertently or not, the maker could be held liable even if they were unaware of, or believed they were exempt from, certain regulations.

It is crucial to involve clinical stakeholders if making or designing solutions

Involving health care staff in validating requirements for devices and in the design of new devices is crucial. During the initial surge of COVID-19 there were chain reactions whereby devices were 3D printed in response to what was happening on an international level. In many cases this was done without first validating the needs for such devices locally.[4,7,9,15] Regarding the design of new solutions, it is imperative that clinical stakeholders are consulted using an iterative design process to arrive at solutions that meet their needs.

Conclusions

The 3D printing community internationally demonstrated how this technology can be mobilized quickly to provide important supports to health care systems during an emergency such as a pandemic. In this article we detail six lessons learned, which, if addressed through research and regulatory/policy guidance, will help optimize the utility of 3D printing during responses to emergency medical disasters in the future, including potential future pandemics.

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Appendix III: Biocompatible 3D printing resins for medical applications: A review of marketed intended use, biocompatibility certification, and post-processing guidance –*Published format*

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Review

Biocompatible 3D printing resins for medical applications: A review of marketed intended use, biocompatibility certification, and post-processing guidance

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ABSTRACT

Over the last thirty years, there has been an increase in the adoption of 3D printing by the medical community to create devices for patients that require custom and rapid solutions. In turn, a demand has been created for a variety of specifically engineered biocompatible materials. The aim of this study was to review the information provided with biocompatible photosensitive resins with regards to their intended uses, cited biocompatibility certifications, and post-processing technique, and arising from this, detail challenges for users when making an informed and safe decision regarding material selection.

A primary level search was performed collecting information from the grey literature available from the websites of manufacturers marketing biocompatible photosensitive resins for 3D printing. Only materials that were stated as biocompatible were included in the study.

The results presented a large range of biocompatible materials with varying intended uses. The majority of materials were specifically for dental applications, followed by general medical use, then specific medical applications. A lack of standardisation was noted with regards to the amount and quality of information that is provided with the materials, therefore, due diligence should be performed by the user when selecting a material for their specific application.

1. Introduction

The application of 3D printing in medicine continues to grow, both in volume and diversity of applications. [1] 3D printing has predominantly been used for the making of anatomical models (60%) and surgical guides (38.7%), with such examples as far back as the 1990's as presented by Tack et al. in their review of 3D printing techniques in medical settings [2]. In the last 5–10 years, there has been a large increase and movement towards the use of the technology for directly treating patients [3–6]. 3D printing has the ability to rapidly create custom devices which has been adopted by areas of the medical community that require custom solutions. Examples include endoprostheses, [7] temporary dental crowns, [8] epitheses, [9] endoluminal stents, [10] maxillofacial guides, [11] treatment templates [12] and bespoke repairs. [13] A recent review by Kermavnar et al. of 3D printing used to directly treat patients detailed the most common use of 3D printing to manufacture medical devices were in the fields of orthopaedics (37%) and orthopaedic oncology (33%), followed by maxillofacial surgery (7%) and neurosurgery (4%) [3]. With that, there are many new applications of the technology emerging. Currently, 3D printing methods offer a range of materials from metals, thermoplastics, photosensitive resins, organics and ceramics. This study specifically focuses on the use of photosensitive resins for vat-polymerisation and resin jetting techniques.

Whilst vat-polymerisation printing techniques are very similar in terms of technology, gantry and method, they do have key technological differences, such as light source, light source wavelength, and exposure duration. These aspects must be specific to the resin being used to ensure the resin fully transitions from a liquid to a solid. [14] Therefore, in this study, the varying techniques of vat-polymerisation method are detailed separately.

There are clear regulatory requirements regarding the design and manufacture of traditional medical devices in order to ensure patient safety. Normally, medical devices are manufactured in an industrial production facility with a system of validation, verification and control methods in accordance with quality management systems, such as ISO 13485. However, there is relatively little guidance regarding

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regulatory requirements for the use of polymer-based 3D printing techniques in medicine as a mainstream method to produce medical devices. At present, what guidance is available is focused predominantly on emergency and humanitarian applications. With the move towards 3D printing of medical devices to directly treat patients, there has recently been increasing attention to develop regulatory guidance in this respect. This requires scrutiny of biocompatible aspects relative to their end uses.

Due to the increase in the use of 3D printing for medical devices to directly treat patients, there is a demand for new materials that provide a variety of biocompatible characteristics for different potential applications. Biocompatible is an umbrella term for materials specifically engineered to interact with living tissues without causing an immunological response. [15] The definition of a biocompatible material refers to the materials ability to perform with an appropriate host response i.e. if a material's intention is to be used in contact with skin for 24 h, the material must be certified to remain chemically stable and not cause an immunological response for that duration. [15, 16] There are many facets to the term biocompatible depending on the intended use. For example, a material could be biocompatible for one or a number of immunological or toxicological responses e.g. skin irritation and sensitisation, cytotoxicity, reproductive toxicity. [17]

Biocompatible materials must be tested and certified with reference to the properties marketed by the manufacturer.In Europe, biocompatibility is assessed according to the ISO 10993 family of standards[18] which comprises 22 sections addressing a series of reactivity tests, quality management processes and risk categorisation standards. The intended use of a 3D printed medical device should determine which tests from the standards are applicable. Devices do not necessarily have to comply with all tests in the standard, however, the printer user must determine the biocompatible requirements as per their intended use and purchase materials which meet those requirements. The equivalent standard in the US is USP VI (the classification of plastics, biological reactivity tests in vivo), regulated by the U.S. Pharmacopeial Convention, which includes three reactivity tests that must be passed to gain class 6 certification. [19] The three in vivo biological reactivity tests are as follows: acute systemic toxicity (systemic injection) test, intracutaneous test and the implantation test. Again, the user must purchase materials that comply with the biocompatibility requirements for their end-use.

Resin manufacturers choose which biocompatibility tests they seek certification for, and should only market those materials according to their corresponding intended uses and certification. In some circumstances, resins are broadly marketed by manufacturers as biocompatible but are supplied with either little or no detail of the specific intended uses or related certifications. In order to achieve biocompatibility in use, it is the responsibility of the user to ensure best practice is used throughout the process by implementing a system of validation and control. The user is required to ensure they use technology and materials which meet the medical device regulations. In the context of applying 3D printing to manufacture medical devices to treat patients, the user has an obligation to ensure they source certified materials corresponding to that use. The manufacturer is required to present information regarding the marketed use of the material, and with that details of the corresponding certification compliance for that intended use.

Studies indicate that for some common 3D printing resins, toxicity has been recorded after post-processing in its fully cured state [20–24]. In one case these effects have been shown to cause reproductive toxicity and genetic mutations, highlighting the need for care [20]. Certified resins are expected to perform as tested as long as they are printed and post-processed in accordance with the protocols provided by the manufacturer. If a user deviates from the manufacturers' protocol, then the biocompatible properties may also deviate. In order for a material to maintain biocompatible properties as per the certification, the manufacturer should provide clear guidance regarding printing and post-processing requirements for the user to follow. The user must adhere to these steps and apply them accordingly with respect to their devices geometry.

The aim of this study was to perform a review of information available to users for making an informed decision regarding the selection of biocompatible resins for 3D printing medical devices. This study specifically focused on photosensitive resins as the literature demonstrates increased use of this material form for these applications. We reviewed commercially available biocompatible photosensitive 3D printing resins in the grey literature regarding marketed intended uses, stated compliance with associated relevant sections of ISO 10993 or USP VI, and post-processing guidance.

2. Method

A primary level online search was performed of the grey literature during March 2021 using the Google advanced search tool to identify biocompatible photosensitive resins for 3D printing. The grey literature was searched as this is the primary method manufacturers advertise and provide information of their products currently on the market. The search string used was; '"3D print*" or "3D-print* or "3D" and "biocomp*" or "bio-comp*" and "resin". Only materials that were marketed as biocompatible were included in the review. If a biocompatible material was identified, the manufacturer's website was keyword searched for the term 'biocompatible' to collect all relevant materials. All materials had to be commercially available. The specific information recorded was: material name, printing method, manufacturer intended use, post-processing information and certification details. A total of 130 biocompatible materials meeting these criteria were identified. The results were separated into rigid and flexible materials.

Information regarding material intended use applications was obtained from the text of materials advertisements. If a material specifically mentioned an application or device, this was recorded under intended use. If not, then the key characteristics were recorded and categorised as 'general medical use'.

The extracted data were taken only from publicly accessible pages, material datasheets and 'fill-out' forms from the manufacturers' websites. With the exception of this, no direct contact was made with the manufacturers to request further information. Also noted were phrases describing the nature of compliance, such as 'capable', 'compliant' or 'compatible' were often used. The range of quality, consistency, and amount of post-processing information is addressed generally in the discussion.

3. Results

Tables 1 and 2 detail the results of the review for rigid and flexible biocompatible photosensitive 3D printing resins, respectively. The review identified in total 99 rigid materials and 31 flexible materials. Regarding rigid materials, the manufacturer with the greatest number of biocompatible marketed materials was 3D Systems (12) followed by Detax (10), Formlabs (10), PrintoDent (9) and Next Dent (8). The printing methods ranged from DLP (46), SLA (14), MJP (6), LCD (5), DLS^{TM} (5) and Polyjet (4). Nineteen materials were available as a tailored option, allowing users to choose the compatible resin for their printing method. Regarding flexible materials, the manufacturer with the greatest number of biocompatible materials was 3D Resyns (12), followed by Detax (4) and KeyPrint (3). Printing methods for these materials ranged from DLP (9), DLS^{TM} (2), SLA (1) and Polyjet (1). Eighteen materials offered a tailored option.

Table 1
Rigid biocompatible photo-sensitive 3D resins.

ID:	Manufacturer / Material / Printing Method:	Manufacturer intended use:	Manufacturer stated certification:
1	3D Systems / Accura ClearVue / SLA	Medical models and medical devices	USP Class VI
2	3D Systems / VisiJet M2R-CL / MJP	Transparent material with medical applications such as surgical guides	ISO 10993 [5, 10] / USP Class VI
3	3D Systems / VisiJet M2R- GRY / MJP	White opaque material with medical applications such as surgical guides	USP Class VI
4	3D Systems / VisiJet M2R-WT / MJP	Injection moulding like finish, applications for medical use i.e. surgical guides	ISO 10993 [5, 10] / USP Class VI
5	3D Systems / VisiJet M3 Crystal / MJP	Translucent material for rapid tooling and medical applications	USP Class VI
6	3D Systems / Figure 4 MED-AMB 10 / DLP	Medical devices, industrial applications. Thermal resistance	ISO 10993 [5, 10]
7	3D Systems / Figure 4 MED-WHT 10 / DLP	Medical devices, industrial applications. Sterilisable in autoclave.	ISO 10993 [5, 10]
8	3D Systems / VisiJet M2S-HT250 / MJP	Heat-deflection 250 °C, gas flow, for tooling and manufacturing aids	USP Class VI
9	3D Systems / VisiJet M2S HT90 / MJP	Functional prototypes, medical devices with fine features and internal structures	USP Class VI (Capable)
10	3D Systems / Figure 4 PRO-BLK 10 / DLP	Injection moulding and soft tool processes	ISO 10993 [5, 10]
11	3D Systems / Figure 4 Rigid White / DLP	Smooth-surface medical devices, handles and fixtures for medical application	ISO 10993 [5, 10]
12	3D Systems / Figure 4 Tough 60C White / DLP	Clinical trials and medical devices such as tools, handles, and small plastic parts	ISO 10993 [5, 10] (Capable)
13	3D Resyns / BioTough D70 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
14	3D Resyns / BioTough D80 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
15	3D Resyns / BioTough D90 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
16	3D Resyns / BioTough D70 MF / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
17	3D Resyns / BioTough D80 MF / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
18	3D Resyns / BioTough D85 MF ULWA / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
19	B9Creations / BIORES RED / DLP	Medical manufacturing, clinical and consumer tech	ISO 10993 [5, 10]
20	B9Creations / BIORES WHITE / DLP	Medical manufacturing, clinical and consumer tech	ISO 10993 [5, 10]
21	B9Creations / BIORES Micro Precision/ DLP	Prolonged skin contact (up to 30 days)	ISO 10993 [5, 10]
22	Carbon / CE 221 / DLS™	Strength, stiffness and temperature resistant	ISO 10993 [5]
23	Carbon / MPU 100 / DLS™	Biocompatible, sterilisable and chemically resistant	ISO 10993 [5,10] / USP Class VI
24	Carbon / RPU 70 / DLS™	High-strength, functional toughness and high ductility	ISO 10993 [5, 10]
25	Carbon / EPU 41 / DLS™	High elastic, tear resistant and energy returning	ISO 10993 [5, 10]
26	Carbon / EPU 40 / DLS™	High elastic, tear resistant and energy damping	ISO 10993 [5, 10]
27	Detax / FreePrint Denture / *Option	Dental use, removable denture bases, total prosthesis.	ISO 10993 [1] (Complies)
28	Detax / FreePrint Ortho / *Option	Drilling templates, orthodontic base components	ISO 10993 [1] (Complies)
29	Detax / FreePrint Splint 2.0 / *Option	Dental splints, fixation and transfer keys	ISO 10993 [1] (Complies)
30	Detax / FreePrint Temp / *Option	Dental temporary crowns & bridges, anterior and posterior tooth restorations	ISO 10993 [1] (Complies)
31	Detax / FreePrint Tray / *Option	Individual impression and functional trays, base resin plates	*Not Found
32	Detax / FreePrint Tray 2.0 / *Option	Individual impressions and functional trays, base plates for dental use	ISO 10993 [1]
33	Detax / LuxaPrint Mould / *Option	In ear monitoring, earmoulds, hearing protection and ITE shells	*Not Found
34	Detax / LuxaPrint Shell / *Option	ITE shells	*Not Found
35	Detax / MedicalPrint Mould / *Option	In ear monitoring, earmoulds, hearing protection and ITE shells	*Not Found
36	Detax / MedicalPrint Shell / *Option	In ear monitoring, foil-earmoulds, hearing protection and ITE shells	*Not Found
37	DSI / Crown & Bridge / LCD	Dental demonstration, models of crowns and bridges	ISO 10993 (Meets)
38	DSI / Gingiva / LCD	For dental demonstration models of gingiva	ISO 10993 (Meets)
39	DSI / Guide / LCD	Surgical dental guide modelling	ISO 10993 (Meets/Satisfies)
40	DSI / Master / LCD	Dental master resin for demonstrational and master-model printing	ISO 10993 (Meets)
41	DSI / Tray / LCD	Aligners, Surgical guides	ISO 10993 (Meets)
42	DWS / DS 3000 / SLA	Printing of dental impression trays, surgical guides,	*Not Found
43	DWS / DS 3500 / SLA	Printing of dental trays	*Not Found
44	DWS / Temporis / SLA	Custom fabrication of dental restorations (class IIa)	CE Class IIa
45	EnvisionTec / E-Guard / DLP	Splints and retainers	ISO 10993 [5,10]
46	EnvisionTec / E-Guide / DLP	High precision dental surgical guides	ISO 10993 [5,10]
47	EnvisionTec / E-Shell 200 / DLP	Hearing aid shells, otoplastics medical devices (class II)	CE / ISO 10993
48	EnvisionTec / E-Shell 300 / DLP	Hearing aid shells, otoplastics (class IIa)	CE / ISO 10993
49	EnvisionTec / E-Shell 3000 / DLP	Hearing aid shells, otoplastics	CE / ISO 10993
50	EnvisionTec / E-Shell 600 / DLP	Hearing aid shells, otoplastics. Crystal quality	CE / ISO 10993
51	EnvisionTec / KeyOrtho IBT / DLP	Indirect bonding tray	*Not found
52	FormLabs / BioMed AMB / SLA	Short term skin/mucosal membrane contact, implant guides, fixation trays	ISO 10993 [1, 5,10]
53	FormLabs / BioMed Clear / SLA	Long term skin/mucosal membrane contact	ISO 10993 [1,3, 5, 10, 17, 18] / USP Class VI
54	FormLabs / Custom Tray / SLA	Print impression trays for implants, dentures, crowns and bridges	ISO 10993 [1, 5, 10]
55	FormLabs / Dental Clear LT / SLA	Surgical guides, splints, fixed prosthetic and clear aligner models	ISO 10993 [1,3,5] (Compliant)
56	FormLabs / Dental Clear LT V2 / SLA	Splints and occlusal guards	ISO 10993 [1, 3,5,10,11]
57	FormLabs / Dental Surgical Guide / SLA	Dental surgical guides and similar applications (class I)	ISO 10993 [5,10]
58	FormLabs / Permanent Crown / SLA	Permanent crowns, inlays, onlays and veneers	ISO 10993 [1, 3, 5, 10]
59	FormLabs / Surgical Guide / SLA	Implant guides and templates.	ISO 10993 [1, 5,10]
60	FormLabs / Denture Teeth / SLA	Dentures	ISO 10993 [1]
61	FormLabs / Denture Base / SLA	Dentures	ISO 10993 [1]
62	KeyPrint / KeySplint Hard / *Option	For rigid dental splints, bite planes, mouthguards and night guards	CE / ISO 10993 [1] / FDA 510k
63	KeyPrint / KeyGuide / *Option	For fabricating transparent surgical guides	ISO 10993 [5,10]
64	KeyPrint / KeyOrtho IBT / *Option	Indirect bonding trays	ISO 10993
65	Mazic D / Surgical Guide / DLP	For guiding course and direction of implant/surgery equipment, drill sleeves.	ISO 10993 [1]
66	Next Dent / C&B MFH / DLP	Crown and bridges, stainable	ISO 10993 [1]
67	Next Dent / Denture 3D+ / DLP	Removable denture bases (class IIa)	ISO 10993 [1]
68	Next Dent / Ortho IBT / DLP	Orthodontic brackets and indirect bonding trays	ISO 10993 [1]
69	Next Dent / Ortho Clear / DLP	Splints and retainers	ISO 10993 [1]
70	Next Dent / Ortho Rigid / DLP	Digital manufacturing of splints (class IIa)	ISO 10993 [1]
71	Next Dent / SG / DLP	Surgical guides for dental implant surgery (class I)	ISO 10993 [1]
72	Next Dent / Tray / DLP	Printing of Multi dental trays	ISO 10993 [1]

(*continued*)

Table 1 (*Continued*)

ID:	Manufacturer / Material / Printing Method:	Manufacturer intended use:	Manufacturer stated certification:
73	Next Dent / Try-In / DLP	Try-in devices (class I)	ISO 10993 [1]
74	PrintoDent / GR-10 Guide / DLP	Printing of dental surgical guides	ISO 10993 [3,5,10,11]
75	PrintoDent / GR-11 Tray / DLP	Printing of customised dental trays	ISO 10993 [3,5,10,11]
76	PrintoDent / GR-14.1 Denture / DLP	Printing of custom fit dentures	ISO 10993 [3,5,10,11]
77	PrintoDent / GR-16 X-Ray DLP	Printing of radiopaque scanning templates	ISO 10993 [1, 3,5,10]
78	PrintoDent / GR-17.1 Temporary It / DLP	Long term temporary dental restoration and denture teeth	ISO 10993 [3,5,10,11]
79	PrintoDent / GR-17 Temporary / DLP	Printing of temporary crowns and bridges	ISO 10993 [1, 3,5,10,11]
80	PrintoDent / GR-19 OA / DLP	Printing of rigid orthodontic splints	ISO 10993 [3,5,10,11]
81	PrintoDent / GR-20 MJF / DLP	Printing of maxillofacial surgery devices	ISO 10993 [3,4,5,10,11]
82	PrintoDent / GR-21Try-In / DLP	Printing of try-in dentures	ISO 10993 [3,5,10,11]
83	SprintRay / IDB 2 / DLP	Printing of brace arches	FDA (Compliant)
84	SprintRay / IBD / DLP	Indirect bonding	FDA (Compliant)
85	SprintRay / Splint / DLP	Printing of splints with high flexural strength	FDA (Compliant)
86	SprintRay / Surgical Guide 2 / DLP	Accurate and distortion free implant guides	FDA (Compliant)
87	SprintRay / Try-In / DLP	For printing try-in dentures	FDA (Compliant)
88	Stratasys / MED610 / Polyjet	Medical applications requiring 30+ days skin contact 24 hours' mucosal contact	ISO 10993 [5,10,3,18] / USP VI
89	Stratasys / MED620 / Polyjet	Approved for temporary in-mouth placement for up to 24 h	ISO 10993 [1]
90	Stratasys / VeroDent MED 670 / Polyjet	Printing of dental/orthodontic models	ISO 10993 [1]
91	Stratasys / VeroDent Plus MED690 / Polyjet	Printing of opaque dental/orthodontic models, e.g. crown and bridge work	ISO 10993 [1]
92	Voco / V-Print / DentBase / DLP	For production of denture braces for removable dentures	*Not Found
93	Voco / V-Print / Splint / DLP	For generative production of dental splints	*Not Found
94	Voco / V-Print / Splint Comfort / DLP	Generative production of thermoflexible dental, therapeutic splints, palatal plates.	*Not Found
95	Voco / V-Print / Surgical Guide / DLP	For printing of dental surgical guides	*Not Found
96	WhipMix / Verisplint OS / DLP	For printing rigid splints	CE / FDA 510k
97	WhipMix / Dentca Denture / DLP	Dentures	FDA clearance
98	WhipMix / Dentca Crown & Bridge / DLP	Crowns and bridges	FDA clearance
99	WhipMix / Surgical Guide / DLS™	Surgical drill guides	*Not Found

* Option (The manufacturer offers a selection of resins to match machine/method) - Digital Light Processing (DLP) – Digital Light Synthesis™ (DLS™) – Liquid Crystal Display (LCD) – Stereolitography (SLA) – Multi-Jet Printing (MJP).

Table 2
Flexible biocompatible photo-sensitive resins.

ID:	Manufacturer / Material / Printing Method:	Manufacturer intended use:	Manufacturer stated certification:
1	3D Systems / Figure 4 Rubber-BLK 10 / DLP	High tear strength and biocompatible – suitable for handles/grips	ISO 10993 [5,10]
2	3D Systems / Figure 4 Rubber-65a BLK / DLP	Mid tear strength production grade rubber	ISO 10993 [5,10]
3	3D Resyns / BioFlex MF ULWA UR A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
4	3D Resyns / BioFlex MF ULWA A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
5	3D Resyns / BioFlex MF UR A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
6	3D Resyns / BioFlex MF A70 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
7	3D Resyns / BioFlex MF ULWA UR A60 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
8	3D Resyns / BioFlex MF UR A60 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
9	3D Resyns / BioFlex MF ULWA A50 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
10	3D Resyns / BioFlex MF A50 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
11	3D Resyns / BioFlex MF ULWA A20 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
12	3D Resyns / BioFlex MF A20 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
13	3D Resyns / BioFlex MF ULWA A10 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
14	3D Resyns / BioFlex MF A10 / *Option	Ultra safe biomedical applications (class I, II and III)	*Not Found
15	Carbon / Sil 30 / DLS ™	Skin contact applications	ISO 10993 [5,10]
16	Detax / FreePrint IBT / *Option	Printing of flexible dental indirect bonding trays (class 1)	ISO 10993 [1] (Complies)
17	Detax / FreePrint SoftSplint / *Option	Printing of flexible dental splints	*Not Found
18	Detax / LuxaPrint Flex / *Option	For generative manufacturing of earmoulds	*Not Found
19	Detax / LuxaPrint Flex Coat / *Option	For generative manufacturing of soft hearing protection.	*Not Found
20	EnvisionTec / E-Shell 500 / DLP	Hearing aid applications	CE / ISO 10993
21	EnvisionTec / E-Guide Soft / DLP	Printing of impact resistant medical devices	ISO 10993
22	EnvisionTec / KeySplint Soft / DLP	Splints and nightguards	ISO 10993
23	FormLabs / IBT / SLA	Indirect bonding trays	ISO 10993 [1, 3,5,10]
24	KeyPrint / KeySplint Soft Clear / DLS™	For printing splints, night guards and bleaching trays in Carbon DLS Systems	ISO 10993
25	KeyPrint / KeySplint Soft / *Option	Orthodontic and dental appliances such as bite planes, mouth guards	ISO 10993
26	KeyPrint / Keytray / *Option	Customised impressions trays (class I)	*Not Found
27	PrintoDent / GR-18.1 IBT / DLP	Printing of orthodontic indirect bonding trays	ISO 10993 [5,10]
28	PrintoDent / GR-22 Flex / DLP	Printing of splints with high elastic properties	ISO 10993 [3,5,10]
29	NextDent / Ortho Flex / DLP	Dental Splints and retainers	ISO 10993 [3,5,10, 11]
30	NextDent / Ortho IBT / DLP	Indirect Bonding Tray (class I)	ISO 10993 [1]
31	Stratasys / MED625FLX / Polyjet	Flexible medical devices requiring 30+ days skin contact, 24 hour mucosal contact	*Not Found

3.1. Intended uses

Regarding the intended uses, the materials can typically be grouped into three categories, dental, medical and general medical use. For a material to be classed as either dental use or medical use, they had to mention a specific device that was to be created i.e. temporary dental crown or hearing aid shell. The majority of the rigid materials were of dental resins (61), followed by general medical use (26), and then medical use (12). For flexible resins, general medical use made up the majority (17), followed by dental (11) and then medical use (3). The materials for general medical use were defined by their chemical, mechanical or biocompatible properties with no specific device mentioned.

Regarding rigid materials, the most common specific dental devices were stated as; splints (12), surgical guides (11), try-in or permanent dentures (11), impression trays (10), temporary or permanent crowns (8), master-models (3), gingiva masks (1), brace arches (1), and radiopaque template (1). The second most frequent category for intended use in rigid materials were general medical applications, however, the descriptions were mostly material specific and did not tend to state specific applications. Specific medical applications were the least frequent type of intended use with just three recommended uses, in the ear shells for hearing aids (8) and surgical guides (3).

Of the flexible materials, 16 were for general medical use and dominated by variants of 3D Resyns 'Bioflex' material, all stating the term 'ultra safe'. The most common stated uses of the dental materials were; trays (5), splints (5) and guards (3). Three flexible materials for specific medical applications were 'LuxaPrint', for manufacturing earmoulds, 'LuxaPrint Coat', for manufacturing soft hearing protection, and 'E-Shell' used for general hearing aid applications.

3.2. Certification

Regarding the rigid materials, 86 out of 99 cited a set of standards or a specific certification from at least one regulatory body. Those certifications comprised citation of ISO 10993 (68), USP VI (10), FDA (9), and CE (7). Twenty-eight materials cited ISO 10993 −1 but only 8 provided details of the risk evaluation endpoints for categorising the material. Of the 99 rigid materials, a section of ISO 10993 containing a specific reactivity test was referenced by 36 materials; ISO 10993−5 (36), ISO 10993−10 (34), ISO 10993−3 (14), ISO 10993−11 (9), ISO 10993−18 (2), ISO 10993 −17 (1), ISO 10993−4 (1). Seventeen materials referenced ISO 10,993 but did not provide details of which of the 22 sub-sections it was in accordance with. Twenty-three materials used terminology such as 'capable, 'compliant', 'complies', 'meets' or 'satisfies' when referring to their stated certification.

Of the 26 biocompatible flexible materials, 14 stated certification from at least one of the regulating bodies. All 14 of the materials referenced ISO 10993 at a high level, and one stated CE certification.

Two materials cited ISO 10993−1 but did not provide detail that was readily available of the risk evaluation endpoints for categorising the material. Seven of the materials detailed certifications that contained a specific reactivity test; ISO 10993−5 (7), ISO 10993−10 (7), ISO 10993−3 (3) and ISO 10993−11 (1). Five materials referenced ISO 10993 but did not provide details of which of the 22 sub-sections of the standard they met. One material used the term 'complies' when referring to the passing of the stated certification.

3.3. Post-processing

All of the materials provided some information regarding post-processing instruction for their materials. In some cases, a small amount of information was given regarding the cleaning, handling and curing of parts, whereas in other cases, detailed guidance regarding best practice of post-processing were supplied.

4. Discussion

4.1. Intended uses

In this study, 87 materials specifically detailed applications for the material. Seventy-two of those materials were for dental applications and 15 were for medical applications. The remaining 43 materials were categorised by their mechanical, chemical or biocompatible abilities i.e. tear-resistance, water-resistance, skin contact. In many cases, manufacturers provided case-study examples of how the material has been used by customers to help suggest possibilities of use to the prospective user.

The information available for dental materials was the most specific regarding intended use applications, often with clear statements such as use for 'temporary crowns'. The majority of medical specific applications comprised materials for hearing devices such as ITE shells for hearing aids. Regarding 'general medical use' the most common term noted was in the 3D Resyns range 'ultra safe' as detailed on all of their biocompatible materials.

It is clear from the review that dental biocompatible materials have a higher consistency of providing clear details regarding end-use applications, but this is not the case always for all the other general medical use materials. Without a clear definition of the intended use, it is difficult to determine the boundaries of the material uses with regards to biocompatibility, and also to gauge the level of post-processing that would be needed in terms of thickness and device geometry.

4.2. Certification

The information provided regarding certification typically referred to either ISO 10993, USP VI, FDA exemption, or CE marking. The ISO 10993 family of standards was the most frequently cited. In some cases, this was cited as just "ISO 10993″ without any detail regarding sub-sections. Thirty different materials cited ISO 10993−1, which on its own does not clarify their compliance with biocompatibility certification. ISO 10993−1 is the risk management framework that provides a method to detail endpoints which in turn dictate the reactivity tests required for those intended uses. It is in place to categorise medical devices based on the nature and duration of their contact with the body and to assess the biological safety of the medical device [18]. Citing ISO 10993−1 just states reference to the risk management framework. No reactivity tests are performed under ISO 10993−1. Hence, referencing just this standard section does not prove biocompatibility certification of the material.

For some materials, however, there were several subsections of ISO 10993 cited. Formlabs BioMed Clear was found to have the highest number of cited certifications with reference to 6 subsections of ISO 10993 and also certification within USP VI. NextDent OrthoFlex had the most certifications for flexible materials with a total of 4 cited standards of ISO 10993. Other materials citing compliance with several specific subsections included Stratasys MED610 (5), PrintoDent GR-17 (5) and GR-20 (5). PrintoDent GR-20 was the only material found to have been tested and certified for ISO 10993−4, which refers to a reactivity test for hemocompatibility.

It is most important for the material to have the necessary certifications to match its intended use. For medical devices, biocompatibility is defined by the immunological response from the host [16]. For example, if the intended use is for external skin contact for up to 24 h, the material is only biocompatible if it can remain in contact with the skin for the stated duration without causing an immunological response. To state 'biocompatibility', a material must be tested and certified according to its intended use, and certified in its final-

device form. It is the responsibility of the user to select a material that is safe for the intended use. Firstly, the user must be aware of their requirements, and secondly, investigate the choice of materials. To make an informed decision, the user will most often rely on marketed information regarding the intended uses and associated certifications regarding biocompatibility. The challenge is that many users perceive they are compliant with "good practice" as long as they procure "biocompatible" resins without performing adequate due diligence.

4.3. Post-processing

If photosensitive resins (biocompatible or not) are under-cured they can be highly toxic, and if over cured the mechanical performance is affected. In some common 3D printing resins, toxicity has been recorded after post-processing in their fully cured states [20–24]. Over curing can lead to brittleness and weaken the material beyond its stated properties. [25] This could lead to device failure in practice and cause harm to the patient. Curing time for materials may differ from one device to the next due to thicker walls, internal structures, pigmentation, or areas blocked from direct ultra-violet exposure. Because of these factors, curing may not be uniform from one device to the next. Photosensitive resins can only achieve biocompatibility when the material has fully undergone the transition from a liquid to a solid via photo-cross-linking [25].

All of the materials identified in this review had at least some instructions for the user regarding technique and good practice for post-processing to achieve and maintain biocompatibility. The information included ultra-violet wavelength settings, safe-handling, washing parts, curing parts and sterilisation. In a number of cases very little information was provided, whereas for others, detailed instructions were provided.

The user is responsible for post-processing so they must be aware of the criticality of this step and the potential risks, so hence must be provided with sufficient information in this respect. The material manufacturer must provide guidelines that can be clearly followed by the user in order to correctly post-process printed parts. The information provided by the material manufacturers, in some cases, recommends extending post-processing lengths if the part being produced was larger. Therefore, the authors recommend that users develop protocols to test the validity of the given post-processing information against the parts being produced. If the part being produced has internal chambers, complex geometries or thicker geometries, it is likely that post-processing technique may need to be customised to ensure that the optimum mechanical and biocompatible properties are achieved.

4.4. Terminology

In the course of this review, it was noted that there was a high degree of variability regarding the preciseness and clarity of terminology used when referring to certification compliance. Eighteen materials used terminology such as 'capable', 'compliant', 'complies', 'meets', 'satisfies', 'deemed acceptable' or 'pending'. Whilst some of these terms are often used as synonyms for 'passed', with regards to biocompatibility, a distinction between passed or not passed must be made in unambiguous terms. The terms listed are open to the interpretation of the user as to whether the material has been certified.

4.5. Limitations

As this study was performed of the grey literature findings will naturally vary from time to time. The review is based on marketed information available on a single web search engine. It is possible that there are more materials available than identified. It is also possible that manufacturers hold more information regarding certification compliance than is either available publically, or was identified in this search.

The authors wish to acknowledge that there are other aspects to achieving and maintaining biocompatibility such as: regular printer calibration, maintaining post-processing equipment, using in-date resin, using PPE to avoid contamination, and sterilising printed parts with the appropriate method.

5. Conclusions

There is a considerable range of specifically engineered biocompatible photosensitive resins available to purchase on the commercial market for a variety of medical applications. The majority of these are marketed specifically for dental applications. The information provided to the user with regards to the intended use, certification and post-processing is highly variable.

When selecting a material, users should perform due-diligence to ensure they are choosing a material that will be appropriate for their application, and that the material manufacturer is able to provide sufficient information to achieve and maintain biocompatibility during use. As the responsibilities of achieving the correct bio-compatible and mechanical properties rests on the user, it is imperative that post-processing technique is scrutinised. Where necessary, users should develop their own protocols to test the validity of the recommended post-processing technique, especially when printed parts feature large or complex geometries.

Glossary

*Option (The manufacturer offers a selection of resins to match machine/method)
Digital Light Processing (DLP)
Digital Light Synthesis™ (DLS™)
Liquid Crystal Display (LCD)
Stereolitography (SLA)
Multi-Jet Printing (MJP)

Conflicts of Interest

The authors confirm there are no conflicts of interest.

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Systematic review

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3D printing in palliative medicine: systematic review

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ABSTRACT

Background Three-dimensional printing (3DP) enables the production of highly customised, cost-efficient devices in a relatively short time, which can be particularly valuable to clinicians treating patients with palliative care intent who are in need of timely and effective solutions in the management of their patients' specific needs, including the relief of distressing symptoms.

Method Four online databases were searched for articles published by December 2020 that described studies using 3DP in palliative care. The fields of application, and the relevant clinical and technological data were extracted and analysed.

Results Thirty studies were reviewed, describing 36 medical devices, including anatomical models, endoluminal stents, navigation guides, obturators, epitheses, endoprostheses and others. Two-thirds of the studies were published after the year 2017. The main reason for using 3DP was the difficulty of producing customised devices with traditional methods. Eleven papers described proof-of-concept studies that did not involve human testing. For those devices that were tested on patients, favourable clinical outcomes were reported in general, and treatment with the use of 3DP was deemed superior to conventional clinical approaches. The most commonly employed 3DP technologies were fused filament fabrication with acrylonitrile butadiene styrene and stereolithography or material jetting with various types of photopolymer resin.

Conclusion Recently, there has been a considerable increase in the application of 3DP to produce medical devices and bespoke solutions in the delivery of treatments with palliative care intent. 3DP was found successful in overcoming difficulties with conventional approaches and in treating medical conditions requiring highly customised solutions.

Key messages

What was already known?

⇒ Specialists in palliative medicine often require short term, rapid solutions to alleviate the patients' distressing symptoms and improve their quality of life. Three-dimensional printing (3DP) is becoming more common to manufacture complex patient-specific devices and is recognised for its ability to provide cost-effective and customisable rapid solutions. Patients in receipt of palliative care can benefit from the advantages of 3DP; but in order to highlight potential opportunities, it is necessary to systematically review its use in this clinical field.

What are the new findings?

⇒ The majority of reports of 3DP use in palliative care were published after the year 2017. The studies showcase a versatile range of potential applications, including for the production of anatomical models, endoluminal stents, navigation guides, obturators, epitheses, endoprostheses and others. The main reasons for using 3DP are the difficulty of producing patient-specific devices with traditional methods, and the lack of commercially available solutions to specific patient needs.

INTRODUCTION

Three-dimensional printing (3DP), also known as additive manufacturing (AM), is becoming increasingly common in modern medicine. Initially, it was limited to manufacturing prototypes, and was synonymous with rapid prototyping (RP),[1] but it is being increasingly used to directly produce finished products and components.[2] Physical objects are built from digital data (ie, computer-aided design models) that can be generated anew using 3D-modelling software, or obtained by 3D-scanning of existing objects in the process of reverse engineering (RE). The final designs are then 3D-printed directly (direct AM), or fabricated with the help of 3D-printed tools/moulds (indirect AM).

Presently, 3DP is gaining increasing recognition in a range of medical practices, including diagnostics, surgical planning

Key messages

What is their significance?

Clinical

⇒ Using 3DP-generated applications as a component of the care provided to patients with palliative care needs can lead to a positive impact on palliative care patient outcomes, particularly when cost, time and the possibility of customisation are critical factors. Guidelines are provided regarding the advantages and disadvantages of specific 3DP technologies and materials, both to inform future clinical practice and identify limitations.

Research

⇒ To the authors' knowledge, this study is the first comprehensive systematic review analysing 3DP as a method of producing medical devices that might be applied to patients receiving palliative care.

and reconstruction, patient education, rehabilitation, tissue engineering and pharmacology.[3] In the production of medical devices and tools, 3DP offers a wide range of advantages over traditional methods, most notably the possibility of cost-effective, small-scale, on-demand, in-house fabrication of geometrically and structurally complex patient-specific products in a relatively short time.[4 5] These advantages can add particular value to the delivery of responsive care to patients with palliative care needs. Namely, the possibility of producing highly customised solutions at low cost allows for individualised management of patients' needs to help them cope with their condition and treatment, and experience optimal quality of life despite the disease. Moreover, reduced lead time enables a quick response to alleviating distressing symptoms and allow a person whose health is deteriorating to spend less time away from their home.

It is of note, that in part due to the relatively recent recognition of palliative medicine as a specialty, even among healthcare professionals a common understanding of the roles of palliative care still needs to be established.[6 7] To facilitate this, the International Association for Hospice and Palliative Care published a new 'Consensus-Based Definition of Palliative Care' in 2019.[8] For clarity, the authors of the present work also acknowledge the following: (1) specialist palliative care is given alongside treatments targeting the underlying disease; (2) when the intention is potentially curative, the intervention does not qualify as truly palliative and (3) interventions provided with palliative intent are typically less invasive and less dangerous procedures, although the same medical approaches can have curative effects in some diseases, and palliative in others (eg, central airway obstruction management with stents,[9] radioactive ^{125}I seed implantation for brachytherapy,[10] bone tumour resection[11] and endoprosthetic reconstruction[12]).

Individual literature reviews exist of 3DP in palliative care, focused on specific types of medical devices, such as central airway stents,[9] oesophageal stents[13] and orthoses.[14] However, to the authors' knowledge, no systematic reviews have been published to date in this field. Thus, the aim of this study is to provide a systematic review of studies reporting the use and the potential uses of 3DP in specialist palliative care, with specific emphasis on the fields of application, technology employed and the advantages of 3DP over conventional methods.

METHODS

Literature search and study selection

A systematic literature search was performed during December 2020 using the following databases: EBSCOhost (including Academic Search Complete, MEDLINE with Full Text, CINAHL Complete), PubMed, Scopus, and Web of Science. Articles of interest included terms related to 3DP in the title (ie, "3D print*",3D-print*", "three-dimensional* print*", "additive* manufactur*", or "rapid* prototyp*"), terms related to palliative care in the abstract (ie, "palliat*", "cancer*", "oncolog*", "tumour*", "tumor*", "malignan*", "terminal* ill*", or "terminal* disease*"), and terms related to palliative care in the full text (ie, "palliat* car*", "palliat*", "end-of-life", "end of life", "quality-of-life", or "quality of life"). If necessary, the search string was adapted to meet the search options of specific databases. An additional search was performed using Scopus to identify studies including any of the terms related to 3DP and the term "palliative" in either the title, abstract or keywords. The study selection was limited to full scientific articles in the English language. All included papers were published prior to the date of the search. Reviews, book chapters and non-scientific papers were excluded from the review, as were studies performed on veterinary patients, involving curative or aesthetic surgical reconstructive procedures, and testing diagnostic technology. Also excluded were studies involving palliative surgical correction of paediatric congenital heart defects, as these are typically managed by cardiologists. Regarding bias, all studies which met the selection criteria were included.

The review protocol was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] The search and study selection criteria are presented in figure 1. TK confirmed the outcomes of the search and selection performed by NJM and CG. Any disagreements among the reviewers were resolved by LOS.

Data extraction and synthesis

The following data were extracted from the selected studies: (1) field of application of 3DP in palliative care, type of 3D-printed device, its stage of development and application; (2) technology used for device fabrication including 3DP technology, 3D-printer make, material, imaging technique, software used and (3) testing of the 3D-printed device, including number

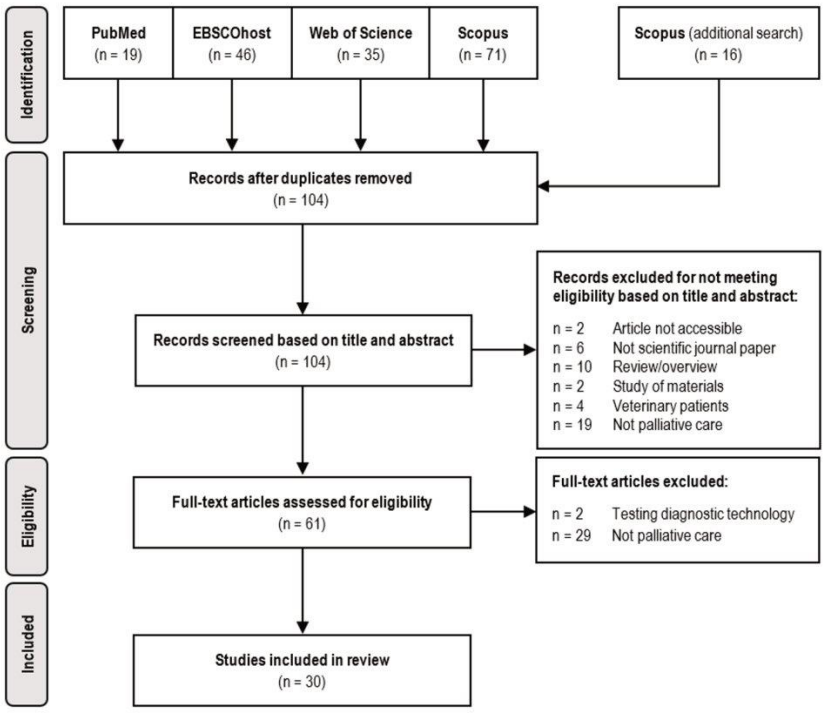

Figure 1 PRISMA flow diagram of literature search and study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

of participants, age and medical status, testing method and outcomes of intervention. 3D-printed device manufacturer, print time and cost were also reviewed.

RESULTS

Thirty relevant papers on the use of 3DP in palliative care were identified and included in the review. The first study was published in 2004, and 20 papers were published in the last 3 years, as shown in figure 2.

Device type and field of application

3DP was applied to different medical sub-specialties within oncology, predominantly gastrointestinal, orthopaedic and radiation oncology. Only three devices were produced for non-oncological applications (figure 3).

In the 30 reviewed studies, 36 different devices were produced (online supplemental table l). The most common were endoluminal stents (9), however, all were used in proof-of-concept studies. Other most commonly 3D-printed devices were anatomical models (6), brachytherapy navigation guides (5), endoprostheses (including one mould; 4), epithesis casts and moulds (3) and obturator casts (2). In single cases, an injection-moulding chamber, surgical cutting guide, PEG-tube sealing device, respirator mask and positive mould, scaffold for chemotherapeutic delivery, and a

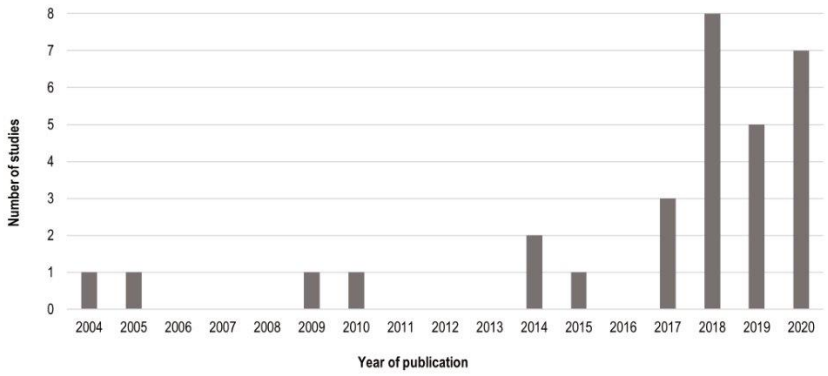

Figure 2 Reviewed studies involving the use of 3DP in palliative care by year of publication. 3DP, three-dimensional printing.

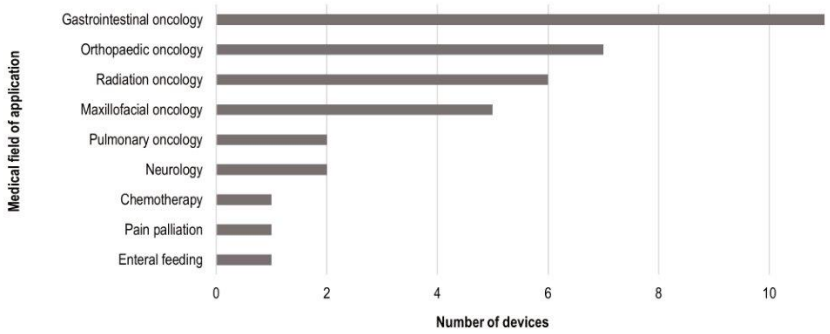

Figure 3 Fields of application of 3DP in palliative care. 3DP, three-dimensional printing.

robot for ultrasound pain palliation were manufactured. Figure 4 summarises the purpose of the devices.

Problems addressed by 3DP

The most common purpose of 3DP was to improve the accuracy and/or efficiency of treatment achievable with traditional methods (13 devices). Seven of the 13 devices were intended to improve the accuracy of drug delivery, 2 were endoluminal stents with improved patency or drug distribution, and 1 was an anatomical model for improved surgical planning. A further three devices were used to address the lack of efficiency in the traditional method (ie, one cutting guide, one endoprosthesis, one obturator mould). In six studies, 3DP was chosen to address the difficulty of device customisation with traditional methods, including endoluminal stents (3), endoprosthesis (1), epithesis (1) and respirator mask (1). In two studies, 3D-printed anatomical models were used to address difficulties of spatial anatomy comprehension from 2D images. Four devices were used to reduce the risks for patients associated with conventional methods, and one anatomical model was used as an alternative to human testing (figure 5).

3DP was used with the intention to reduce the cost and manufacturing time of two epitheses and two endoluminal stents. Time-efficiency was reported in four studies with print durations ranging up to to 36 hours,[16] and two studies highlighted the potential for delivering custom 3D-printed devices to patients within 24 hours.[17 18] Cost-effectiveness of 3DP was emphasised in two cases (US$30 for a head mould to replace a US$200–US$400 CT scan[16] and a US$5 custom-fit BiPAP mask[16]), and one study considered the price disadvantageous (US$500 for materials and printing of an obturator definitive cast).[19]

3DP technology

Thirteen devices were manufactured using Fused Filament Fabrication (FFF),[16 20–30] one of which used a custom built FFF gantry specifically designed for the orbital printing of stents.[26] Six devices were produced using StereoLithograPhy (SLA),[18 22 31–33] five using Material Jetting (MJ),[17 19 34–36] two using Selective Laser Sintering (SLS)[18 33] and in single cases, direct metal laser melting[37] and electron beam melting[33] were employed. One study reported the use of selective laser lithography[12] (the authors of the present review are unfamiliar with this technology). In seven studies, 3DP technology was not specified; however, four of these detailed the type of material used (ie, photopolymer resin, medical resin, and PolyMethyl MethAcrylate (PMMA)).

Ten of the reviewed papers did not detail the material employed. Across the other studies, the most common materials were photopolymer resin (including Flexible Resin, MED610, Tango family and VisiJet C4 Spectrum Core; 8) used with MJ or

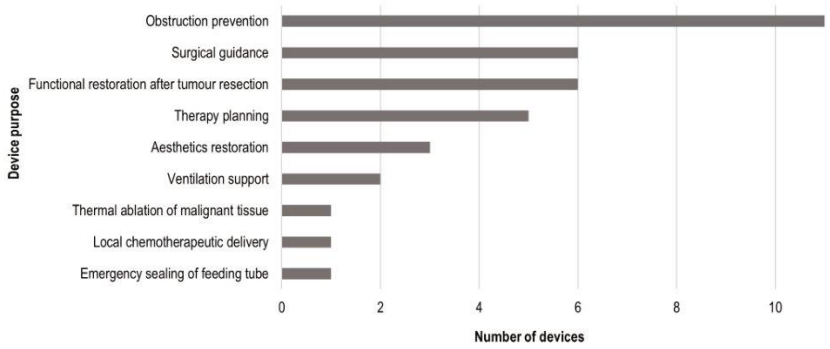

Figure 4 Purpose of the reviewed 3D-printed devices in palliative care. 3D, three dimensional.

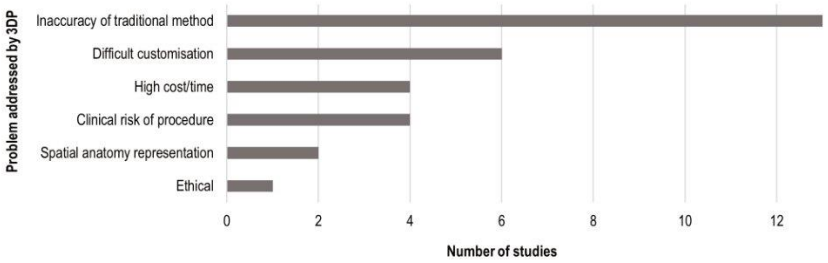

Figure 5 Problems addressed by 3DP in the reviewed studies. 3DP, Three-Dimensional Printing.

SLA, and Acrylonitrile Butadiene Styrene (ABS; 6) used with FFF. Also employed were Polycaprolactone (PCL, including in combination with Paclitaxel—PCL/PTX; 2), PolyLActic acid (PLA, including in combination with thermoplastic polyurethane—PLA/TPU; 2), polymethyl methacrylate (PMMA; 2), PolyVinyl Alcohol (PVA, including in combination with TPU—TPU/PVA; 2), Titanium alloy (2) and Polyurethane (PU; 1).

Patient-specific devices were mainly reverse engineered, which involved surface 3D scanning or CT/MRI, and designing the device based on the digital data of patients' anatomy. Devices that were directly designed included nine endoluminal stents, not tested on patients, a coplanar navigation guide, PEG tube sealing device, scaffold for chemotherapeutic delivery and robotic system for ultrasound palliation of pain. Unlike RE, these devices were designed independently of the specific patients' anatomy. Indirect AM was used to create moulds for obturators, epitheses and respirator masks manufactured from silicone; the other devices were directly 3D printed.

Clinical testing

Eleven papers described proof-of-concept studies that did not involve testing of the devices on human participants. Eight of these were studies of endoluminal stents, one was a phantom model, one a scaffold for chemotherapeutic delivery, and one was a robot for ultrasound pain palliation. In the remaining 19 studies which did include human testing, the number of participants ranged from 1 to 92. The most substantial participant groups were recruited in studies of brachytherapy navigation guides (25–92 participants).[38] The only study that included a control group was of a coplanar navigation guide that was tested on 25 participants.[39] Ten articles were case reports describing the use of 3D-printed devices for clinical care.

The devices were tested using objective methods in 18 studies, 15 of which produced quantitative results and 2 qualitative. Eight studies used qualitative subjective methods. Two studies used a combination of subjective and objective methods, and two did not report any testing of the device.

Outcomes of interventions

All reviewed studies reported generally favourable outcomes. Eleven studies confirmed the feasibility of their concept. Nine of these developed endoluminal stents that showed promising results regarding mechanical[18 29] and drug-eluting properties.[22 25–27] It was also reported that such stents could be delivered to patients within 24 hours[18] or over a weekend at a relatively low cost.[32] In the other proof-of-concept studies, stent abutment was proven to cause prolonged passage of soft and solid diets[35]; a scaffold for chemotherapeutic delivery was shown to significantly reduce the viability of prostate cancer cells[20]; and MRI safety and compatibility were verified for an ultrasound pain palliation robot.[30]

Anatomical models produced positive outcomes in therapy and surgical planning. They demonstrated a high concordance rate with diagnostic accuracy of invasive procedures,[36] and facilitated joint-preserving posterior acetabular resection.[11] In one study, an uncommon anatomical feature was detected that was not recognised in 2D images, but had an important effect on the intraoperative approach.[40] Head models were produced with satisfactory accuracy to make immobilisation masks without the need for additional patient visits, which lowered treatment costs.[16]

All brachytherapy navigation guides were successfully used, with occasional minor side effects related to the treatment itself. One study included a control group and found significantly higher dosimetry values in target tissues when navigation guides were used.[39]

In general, the fit of patient-specific obturators was satisfactory, and few problems were reported in individual cases (eg, leakage while drinking liquid, nasal voice, numbness, dry mouth).[34] Patients' pronunciation, mastication and swallowing were improved, nasal regurgitation was prevented,[19 34] and the overall psychological and social well-being was enhanced.[34]

Epitheses demonstrated the possibility of improving the patients' quality of life and comfort, both semi-functionally and aesthetically.[24] A nasal prosthesis was produced in shorter time and at lower cost compared with traditional techniques.[23] Endoprostheses for palliative orthopaedic reconstruction were successfully implanted, with significant postoperative pain

reduction and improved function of the limb,[28] and with no cases of poor outcome, severe complications, endoprosthesis failure or migration.[12 28 33 37] A PEG tube sealing device enabled recommenced feeding regime without leakage within 24 hours from the clinicians' request.[17] Finally, the vast majority of patient-specific respirator masks were rated higher than generic masks in all aspects of comfort, leakage, preference, recommendation and tolerance.[31]

When referring to the technology employed, the term '3D Printing' was most often used (25), followed by '3DP' (14), 'RP' (12), 'AM' (7) and 'computer-aided manufacturing' (4).

DISCUSSION

The use of 3DP in palliative care

This review identified certain trends in the use of 3DP for the purposes of palliative care. The first study was published in 2004, and two-thirds of the reviewed papers were published after the year 2017. This indicates a considerable increase in the use of 3DP in palliative care in the last few years, which could be directly related to the release/expiration of 3DP patents. Between 2009 and 2014, the original patents for FFF and SLA expired,[41] leading to the expansion of the 3DP market and subsequent decrease of 3DP entry cost. It is likely that the increase in publications presented in this review is directly related to the democratisation of 3DP. The most prominent fields of application that included clinical testing were radiation oncology (brachytherapy navigation guides) and orthopaedic oncology (anatomical models and endoprostheses). These studies also involved the largest numbers of participants. Brachytherapy navigation guides were among the simplest devices manufactured by 3DP in the included studies, making them relatively easy to implement across a larger number of patients. Anatomical models are relatively easy to make, derived from existing medical imaging, with no ethical constraints or need for regulatory approval, being used for training/education purposes with no body contact, implanting, or any procedure directly impacting the patient. 3DP has been used to manufacture anatomical models dating as far back as the early 1990s,[42] recently becoming a more familiar and accessible medical application of this technology. Comparably, there have been enough studies to verify 3DP as a go-to technology for endoprostheses and surgical guides. In a review of 3DP techniques in a medical setting in 2016, surgical guides were listed as the most common devices produced (60.0%), followed by anatomical models for surgical planning (38.7%) and implants (12.7%).[43]

Clinical aspects of 3DP in palliative care

Roughly two-thirds of the reviewed studies reported the outcomes of 3DP-assisted procedures, and one-third were proof-of-concept studies. In general, the clinical outcomes were considered superior to those of conventional approaches. However, only one study (coplanar navigation guide) included a control group that received the treatment without the device.[39] The lack of a control group can impair the validity of the conclusions drawn, as it is uncertain to what extent clinical results can be attributed solely to the use of the 3D-printed device.

In recent years, 3DP has becoming common practice to treat medical conditions that require highly customised solutions (eg, reconstruction after extensive resection in orthopaedic oncology) and/or high-precision treatment (eg, brachytherapy of unresectable visceral tumours). It can also be used to create devices that do not otherwise exist (eg, a PEG tube sealing device[17]) or are difficult to produce with traditional approaches (eg, obturator for patients with trismus[34]).

Technological guidelines for 3DP use in palliative care

The choice of 3DP technology

In the reviewed studies, 3DP was predominantly used to overcome the difficulties of producing customised devices with traditional methods. FFF was the most commonly used 3DP technology (13 of the reviewed devices, including anatomical models and oesophageal stents). Despite the poor surface finish with an apparent staircase effect typical for low-resolution desktop FFF printers,[23] it is favoured for its low cost, versatility and wide range of available thermoplastic filaments, allowing clinicians to match material characteristics of the devices with their function. However, in the studies reviewed, there was little evidence of correlation between the type of medical device produced and the choice of 3DP technology, which suggests that 3DP technology was selected based on availability to the clinician rather than its suitability for the specific device. This suggests that some or many 3D-printed medical devices are produced using suboptimal methods due to the lack of funding, accessibility or familiarity with the technology. Table 1 provides a brief overview of the specifications of 3DP technology to inform future clinical practice.[44–47]

When cost and accessibility are the main concerns, FFF technology is usually opted for, not MJ or SLS. For example, the head mould for radiotherapy immobilisation mask would be too expensive to manufacture using other technologies, and the proof-of-concept studies of stents used FFF possibly due to accessibility for research purposes. For devices in direct contact with the skin or mucosa, such as obturators, smooth surface finish is often important, and thus, SLA, DLP or MJ are favoured. Likewise, the surface finish of epitheses should resemble the texture of skin, which cannot be achieved with FFF, as pointed out in a study of a nasal epithesis.[23] Similar to surface finish, FFF would be rejected for accuracy and resolution in place of MJ, DLP, SLA or SLS, especially when producing highly detailed parts, such as the thread of a Percutaneous

Table 1 Overview of key characteristics of the most common 3DP technologies and materials

	FFF	SLA	DLP	MJ	SLS
Overall cost	Low	Medium	Low	Very high	High
Desktop printers	Yes	Yes	Yes	Yes	Yes
Accuracy	Low	High	High	High	High
Resolution	Low	High	Very high	Very high	Medium
Surface finish	Staircase effect	Smooth	Smooth	Smooth	Grainy
Mechanical properties of printed parts	Satisfactory (anisotropy)	Satisfactory (brittle, affected by moisture and sunlight)	Satisfactory (brittle, affected by moisture and sunlight)	Satisfactory (brittle, affected by moisture and sunlight)	Very good
Complex designs	No	Limited	Limited	Yes	Yes
Multimaterial printing	Yes	No	No	Yes	No
Rigid biocompatible materials—examples	ABS-M30i, PC-ISO, PLA, PMMA, ULTEM™ 1010, ULTEM™ 9085	Accura ClearVue, BioMed Clear, Dental SG Resin, E-Shell 3000, NextDent SG, WaterShed XC 11122	Dental SG Resin, E-Shell 3000	MED610, VeroDent, VisiJet M2R-CL, VisiJet M3 Crystal	CAPA 6501, Duraform PA, EOS PA2200, EOS PEKK, PA 12, PCL
Flexible biocompatible materials—examples	TPU (Tecoflex)	Elastic 50A Resin, E-Guide Soft	E-Guide Soft	MED625FLX, VisiJet M2E-BK70	TPU

ABS, Acrylonitrile Butadiene Styrene; DLP, Digital Light Processing; 3DP, Three-Dimensional Printing; FFF, Fused Filament Fabrication; MJ, Material Jetting; PA, Poly Amide (Nylon); PC, PolyCarbonate; PCL, PolyCaproLactone; PEKK, PolyEtherKetoneKetone; PLA, PolyLactic Acid; PMMA, PolyMethyl MethAcrylate; SLA, StereoLithograPhy; SLS, Selective Laser Sintering; TPU, ThermoPlastic Urethane.

Endoscopic Gastrostomy (PEG) tube sealing device or implants.

The choice of 3DP materials

Half of the reviewed papers did not detail the material employed. Across the other studies, the most common material, ABS, is used largely for moulds for its high strength, toughness and impact resistance, flexibility, durability and temperature resistance which allows for mould reusability.[23 47 48] For other FFF applications, PLA can be favoured over ABS due to its ease of printing, accessibility and price.[16] PCL is used to manufacture endoluminal stents because of its biocompatibility and bioresorbability.[26] Similarly, biocompatibility is the reason for using MED610 for devices that are expected to stay in prolonged contact with the patient's skin.[17] Endoprostheses for palliative purposes can stray from the typical use of titanium alloys,[33 37] as integration between the host bone and endoprosthesis is not expected in patients with bone metastases. In this case, PMMA can be employed as an alternative 3D-printable biocompatible material that is generally available and sufficiently strong to replace non-weight bearing bone, while also being more cost-efficient.[12 49]

Navigation guides for brachytherapy should be safe for skin contact, and are mainly fabricated from photopolymer resins. A common issue with photopolymer resins is the cytotoxicity of the raw material, therefore, a careful balance in its composition is required to preserve printability and ensure safety for use.[50] Among the most versatile biocompatible polymers used with photo-curing techniques are acrylate- and methacrylate-based resins.[47]

Manufacturing approaches

Patient-specific devices are reverse engineered by using digital data of patients' anatomy, as opposed to being directly designed. Indirect AM can be used to create moulds for devices that need to be manufactured from non-printable materials, e.g. silicone, like obturators and epitheses. 3DP materials approved for human use with similar properties to silicone are scarce, and most biocompatible silicone resins are not yet commercially available.[50] Among those currently on the market, 3D-Bioplotter UV Silicone 60A MG (EnvisionTEC) is a transparent medical-grade silicone, approved for 29-day direct skin contact, characterised by medium hardness, no odour, and the possibility of colouring prior to printing.[51] Similarly, TrueSilTM (Spectroplast AG) is biocompatible and available in different hardnesses for different applications (eg, mouthpieces, insoles, earbuds, prosthetics).[52] Elastic Resin (Formlabs) mimics casted silicone well, but it is not biocompatible.[53]

Regulatory aspects of 3DP in medicine

Currently, 3D-printed medical devices must conform to the same regulations as those that are manufactured using traditional methods. The regulations vary across different countries (eg, Regulation (European Union, EU) 2017/745 on Medical Devices Reporting[54] in the EU; Title 21 Code of Federal Regulations[55] in the USA), and have been extensively reviewed in other literature.[56 57] The standard approval process for new medical devices tends to be lengthy, requiring several years of preclinical and clinical testing. As this can present a substantial barrier to urgently treating rare, life-threatening or severely debilitating medical conditions, not uncommon in palliative care, non-standard

regulatory pathways have been established for rapid approval of medical devices in exceptional circumstances. These pathways allow for clinicians and/or manufacturers to apply for exemptions to use non-certified medical devices on humanitarian grounds. The use must be justified through a significant reduction in mortality or morbidity compared with alternative compliant treatments, and applications are assessed on a case-by-case basis.

The vast majority of studies included in the present review did not detail the regulatory frameworks followed. An overview of regulatory aspects applicable is provided the authors' previous systematic review of 3D-printed medical devices used on patients[3]. Especially when bespoke medical devices are 3D-printed to be used without prior testing under the above-mentioned humanitarian exemptions, it is of utmost importance that an appropriate quality management system is in place, which can ensure that appropriate technologies and materials (eg, certified biocompatible materials) are employed in the printing process, and that the postprocessing requirements are met to warrant mechanical, chemical and biological safety of the end product.[58]

3DP and design collaboration

This systematic review highlights how 3DP can potentially be used as part of a design process to address previously unmet clinical needs for which current solutions are either not available or not suitable. The majority of the studies indicated authorships which were interdisciplinary, typically between clinical and design/technical groups. The papers typically focused on the clinical problems and the reporting of the solutions obtained, and therefore, it is not possible to ascertain and synthetise the desgin processes followed across the studies. The current authors anecdotal experience is that clinicians sometimes issue requests to research groups in universities for design assistance with very specific clinical challenges. Arising from these requests, clinical design collaborations are initiated which often form the basis of followon 3DP/innovation research. By way of example, we previously reported on a clincal request to our group for assistance to produce an alternative eye cover for a teen with Rhabdomyoscarcoma.[59] Access to3DP was not part of the initial request but was used by the design group to make the solution. Arising from the engagement, the local palliative care clinical team and the design group thereafter established other research opportunites regarding 3DP in palliative care. Hence, once initial experience is established, then followon design interactions using 3DP are made possible.

Our experience is that some clinicians have experience in 3DP, either through previous clinical innovations or due to access to promoted clinical-based 3DP programmes. In these situations, such clinicians may develop their own concepts for which their key requirement thereafter is access to designers to collaborate in refining the design and print the concepts/devices.

Limitations

There may be other studies not identified by our systematic search due to the terminology issues addressed above, thus, it is possible that some 3D-printed devices intended for palliative care were not included in this review. Moreover, the identified cases of palliative correction of congenital heart defects typically managed by cardiologists were excluded. Nevertheless, the authors expect the key findings of the present work to be a reasonably complete reflection of the current state regarding the use and potential for increased use of 3DP in the provision of care to patients with palliative care needs.

CONCLUSIONS

This systematic review revealed the use of 3DP in palliative care for approximately two decades, with a considerable increase in its use since 2017. Reviewed were 36 devices produced across 30 studies. The device type, field of application, problem addressed, technology used, clinical testing methods and the outcomes of intervention were analysed.

The most common proof-of-concept devices were endoluminal stents, and the most common devices that included clinical testing were anatomical models, brachytherapy navigation guides and endoprostheses. Of the 3DP technologies, FFF was most frequently employed, followed by SLA and MJ. In most of the studies that specified the material used, ABS was chosen, mainly for creating moulds, followed by unspecified photopolymer resins. The majority of devices were designed using RE to correspond to the patient's anatomy. The outcomes of interventions were generally favourable, and the difficulties associated with conventional procedures were successfully overcome. 3DP was found especially valuable in the treatment of medical conditions that require highly customised solutions and/or high-precision procedures, while also ensuring cost-efficiency and time-efficiency. With 3DP, entirely new devices can also be created for rapid response to unique clinical situations.

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