Reporting fidelity in the literature for computer aided design and additive manufacture of implants and guides

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Abstract

The aim of this study was to critically evaluate the nature and reporting fidelity of literature about applications of computer aided design (CAD) and metal additive manufacture (AM) to surgical guides and implants. Increasingly, non-specialist designers such as surgeons or prosthetists are partaking in some or all of the design process. To comply with local regulations, it is imperative that quality is ensured during the design process, yet it is rare for literature to report on the design process of medical devices with sufficient detail to allow proper evaluation or reproduction.

This study reviewed the CAD/AM literature for implant and guide design, focussing on detailed justifications for design decisions, economic impacts, and production methods. This review showed that the fidelity of reporting in the literature was low; with opportunities to report crucial design decisions, engineering parameters, and how these relate to clinical results being frequently missed.

This research proposes the low fidelity in reporting is likely due to a combination of: reporting for different specialisms, resulting in a lack of expert knowledge in certain areas and assumed knowledge in others; commercial sensitivity of design and manufacturing methods; low volume of clinical cases; and a large gap in translating research to clinical applications. This study concluded that higher fidelity in reporting methods are required when discussing the design of AM medical implants, which would allow comparisons between studies, provide evidence to support design quality, and enable evidence-based decision-making.

Keywords: additive manufacturing; computer-aided design; implants; medical devices; regulations

1 Introduction

CAD/AM technologies have reached a point of functional and regulatory readiness for healthcare application, meaning they can be widely exploited[1]. AM in metal materials has made it possible to fabricate long term implantable and transient use patient specific devices that overcome many of the traditional design limitations associated with using off-the-shelf plating systems[2]. Maxillofacial surgeons were some of the earliest adopters of CAD/AM methods and continue to be a primary user group[3]. However, despite CAD/AM techniques being mainstream in academic research, clinical papers investigating AM in maxillofacial surgical applications are often difficult to reproduce due to reports with low design and technical fidelity[4]. There is also a limited weight of evidence that can be extrapolated from the single case studies or small case series, which are most commonly reported in this field. Consequently, there may be scepticism within the healthcare sector towards routinely adopting CAD and AM. This relatively small volume of evidence, combined with the lack of detail on design decisions and economic impacts, is problematic when improved patient outcomes and sustainability are both key determinants for using new technologies[1].

Recently, the role of surgeon and specialist designer has become blurred due to the improved accessibility and perceived affordability of the relevant hardware and software. This has led to some hospitals investing in CAD/AM technology, with surgeons and other medical specialists carrying out their own planning, design and fabrication. This has important implications, especially in relation to evolving regulations. According to the Medical Device Regulations [5] it is essential that design and fabrication control is built in through quality management systems (QMS), and that these systems are continuously improved based on appropriate feedback. For example, reporting on the parameters of a design feature detail and the associated clinical impact would be a component of this feedback. A design QMS should be familiar to specialist medical design engineers, but the

process is far less common with medical professionals. As the regulatory landscape and user base evolves, the published evidence must be held to a sufficiently high standard.

This review paper evaluated the nature and reporting fidelity of literature surrounding CAD and metal AM of medical devices, and assessed the degree to which the literature permits methodological evaluations and reproductions – especially in the context of regulatory and quality control requirements. This was achieved by critically reviewing published literature that utilised metal AM for the design and manufacture of long-term implants, and transient use tools and guides.

2 Methods

2.1 Literature search

A literature review was performed using PubMed, Google Scholar, Cochrane and MetSearch databases. Search terms were tailored to comply with the MeSH (Medical Subject Headings) vocabulary. Search criteria included combinations and variations of the following terms: 3d (three dimensional) print(ed)(ing), additive manufacturing, computer (aided design)(assisted), (digital) design, instrumentation, (mesh)(porous)(scaffold) implant(s), osseointegration, prosthes(es)(is) design/methods, patient specific modeling, planning, printing, surface (architecture)(porosity), surgery, spin(e)(al), three dimensional, titanium, (inter)vertebra(l), veterinary. Papers were filtered to remove: conference abstracts, non-English language and posters.

This study used the following exclusion criteria when manually reviewing abstracts: bioprinting, coatings, conventional stock implants, dental, hydrogels, in vitro tissue regeneration, medical science, medical models, modelling, non-AM, non-devices, non-metallic, prosthodontics, scaffolds,

surface finishing, technical/materials proof of concept, tissue engineering, research methodology developments, visualisation applications.

Following from the initial literature review, 1029 identified papers were assessed for appropriateness to the objectives stated in this study. After reviewing the abstracts of papers in line with the exclusion criteria stated above, and removing duplicates, 933 papers were rejected, with 96 papers remaining for assessment against data extraction eligibility. A further 125 papers were identified for eligibility review using associated references from the original papers. Of the 221 full-text articles reviewed for data extraction eligibility, a further 136 articles were excluded according to the exclusion criteria, leaving 85 articles included for data extraction.

2.2 Data extraction

Where appropriate, the following data fields along with associated details were extracted from the identified papers:

- Literature type
- Economics
- Critical design features, including:
    - Surface finish
    - Porosity of solid
- Characterisation of methods:
    - Materials
    - Fabrication process
- Service model

2.3 Literature groups

The literature groups were defined as follows. A *Case study* investigated a custom device for 1 patient, whereas a *Case series* investigated more than 1 patient. *Fundamental science* covered scientific research in a non-clinical context, including research that may use patient data or cadaveric specimens, but which was not delivered to the patient. *Applied non-clinical* research was similar to the *Fundamental science* group, but investigated an obvious designed application. *Animal study* was a category separated to identify papers where animals were used for scientific research, which is different to *Clinical animal study* where the main purpose was for the treatment of a sick animal. Papers that gave an opinion or reviewed the literature were grouped under the *Review* category, however, these papers were mainly used to identify primary sources which were then included in the literature review themselves. A final category of *Theoretical* was created to capture literature which did not include clinical investigation, traditional scientific research or review current literature.

3 Results

3.1 Literature types

Papers were grouped into categories shown in Table 1. Half of the literature reviewed was comprised of scientific papers (fundamental science, animal studies or applied non-clinical cases). This was significantly greater than the number of human clinical studies/series, which accounted for 25% of the reviewed literature.

In the human clinical investigations, a combined total of 93 patients were investigated. 76 patients were distributed across 5 case series. 17 patients were investigated as individual case studies (Mobbs et al. investigated more than one case in their study[21]), with anatomy sites of: 3 pelvis; 3

chest wall/sternum; 5 spinal; 1 distal tibia/ankle; 4 cranio maxillofacial; and 1 hip. The clinical animal cases investigated a custom bird beak[27] and total knee replacement in a dog[28].

Scientific literature predominantly investigated lattice structures. Within the fundamental science category, the majority of literature investigated optimisation of design, reducing computational complexity, increasing/controlling bone ingrowth and predicting/measuring mechanical strength of porous structures. Andani et al. specifically investigated the application of nickel-titanium lattices to reduce stress shielding through mechanical matching of bone properties[56]. Another common theme of fundamental science literature was the AM process, where print parameters were optimised for improved specimen build. The study by Lin et al. was of particular interest for investigating porosity of specimens, ensuring a fully sintered skin with a defined porous core[67]. Pinto et al. also investigated the AM process but concentrated on accuracy, investigating the sensitivity of geometric errors of AM specimens[69]. Finally, fundamental science papers also investigated finite element modelling to predict strength of implants[61], and biocompatibility of nickel-titanium for selective laser melting (SLM)[66]. Applied non-clinical literature investigated AM for cranio maxillofacial, pelvis/hip, hand, and spinal applications.

Animal studies used canine, caprine, leporine, murine, ovine, and porcine models. All animal studies reported implant fixation or bone ingrowth/regeneration. Papers of interest that investigated more than just bone ingrowth into a lattice structure included: the use of degradable magnesium implants[50]; comparison of a Ti-6Al-4V and polyether ether ketone (PEEK) spinal fusion cage[48]; a pre-clinical trial, investigating the effect of the *Osteoanchor* surface architecture for cementless orthopaedic hip implants[39]; and a study of the effect of tuning stiffness on bone ingrowth using a mandible implant[41].

There were 18 review papers included in this study: 8 papers investigated material structure, scaffolds or biocompatibility, with a strong emphasis noted on the effect of bone regeneration and osseointegration; 3 papers covered specific medical specialities (acetabular[72], chest wall reconstruction[74] and spine inter-body implants[81]) while 1 paper reviewed current and projected medical applications of 3d printing[89], and 1 paper investigated 3d analysis and surgical planning[73]; 2 papers discussed veterinary applications; 1 paper compared the positives and negatives of 3d printing in surgery[79]; 1 paper reviewed patent trends in AM[77]; and 1 paper discussed AM technology, application and research needs[85]. An additional category of *Theoretical* was created for Emelogu et al.'s paper, which discussed the supply chain economic feasibility of AM for biomedical implants[90].

3.2 Economics

Papers that provided more quantified details than subjective derivatives of 'AM is/is not cost effective' are listed in Table 2. The most detailed economic breakdown was presented by Cronskär et al., providing a direct comparison between conventional machine methods and electron beam melting (EBM) for the production of custom hip stems[37].

3.3 Critical design features.

3.31 Justification of design features

For rigorous evaluation, design features should be described in two ways: the feature should be described in enough detail so that it can be replicated or compared; the justification for requiring the feature should be explained. With this information, future studies can improve the design of medical devices by understanding critical design features fully, understanding the cognitive

processes behind their inclusion, and so iteratively optimise their performance in new scenarios. Table 3 provides the details of design features from the literature, with their justifications, if provided.

Only a few papers cited references that claimed to support their design choice. However, often the references themselves did not provide information that would allow the design feature to be replicated. For example, Kim et al. state they use a rugged surface and porous structure as these had been previously reported as improving the degree of osseointegration[19]; however, when referring to the cited references, no design details were provided that would allow this justification to stand. Girasole et al. state they used an acid etched, roughened titanium cage, but provide no detail of the etching process or roughness characteristics[92]. The porous structure by Palmquist et al. is described as having a pore size of 500-700 μm, with a structure thickness of 500-1000 μm[19], however Kim et al. do not state how this relates to the porous design parameters of their implant. Li et al. do not use AM to produce their structure but instead a 'polymeric sponge replication' method, to create a porous structure with pore size of 400-700 μm and porosity of 90%[93], which, again, Kim et al. do not relate to their final design. Similarly, Xu et al. state that size and shapes of their pores were fine-tuned from previous results[18], however, the cited reference for previous results discussed the pull-out strength of screws with roughened surfaces and did not investigate pore details[94].

3.32 Surface Finish

Different AM process and finishing techniques result in various surface finishes. The level of detail provided of surface finishing process varied greatly through the literature. Surface finish affects biofilm formation and cell attachment[95], and can also promote osseointegration of implants[96].

Surface finish of titanium implants could include heat treatment, alkali treatment, removal of Na ions, HA (hydroxyapatite) coatings, and modifications of topography[80], to name a few. Surface finish can also be created at multiple scales, with plasma spraying capable of producing a micro-scale roughness[80]. Cronskar et al. found that surface of EBM specimens was 97 µm, compared to 1.3 µm for machined specimens, causing a reduction in fatigue strength[37].

3.33 Porosity of solid

Porous structures are utilised in medicine to enable targeted drug delivery[97], mechanically match an implant strength to surrounding bone[36], reduce the amount of material and weight[11], promote osseointegration[35], and allow fluid transfer[60]. Various commercial non-AM porous materials are currently available, for example Zimmer's Trabecular Metal™ Technology[98]. Porosity of solid can now be created during the AM process[99], with the additional advantage of reducing thermal stresses during the build. Table 4 lists some of the literature which employed an AM porous design, and states the reason this design was chosen. The disparity of detail provided in the literature is obvious, and underlines the variation in reporting quality.

3.4 Characterisation of methods.

3.41 Fabrication process

A variety of AM fabrication processes were utilised by the papers reviewed in this study, and are described in varying degrees of detail in the literature. Some papers stated generic manufacturing processes, such as "3d printing"[9, 12, 16], "free-form fabrication"[52], or "rapid prototyping"[32], which provided very limited detail as to the specific production method. However, the main fabrication processes described by most studies included EBM and SLM (Table 5). *Review* and *Theoretical* papers are excluded from Table 5; instead, original sources were identified as part of the

literature review. *Fundamental science* papers that did not use AM, but concentrated on design and finite element analysis, are not included in Table 5. Liska et al. investigated a total knee replacement in a dog, and 'machined' their implants[28]. Although the study did not investigate AM, it highlighted the lack of detail in reporting fabrication processes in general, and was included for review as it investigated a novel application of a custom metallic implant. In some cases, only the machine used was noted rather than a fabrication process. In this paper, fabrication process were inferred when the machine used could be clearly identified as a manufacture-specific process, for example if an Arcam machine was used then the process was inferred to be EBM.

When the specific fabrication process was considered for clinical applications only (*Case study, Case series, Clinical animal study*), a similar number of papers report using EBM and SLM (7 and 8, respectively). However, when considering research articles only (*Applied non-clinical, Animal study, Fundamental science*), there was significantly fewer reports of EBM compared to SLM (7 and 27, respectively). Two papers compared EBM to SLM [43, 49].

The level of reported information on fabrication process varied between literature types. The most thorough information appeared in *Fundamental science* papers, often stating parameters like particle size, laser power, scan speed, hatch spacing, and layer thickness. However, it is understandable that many papers do not include this information due to their commercially sensitive, confidential nature.

3.42 Materials

In dental applications, AM implants were normally made from titanium or cobalt chrome[100]. The majority of literature surrounding maxillofacial and orthopaedic implants reported that medical

implants were predominantly AM fabricated using titanium or one of its alloys (Table 6). The reasons given for using this were due to titanium's: biocompatibility[27]; high strength to weight ratio[67]; lower young's modulus of 114 GPa that was closer to bone than cobalt chrome (224 GPa) and stainless steel (210 GPa)[53]; superior corrosion resistance[101]; and it being a well-established implant material[102]. Contrary to this, concerns have been raised with Ti-6Al-4V associated with vanadium which was reported as being released into the body[74]. However, no clinical evidence investigated this as part of a study. Further, El Sawy et al. reported that benchtop studies overestimated the actual release of vanadium into the body[103]. Therefore, there is the need for further clinical investigation in this area to definitively state this as a long-term concern for using Ti-6Al-4V for AM implants. Table 6 shows the material classifications stated in literature. Similar to the *Fabrication Process* section, papers were excluded from Table 6 if they concentrated on design or finite element modelling only, or if they were *Review* or *Theoretical* papers.

Another metal considered for implant manufacture was magnesium, due to the attractive prospect of a degradable implant. Chaya et al. showed degradation of 0.55 +/- 0.02 mm per year[50], but noted excessive hydrogen gas formation due to the degradation process. The advantages of using magnesium were claimed as: low rates of infection[50]; and increased fixation stability, strength and power[76]. However, the literature included in this study did not use AM to produce magnesium implants, and this metal is still in its infancy stage for use as an implant material.

Although this study reviewed metal AM, it is worth discussing a non-metal alternative material that has some popularity - PEEK. The AM variant of this material is polyether ketone ketone (PEKK). Reported advantages of using PEEK include its radio-transparency and its reduced thermal conductivity[104], and a modulus similar to bone[105] that could reduce stress shielding. However, PEEK is considerably more expensive than alternate materials and does not integrate well with

surrounding tissue[48]. Further, better osteoblast adhesion and differentiation have been found through using Ti-6Al-4V compared to PEEK[48]. Lower reported failures have been noted for PEEK compared to titanium mesh cranioplasties, however, a review by Punchak et al. highlighted a significant lack of published data to provide a statistical significance to support this[106]. With limited reported evidence, it is difficult for prescribing practitioners to make a financial decision for the use of PEEK.

3.5 Service model

It was difficult to determine in many studies whether design was performed in-house (hospital) or if it was out-sourced to a commercial entity. For manufacturing, it was also challenging to establish if a reference to a supplier was for out-sourcing the manufacturing process, or a reference to the machine supplier with in-house manufacture. Adding to this confusion, some studies used a combination of both in-house and commercial facilities. In some papers, it was clear that an external manufacturer had been used for AM, however, the detail given was poor. De Freitas et al. simply state they used an "orthopaedic manufacturer"[32]. Even when it is clear which manufacturer was used, the level of detail included on manufacturing parameters is poor, most likely due to commercial sensitivity.

4 Discussion

4.1 Overview of literature

Although this study restricted its search to a limited review scope, it was apparent that literature in this area was heavily weighted towards reporting fundamental science compared to clinical outcomes. This highlights the gap of translating scientific results into clinical applications and a relative lack of quality reporting of clinical evidence. Design, or design engineering considerations

were, for the most part, poorly addressed. Animal studies investigated cell coverage, bone ingrowth, and fixation of implants (torsional and pull out strength), whereas fundamental science studies tended to concentrate on lattice design and mechanical strength.

A problem with clinical data studies, compared to fundamental science, is the low sample sizes. When clinical cases are reported, there is often only 1 patient included in the investigation due to the relative rarity of disease/injury of this severity, and the device is designed specifically for that patient. There is often no direct comparison of patient outcomes to an alternative treatment method as conventionally this type of case would not be treated, or would not be treated knowingly with an inferior method. Although there was a reasonable number of patients (92 patients over 21 papers) included in this study, 17 of these cases (from 16 of the papers) had a sample size of one. Only 5 papers reported a *Case Series* of more than one patient to compare a traditional treatment method to the AM device.

Recently, there is a strong emphasis on minimising the use of animals in research. In the UK, this drive is led by the NC3Rs (National Centre for the Replacement Refinement & Reduction of Animals in Research), through frameworks such as ARRIVE (Animal Research: Reporting of In Vivo Experiments), which aims to improve the quality of animal research by increasing the amount of information published and minimising unnecessary studies[107]. None of the literature reviewed in this study described the reasons behind their choice of animal models. Without the justification of bone growth, loading conditions or anatomy of these animal models being similar to that of humans, it is not possible to state the relevance of the work in relation to clinical applications. Further, it was disappointing that the lack of detail in those reports meant that experiments were not obviously reproducible or able to be critically compared. Studies should state their rationale and describe the

design in greater detail to justify that an animal model was necessary and appropriate, and to reduce the use of future animal models.

4.2 Publication bias

There were no instances of published design or fabrication failures. Underreporting, exacerbated by poor post-market surveillance, is an acknowledged problem across the peer-review system as a whole[108]. Failing to publish negative traits has been described in the pharma industry by Ben Goldacre[109], but is relevant to the medical industry in general. Similar to the attitude adopted by the aviation sector, it would be of great benefit to the healthcare industry if the culture changed to reporting, and thus learning from, failures[110]. It would be valuable for practitioners to learn about which specific design or fabrication decisions for CAD AM failed to achieve their aims, as much as those that met them. Tarsitano et al. did report mesh exposure in one patient, but this is common in over a quarter of patients treated in this way[7]. It was not discussed if the design of the mesh could be improved to prevent this type of failure. Some journals, such as the *Journal of long-term effects of medical implants*, are trying to rectify this bias and create a better understanding of failure mechanisms by encouraging surgeons and academics to report medical failures of pre-clinical and clinical studies involving implants.

4.3 Fabrication and finishing

The manufacturing processes described in the reviewed literature varied in detail, with little comparison between techniques or justification of one choice over another, although two comparisons have been made of osseointegration performance between EBM and SLM parts[43, 49]. A larger portion of all literature used laser melting fabrication processes, although most clinical literature was evenly distributed between EBM and SLM. This showed a discrepancy in translating

research into clinical applications, as it would be expected that similar proportions of fabrication processes used in scientific research would translate to clinical application. The clinical literature tended to report fabrication more poorly than scientific research papers; 6 out of 8 papers that did not state fabrication process were clinical literature (Table 5).

There is much literature that investigates the effects of process parameters on the completeness of powder melting[111], accuracy of geometry[112], structural strength[99], surface finish[113] and build residual stresses[114]. Therefore, if literature does not report fabrication process information, it is not possible to compare: fatigue life of parts[115], which is affected by surface finish[116]; accuracy of fit[117], as geometry tolerances will differ due to process variation and build direction[118]; ease of powder removal from part[119], and thus cleanliness and appropriateness for clinical application[120], due to partially melted powder; to name but a few examples. The importance of providing adequate fabrication information is illustrated by: Gu et al., where changing the scan speed to 400 mm/s resulted in disorderly liquid solidification and balling effect[65]; and Lin et al., where varying the laser parameter was used to create porosity within a part[67].

Inconsistencies in reporting often occur due to ill-defined terminology. For example, Wennerberg et al. highlighted that ‘rough’ and ‘smooth’ are often used to describe surfaces of AM produced devices, however, quantification of ‘rough’ and ‘smooth’ are often omitted[121]. This problem is not limited to AM patient specific implants. Peel and Eggbeer (2016) have illustrated the relative lack of design intent when using conventional design and fabrication methods[1]. Similar vagueness can be noted in the description of finishing technique methods. Rotaru et al. described their surface finishing technique as “sand blasting”[23]. However, Ruppert et al. provided more detail reporting their finishing techniques, where they acid etched their implants with 48% sulphuric acid at 60°C, agitated with stir bar for 30 minutes[43].

Post-processing and finishing can include removing powder and support structures, cutting parts from build plates, tapping threads, creating counter sinks for screws heads, and polishing. The issues with hand finishing, compared to the automated AM process, include the additional processing time of implants and the inability to control the human error of a process compared to AM. The effect of hand finishing techniques on a final medical implant was not reported well in literature, despite the influence of human variation on geometry tolerance and surface roughness.

4.4 Economics

Another factor rarely addressed in published literature was the economics surrounding AM for medical applications. Lack of reporting on economics has similarly been reported by Fera et al. for AM in the industrial field[122]. Hilton et al. claimed that 'low cost' was an aim of their study, however they neglected to report costs in their work[20]. Further, contradictory statements such as "complicated fabrication with *no cost increase*"[27], yet the process being an "*expensive* procedure"[23] was reported, with little evidence to support claims. Table 2 listed the reporting of economics within the searched literature. The costs vary greatly, from $150 for an EBM knee, to £13,000 for an AM acetabular implant. Generally, these papers do not disclose a breakdown of costs, meaning a comparison cannot be drawn between manufacturing process, material selection, design methods, training expenses and time, facility costs, maintenance requirements, finishing techniques, etc. It is apparent that many authors' do not consider these additional costs when stating a simple device price, and therefore assessing the quality of reported outputs is difficult. Sometimes, a genuine reason for not fully disclosing costs is due to confidential commercial information[37]. However, Cronskär et al. successfully, and apparently independently, compared costs of AM to conventional methods for customised hip stems by using relative numbers, and reported a reduction of 35% by using EBM[37].

One paper reviewed in this study stated the range in cost of customised titanium plates for upper maxilla waferless repositioning was €500-1000[8], to include: the complete kit device (cutting guides, and titanium fixation plates); plus the hardware and work time to plan surgery. It is implied that guides were manufactured in polymer, however there was an inconsistency in reporting the manufacturing process of guides in this paper. There was no definition of work time, but the implant and guides were designed and manufactured by an external group (SINTAC). Therefore, work time of in-house processes may have included: CT (computed tomography) reconstruction; creation of dental models; and expertise in surgical planning. Despite the confusion in fabrication process, Mazzoni et al's paper is one of the higher quality examples reviewed in this study[8]. The findings of their work *should* provide a valuable contribution of evidence to support AM for medical applications, but the fidelity of their reporting means that results and experiments are not repeatable or comparable to other studies.

Reduction in surgical time was reported as an additional economic justifier for using CAD/AM in implant production. Spinal surgery can take over 16 hours[21]; reducing this time would improve patient outcomes and save the healthcare institute time and resources. Jardini et al. reported a reduction in surgery time of 3 hours, where surgery originally took 6 hours when implants were shaped in surgery[22]. Salmi et al. also reported a decrease in surgical time for orbital floor reconstruction, from 45 to 30 minutes, when using an AM implant compared to an implant bent in surgery[24]. However, these surgical time reductions were misleading, as the reduction is due to the implant no longer being made *during* the surgery time. Using 3d technologies and polymer AM, it is possible to pre-bend traditional implants before surgery[2], which would result in a similar reduction of surgical time. It was not discussed in these papers if the decrease in time was due to benefits of the AM implant being easier to fit or providing an increase in surgeon confidence compared to a

traditional bent plate, or if the reduction was purely due to not needing to form the plate during the surgery. A study by Logan et al. found no difference in time for free-hand reconstruction of a mandible compared to that using pre-planned surgical patient-specific guides[31]. Although this was a benchtop study, the findings were interesting as results were more consistent for the digitally planned surgery.

4.5 The value of design

One of the only papers reviewed in this study that investigated a surgical instrument, and which included economic information, was by Fuller et al.[30]. They stated that the stainless steel instrument for hand surgery, manufactured by direct metal laser sintering, cost $1,200. The authors reported that the most expensive associated cost was creating the computer model; the engineer logged around 65 hours creating and revising the device, which was estimated to cost $100-150 per hour ($6,500-9,750 total), and there was additional time spent with another colleague reviewing and trialling prototypes. The suggested solution proposed to "circumvent this cost" was that a surgeon could "find a student or salaried employee at a much more moderate price"[30]. Although in this case the tool designed was intended for general use rather than patient-specific applications and so a final design would be manufactured at unit price ($1,200), it is important to consider that when developing medical devices for AM this design process is still necessary.

Another study reported 12 hours spent outside of surgery editing computer generated surgical plans and petitioning for Institutional Review Board approval[12], with no breakdown provided for the design time process. For patient-specific devices this design cost is required for each and every device. The discussion around design experience required to create a computer model, raised by Fuller et al., emphasised the disparity in knowledge between surgeons and designers[30]. It is vital that designers collect surgical input and requirements from clinical specialists. However, it is just as

important that clinicians understand the importance of design expertise to ensure the manufacture of safe and effective devices, complying with local medical device regulations and therefore quality management systems.

4.6 Ensuring quality in design

Ventola et al. reported that a few simple AM medical devices have received 510k FDA (Food and Drug Administration) approval[89]. However, they also postulated that due to the cost and time for large, randomised control trials (part of the FDA demanding regulatory requirements), it would be difficult to gain 510k for complex medical devices and treatments. The importance of reporting on design features, especially for patient-specific implants, is of growing importance. Easy access to 3d technologies within healthcare settings is resulting in a shift from the surgeon as a customer, to the surgeon (or other clinician) as a designer. This is of particular significance with evolving regulatory requirements, as the responsibility for ensuring safe and effective design rests firmly with the hospital, and thus the clinician-designer. Open access repositories, software and libraries make 3d technologies accessible and help to disseminate knowledge[123]. Further, Martelli et al. suggested that the sharing of hardware, software and material between surgical teams was the “best way to promote the dissemination of this technology within hospitals”[79]. However, based on the evidence reviewed in this article, design is often not understood by a surgeon, in terms of its value or what design actually is.

Design has been controlled in batch-production through the use of design files[124], while for designing tissue-engineered scaffolds it was stressed that rigorous characterisation, documentation, and standardisation of design operating procedures would minimise inconsistent design approaches[125]. Hospitals will be required to meet the same standards as external device suppliers as they adopt 3d technologies and start to produce devices in-house. Thus QMS could be employed

to ensure quality of the devices[126]. Clinical evidence can inform design decisions, but a large literature gap was noted in reporting regulatory requirements of patient-specific device design performance characteristics. Post-market surveillance, a requirement for regulatory compliance[5], provides clinical evidence that can be utilised in clinical evaluations and investigations to support device design. Therefore, the quantity and quality of evidence surrounding patient specific AM devices will be of increased significance in the future.

5 Conclusions

Although AM and 3d technologies are used successfully in medical applications, there is a lack of detailed published evidence documenting this from a design engineering (i.e. implementation) perspective. Publication lag in reporting data, and non-open-sourced papers, hinder the transfer of knowledge. Then there is the consideration of time and pressure constraints on surgeons, with the implication that case studies are not always reported. Finally, there is the additional concern of the bias towards publishing favourable results[1, 109], a problem systemic to both journals and academics. This can present a skewed representation within the field. Coupled with the lack of consistent methods and reporting outcomes, very few comparisons can be made between studies to assess their success or significance. Similarly poor reporting fidelity has been noted in pharmacological work, where it was found difficult to reproduce data from other novel studies[127]. There is a clear need for a standard reporting template, such as that which is presented in Table 7, to ensure all designers or acting designers capture and report essential information, to enable proper evaluation of design decisions.

The following suggestions should be considered when publishing articles surrounding additive manufacture of medical implants:

- Report and justify manufacturing methods in more detail, in particular technology platform, material type and post processing
- Report and justify design methods in more detail, including software
- Provide evidence or else hypotheses to support detailed design decisions, for example: if using a 'rough' surface to promote osseointegration, quantify the roughness and compare the results to previous studies
- In clinical studies, report supporting evidence, or justify omissions, regarding claims about contraindications, clinical outcomes, accuracy, timescales, and cost
- Report results openly, both negative and positive, to ensure that mistakes are not repeated
- Include whether design and/or manufacture were performed in-house or subcontracted to an external company/group
- Break down economics more clearly, and in particular highlight if costs include material only, or design time, investment and maintenance of machines, technician time, software licenses, etc.

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References

[1] S. Peel, D. Eggbeer, Additively manufactured maxillofacial implants and guides–achieving routine use, Rapid Prototyping J. 22(1) (2016) 189-199.

[2] R. Bibb, D. Eggbeer, A. Paterson, Medical modelling: the application of advanced design and rapid prototyping techniques in medicine, Woodhead Publishing2014.

[3] N.J. Mankovich, A.M. Cheeseman, N.G. Stoker, The display of three-dimensional anatomy with stereolithographic models, J. Digit. Imaging 3(3) (1990) 200.

[4] S. Peel, S. Bhatia, D. Eggbeer, D.S. Morris, C. Hayhurst, Evolution of design considerations in complex craniofacial reconstruction using patient-specific implants, Proc. Inst. Mech. Eng. H 231(6) (2017) 509-524.

[5] European Council, Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance.), in: E. Council (Ed.) European Union, 2017.

[6] H. Liang, T. Ji, Y. Zhang, Y. Wang, W. Guo, Reconstruction with 3D-printed pelvic endoprostheses after resection of a pelvic tumour, Bone Joint J. 99(2) (2017) 267-275.

[7] A. Tarsitano, S. Battaglia, L. Ciocca, R. Scotti, R. Cipriani, C. Marchetti, Surgical reconstruction of maxillary defects using a computer-assisted design/computer-assisted manufacturing-produced titanium mesh supporting a free flap, J. Craniomaxillofac. Surg. 44(9) (2016) 1320-1326.

[8] S. Mazzoni, A. Bianchi, G. Schiariti, G. Badiali, C. Marchetti, Computer-aided design and computer-aided manufacturing cutting guides and customized titanium plates are useful in upper maxilla waferless repositioning, J. Oral. Maxillofac. Surg. 73(4) (2015) 701-707.

[9] F. Shuang, W. Hu, Y. Shao, H. Li, H. Zou, Treatment of intercondylar humeral fractures with 3D-printed osteosynthesis plates, Medicine 95(3) (2016).

[10] E.-K. Park, J.-Y. Lim, I.-S. Yun, J.-S. Kim, S.-H. Woo, D.-S. Kim, K.-W. Shim, Cranioplasty enhanced by three-dimensional printing: custom-made three-dimensional-printed titanium implants for skull defects, J. Craniofac. Surg. 27(4) (2016) 943-949.

[11] K. Wong, S. Kumta, N. Geel, J. Demol, One-step reconstruction with a 3D-printed, biomechanically evaluated custom implant after complex pelvic tumor resection, Comput. Aided Surg. 20(1) (2015) 14-23.

[12] A.R. Hsu, J.K. Ellington, Patient-specific 3-dimensional printed titanium truss cage with tibiotalocalcaneal arthrodesis for salvage of persistent distal tibia nonunion, Foot Ankle Spec. 8(6) (2015) 483-489.

[13] J.L. Aranda, M.F. Jiménez, M. Rodríguez, G. Varela, Tridimensional titanium-printed custom-made prosthesis for sternocostal reconstruction, Eur. J. Cardiothorac. Surg. 48(4) (2015) e92-e94.

[14] S.M. Toso, K. Menzel, Y. Motzkus, N. Adolphs, B. Hoffmeister, J.-D. Raguse, Patient-specific implant in prosthetic craniofacial reconstruction: first report of a novel technique with far-reaching perspective, J. Craniofac. Surg. 26(7) (2015) 2133-2135.

[15] X. Chen, L. Xu, Y. Wang, Y. Hao, L. Wang, Image-guided installation of 3D-printed patient-specific implant and its application in pelvic tumor resection and reconstruction surgery, Comput. Methods Programs Biomed. 125 (2016) 66-78.

[16] K. Phan, A. Sgro, M.M. Maharaj, P. D'Urso, R.J. Mobbs, Application of a 3D custom printed patient specific spinal implant for C1/2 arthrodesis, J. Spine Surg. 2(4) (2016) 314.

[17] W.J. Choy, R.J. Mobbs, B. Wilcox, S. Phan, K. Phan, C.E. Sutterlin, Reconstruction of thoracic spine using a personalized 3D-printed vertebral body in adolescent with T9 primary bone tumor, World Neurosurg. 105 (2017) 1032. e13-1032. e17.

[18] N. Xu, F. Wei, X. Liu, L. Jiang, H. Cai, Z. Li, M. Yu, F. Wu, Z. Liu, Reconstruction of the upper cervical spine using a personalized 3D-printed vertebral body in an adolescent with Ewing sarcoma, Spine 41(1) (2016) E50-E54.

[19] D. Kim, J.-Y. Lim, K.-W. Shim, J.W. Han, S. Yi, D.H. Yoon, K.N. Kim, Y. Ha, G.Y. Ji, D.A. Shin, Sacral reconstruction with a 3D-printed implant after hemisacrectomy in a patient with sacral osteosarcoma: 1-year follow-up result, Yonsei Med. J. 58(2) (2017) 453-457.

[20] T. Hilton, N. Campbell, K. Hosking, Additive manufacturing in orthopaedics: clinical implications, SA Orthop. J. 16(2) (2017) 63-67.

[21] R.J. Mobbs, M. Coughlan, R. Thompson, C.E. Sutterlin III, K. Phan, The utility of 3D printing for surgical planning and patient-specific implant design for complex spinal pathologies: case report, J. Neurosurg. Spine 26(4) (2017) 513-518.

[22] A.L. Jardini, M.A. Larosa, C.A. de Carvalho Zavaglia, L.F. Bernardes, C.S. Lambert, P. Kharmandayan, D. Calderoni, R. Maciel Filho, Customised titanium implant fabricated in additive manufacturing for craniomaxillofacial surgery: this paper discusses the design and fabrication of a metallic implant for the reconstruction of a large cranial defect, Virtual Phys. Prototyp. 9(2) (2014) 115-125.

[23] H. Rotaru, R. Schumacher, S.-G. Kim, C. Dinu, Selective laser melted titanium implants: a new technique for the reconstruction of extensive zygomatic complex defects, Maxillofac. Plast. Reconstr. Surg. 37(1) (2015) 1.

[24] M. Salmi, J. Tuomi, K.-S. Paloheimo, R. Björkstrand, M. Paloheimo, J. Salo, R. Kontio, K. Mesimäki, A.A. Mäkitie, Patient-specific reconstruction with 3D modeling and DMLS additive manufacturing, Rapid Prototyping J 18(3) (2012) 209-214.

[25] A. Turna, K. Kavakli, E. Sapmaz, H. Arslan, H. Caylak, H.S. Gokce, A. Demirkaya, Reconstruction with a patient-specific titanium implant after a wide anterior chest wall resection, Interact. Cardiovasc. Thorac. Surg. 18(2) (2013) 234-236.

[26] P. Demondion, O. Mercier, F. Kolb, E. Fadel, Sternal replacement with a custom-made titanium plate after resection of a solitary breast cancer metastasis, Interact. Cardiovasc. Thorac. Surg. 18(1) (2013) 145-147.

[27] C. Song, A. Wang, Z. Wu, Z. Chen, Y. Yang, D. Wang, The design and manufacturing of a titanium alloy beak for Grus japonensis using additive manufacturing, Mater. Des. 117 (2017) 410-416.

[28] W.D. Liska, D.J. MARCELLIN-LITTLE, E.V. Eskelinen, C.G. Sidebotham, O.L. Harrysson, A.K. HIELM-BJÖRKMAN, Custom total knee replacement in a dog with femoral condylar bone loss, Vet. Surg. 36(4) (2007) 293-301.

[29] A. Mroz, K. Skalski, W. Walczyk, New lumbar disc endoprosthesis applied to the patient's anatomic features, Acta Bioeng. Biomech. 17(2) (2015).

[30] S.M. Fuller, D.R. Butz, C.B. Vevang, M.V. Makhlouf, Application of 3-dimensional printing in hand surgery for production of a novel bone reduction clamp, J. Hand Surg. Am. 39(9) (2014) 1840-1845.

[31] H. Logan, J. Wolfaardt, P. Boulanger, B. Hodgetts, H. Seikaly, Exploratory benchtop study evaluating the use of surgical design and simulation in fibula free flap mandibular reconstruction, J. Otolaryngol. Head Neck Surg. 42(1) (2013) 42.

[32] E.P. de Freitas, S.C. Rahal, A.C. Shimano, J.V.L. da Silva, P.Y. Noritomi, A.O. El-Warrak, A. Melchert, Bridging plate development for treatment of segmental bone defects of the canine mandible: mechanical tests and finite element method, J. Vet. Dent. 33(1) (2016) 18-25.

[33] S. Arabnejad, B. Johnston, M. Tanzer, D. Pasini, Fully porous 3d printed titanium femoral stem to reduce stress-shielding following total hip arthroplasty, J. Orthop. Res. 35(8) (2017) 1774-1783.

[34] S. Merkt, A. Kleyer, A.J. Hueber, The additive manufacture of patient-tailored finger implants, Laser Tech. J. 11(2) (2014) 54-56.

[35] K. Moiduddin, S. Darwish, A. Al-Ahmari, S. ElWatidy, A. Mohammad, W. Ameen, Structural and mechanical characterization of custom design cranial implant created using additive manufacturing, Electron. J. Biotechnol. 29 (2017) 22-31.

[36] O. Harrysson, O. Cansizoglu, D.J. Marcellin-Little, D.R. Cormier, H.A. West, Direct metal fabrication of titanium implants with tailored materials and mechanical properties using electron beam melting technology, Mater. Sci. Eng. C 28(3) (2008) 366-373.

[37] M. Cronskär, M. Bäckström, L.-E. Rännar, Production of customized hip stem prostheses–a comparison between conventional machining and electron beam melting (EBM), Rapid Prototyping J. 19(5) (2013) 365-372.

[38] A. Mazzoli, M. Germani, R. Raffaeli, Direct fabrication through electron beam melting technology of custom cranial implants designed in a PHANToM-based haptic environment, Mater. Des. 30(8) (2009) 3186-3192.

[39] N. Harrison, J.R. Field, F. Quondamatteo, W. Curtin, P.E. McHugh, P. Mc Donnell, Preclinical trial of a novel surface architecture for improved primary fixation of cementless orthopaedic implants, Clin. Biomech. 29(8) (2014) 861-868.

[40] J. Wieding, T. Lindner, P. Bergschmidt, R. Bader, Biomechanical stability of novel mechanically adapted open-porous titanium scaffolds in metatarsal bone defects of sheep, Biomaterials 46 (2015) 35-47.

[41] T. Schouman, M. Schmitt, C. Adam, G. Dubois, P. Rouch, Influence of the overall stiffness of a load-bearing porous titanium implant on bone ingrowth in critical-size mandibular bone defects in sheep, J. Mech. Behav. Biomed. Mater. 59 (2016) 484-496.

[42] J. Van der Stok, O.P. Van der Jagt, S. Amin Yavari, M.F. De Haas, J.H. Waarsing, H. Jahr, E.M. Van Lieshout, P. Patka, J.A. Verhaar, A.A. Zadpoor, Selective laser melting-produced porous titanium scaffolds regenerate bone in critical size cortical bone defects, J. Orthop. Res. 31(5) (2013) 792-799.

[43] D.S. Ruppert, O.L. Harrysson, D.J. Marcellin-Little, S. Abumoussa, L.E. Dahners, P.S. Weinhold, Osseointegration of coarse and fine textured implants manufactured by electron beam melting and direct metal laser sintering, 3D Print. Addit. Manuf. 4(2) (2017) 91-97.

[44] S. Ponader, C. Von Wilmowsky, M. Widenmayer, R. Lutz, P. Heinl, C. Körner, R.F. Singer, E. Nkenke, F.W. Neukam, K.A. Schlegel, In vivo performance of selective electron beam-melted Ti-6Al-4V structures, J. Biomed. Mater. Res. Part A 92(1) (2010) 56-62.

[45] S. Arabnejad, R.B. Johnston, J.A. Pura, B. Singh, M. Tanzer, D. Pasini, High-strength porous biomaterials for bone replacement: a strategy to assess the interplay between cell morphology,

mechanical properties, bone ingrowth and manufacturing constraints, Acta Biomater. 30 (2016) 345-356.

[46] M. de Wild, R. Schumacher, K. Mayer, E. Schkommodau, D. Thoma, M. Bredell, A. Kruse Gujer, K.W. Grätz, F.E. Weber, Bone regeneration by the osteoconductivity of porous titanium implants manufactured by selective laser melting: a histological and micro computed tomography study in the rabbit, Tissue Eng. Part A 19(23-24) (2013) 2645-2654.

[47] N. Taniguchi, S. Fujibayashi, M. Takemoto, K. Sasaki, B. Otsuki, T. Nakamura, T. Matsushita, T. Kokubo, S. Matsuda, Effect of pore size on bone ingrowth into porous titanium implants fabricated by additive manufacturing: an in vivo experiment, Mater. Sci. Eng. C 59 (2016) 690-701.

[48] S.H. Wu, Y. Li, Y.Q. Zhang, X.K. Li, C.F. Yuan, Y.L. Hao, Z.Y. Zhang, Z. Guo, Porous titanium-6 aluminum-4 vanadium cage sas better osseointegration and less micromotion than a poly-ether-ether-ketone cage in sheep vertebral fusion, Artif. Organs 37(12) (2013).

[49] J. Biemond, G. Hannink, N. Verdonschot, P. Buma, Bone ingrowth potential of electron beam and selective laser melting produced trabecular-like implant surfaces with and without a biomimetic coating, J. Mater. Sci. Mater. Med. 24(3) (2013) 745-753.

[50] A. Chaya, S. Yoshizawa, K. Verdelis, N. Myers, B.J. Costello, D.-T. Chou, S. Pal, S. Maiti, P.N. Kumta, C. Sfeir, In vivo study of magnesium plate and screw degradation and bone fracture healing, Acta Biomater. 18 (2015) 262-269.

[51] A. Fukuda, M. Takemoto, T. Saito, S. Fujibayashi, M. Neo, D.K. Pattanayak, T. Matsushita, K. Sasaki, N. Nishida, T. Kokubo, Osteoinduction of porous Ti implants with a channel structure fabricated by selective laser melting, Acta Biomater. 7(5) (2011) 2327-2336.

[52] P. Thomsen, J. Malmström, L. Emanuelsson, M. Rene, A. Snis, Electron beam-melted, free-form-fabricated titanium alloy implants: material surface characterization and early bone response in rabbits, J. Biomed. Mater. Res. Part B 90(1) (2009) 35-44.

[53] J. Wieding, A. Wolf, R. Bader, Numerical optimization of open-porous bone scaffold structures to match the elastic properties of human cortical bone, J. Mech. Behav. Biomed. Mater. 37 (2014) 56-68.

[54] J. Matena, S. Petersen, M. Gieseke, A. Kampmann, M. Teske, M. Beyerbach, H.M. Escobar, H. Haferkamp, N.-C. Gellrich, I. Nolte, SLM produced porous titanium implant improvements for enhanced vascularization and osteoblast seeding, Int. J. Mol. Sci. 16(4) (2015) 7478-7492.

[55] P.K. Srivas, K. Kapat, P. Dadhich, P. Pal, J. Dutta, P. Datta, S. Dhara, Osseointegration assessment of extrusion printed Ti6Al4V scaffold towards accelerated skeletal defect healing via tissue in-growth, Bioprinting 6 (2017) 8-17.

[56] M.T. Andani, C. Haberland, J.M. Walker, M. Karamooz, A. Sadi Turabi, S. Saedi, R. Rahmanian, H. Karaca, D. Dean, M. Kadkhodaei, Achieving biocompatible stiffness in NiTi through additive manufacturing, J. Intell. Mater. Syst. Struct. 27(19) (2016) 2661-2671.

[57] L. Wang, J. Kang, C. Sun, D. Li, Y. Cao, Z. Jin, Mapping porous microstructures to yield desired mechanical properties for application in 3D printed bone scaffolds and orthopaedic implants, Mater. Des. 133 (2017) 62-68.

[58] S. Van Bael, Y.C. Chai, S. Truscello, M. Moesen, G. Kerckhofs, H. Van Oosterwyck, J.-P. Kruth, J. Schrooten, The effect of pore geometry on the in vitro biological behavior of human periosteum-derived cells seeded on selective laser-melted Ti6Al4V bone scaffolds, Acta Biomater. 8(7) (2012) 2824-2834.

[59] W. Xue, B.V. Krishna, A. Bandyopadhyay, S. Bose, Processing and biocompatibility evaluation of laser processed porous titanium, Acta Biomater. 3(6) (2007) 1007-1018.

[60] Z. Zhang, D. Jones, S. Yue, P. Lee, J. Jones, C. Sutcliffe, E. Jones, Hierarchical tailoring of strut architecture to control permeability of additive manufactured titanium implants, Mater. Sci. Eng. C 33(7) (2013) 4055-4062.

[61] E.A. Nasr, A.M. Al-Ahmari, K. Moiduddin, M. Al Kindi, A.K. Kamrani, A digital design methodology for surgical planning and fabrication of customized mandible implants, Rapid Prototyping J. 23(1) (2017) 101-109.

[62] H. Attar, M. Calin, L. Zhang, S. Scudino, J. Eckert, Manufacture by selective laser melting and mechanical behavior of commercially pure titanium, Mater. Sci. Eng. A 593 (2014) 170-177.

[63] H. Attar, M. Bönisch, M. Calin, L.-C. Zhang, S. Scudino, J. Eckert, Selective laser melting of in situ titanium–titanium boride composites: processing, microstructure and mechanical properties, Acta Mater. 76 (2014) 13-22.

[64] A. Barbas, A.-S. Bonnet, P. Lipinski, R. Pesci, G. Dubois, Development and mechanical characterization of porous titanium bone substitutes, J. Mech. Behav. Biomed. Mater. 9 (2012) 34-44.

[65] D. Gu, Y.-C. Hagedorn, W. Meiners, G. Meng, R.J.S. Batista, K. Wissenbach, R. Poprawe, Densification behavior, microstructure evolution, and wear performance of selective laser melting processed commercially pure titanium, Acta Mater. 60(9) (2012) 3849-3860.

[66] T. Habijan, C. Haberland, H. Meier, J. Frenzel, J. Wittsiepe, C. Wuwer, C. Greulich, T. Schildhauer, M. Köller, The biocompatibility of dense and porous nickel–titanium produced by selective laser melting, Mater. Sci. Eng. C 33(1) (2013) 419-426.

[67] W.-S. Lin, T.L. Starr, B.T. Harris, A. Zandinejad, D. Morton, Additive manufacturing technology (direct metal laser sintering) as a novel approach to fabricate functionally graded titanium implants: preliminary investigation of fabrication parameters, Int. J. Oral Maxillofac. Implants 28(6) (2013) 1490-1495.

[68] E. Marin, M. Pressacco, S. Fusi, A. Lanzutti, S. Turchet, L. Fedrizzi, Characterization of grade 2 commercially pure Trabecular Titanium structures, Mater. Sci. Eng. C 33(5) (2013) 2648-2656.

[69] J.M. Pinto, C. Arrieta, M.E. Andia, S. Uribe, J. Ramos-Grez, A. Vargas, P. Irarrazaval, C. Tejos, Sensitivity analysis of geometric errors in additive manufacturing medical models, Med. Eng. Phys. 37(3) (2015) 328-334.

[70] B. Vandenbroucke, J.-P. Kruth, Selective laser melting of biocompatible metals for rapid manufacturing of medical parts, Rapid Prototyping J. 13(4) (2007) 196-203.

[71] P.H. Warnke, T. Douglas, P. Wollny, E. Sherry, M. Steiner, S. Galonska, S.T. Becker, I.N. Springer, J. Wiltfang, S. Sivananthan, Rapid prototyping: porous titanium alloy scaffolds produced by selective laser melting for bone tissue engineering, Tissue Eng. Part C 15(2) (2008) 115-124.

[72] M.C. Wyatt, Custom 3D-printed acetabular implants in hip surgery–innovative breakthrough or expensive bespoke upgrade?, Hip Int. 25(4) (2015) 375-9.

[73] D.M. Steinbacher, Three-dimensional analysis and surgical planning in craniomaxillofacial surgery, J. Oral Maxillofac. Surg. 73(12) (2015) S40-S56.

[74] C.S. Ng, Recent and future developments in chest wall reconstruction, Semin. Thorac. Cardiovasc. Surg., Elsevier, 2015, pp. 234-239.

[75] O.L. Harrysson, D.J. Marcellin-Little, T.J. Horn, Applications of metal additive manufacturing in veterinary orthopedic surgery, JOM 67(3) (2015) 647-654.

[76] J.A. Auer, D.W. Grainger, Fracture management in horses: where have we been and where are we going?, Vet. J. (London, England: 1997) 206(1) (2015) 5.

[77] M.R. Salvador, P.C. Zamudio, A.S.A. Carrasco, E.O. Benítez, B.A. Bautista, Strategic foresight: determining patent trends in additive manufacturing, J. Intell. Stud. Bus. 4(3) (2014).

[78] R. Kasir, V.N. Vernekar, C.T. Laurencin, Inductive biomaterials for bone regeneration, J. Mater. Res. 32(6) (2017) 1047-1060.

[79] N. Martelli, C. Serrano, H. Van Den Brink, J. Pineau, P. Prognon, I. Borget, S. El Batti, Advantages and disadvantages of 3-dimensional printing in surgery: a systematic review, Surgery (US) 159(6) (2016) 1485-1500.

[80] P.J. Rao, M.H. Pelletier, W.R. Walsh, R.J. Mobbs, Spine interbody implants: material selection and modification, functionalization and bioactivation of surfaces to improve osseointegration, Orthop. Surg. 6(2) (2014) 81-89.

[81] X. Tan, Y. Tan, C. Chow, S. Tor, W. Yeong, Metallic powder-bed based 3D printing of cellular scaffolds for orthopaedic implants: a state-of-the-art review on manufacturing, topological design, mechanical properties and biocompatibility, Mater. Sci. Eng. C 76 (2017) 1328-1343.

[82] K. Alvarez, H. Nakajima, Metallic scaffolds for bone regeneration, Materials 2(3) (2009) 790-832.

[83] A. Butscher, M. Bohner, S. Hofmann, L. Gauckler, R. Müller, Structural and material approaches to bone tissue engineering in powder-based three-dimensional printing, Acta Biomater. 7(3) (2011) 907-920.

[84] S. Yang, K.-F. Leong, Z. Du, C.-K. Chua, The design of scaffolds for use in tissue engineering. Part I. Traditional factors, Tissue Eng. Part A 7(6) (2001) 679-689.

[85] N. Guo, M.C. Leu, Additive manufacturing: technology, applications and research needs, Front. Mech. Eng. 8(3) (2013) 215-243.

[86] S.J. Hollister, C. Lin, E. Saito, R. Schek, J. Taboas, J. Williams, B. Partee, C. Flanagan, A. Diggs, E. Wilke, Engineering craniofacial scaffolds, Orthod. Craniofac. Res. 8(3) (2005) 162-173.

[87] L. Murr, S. Quinones, S. Gaytan, M. Lopez, A. Rodela, E. Martinez, D. Hernandez, E. Martinez, F. Medina, R. Wicker, Microstructure and mechanical behavior of Ti–6Al–4V produced by rapid-layer manufacturing, for biomedical applications, J. Mech. Behav. Biomed. Mater. 2(1) (2009) 20-32.

[88] A.T. Sidambe, Biocompatibility of advanced manufactured titanium implants—a review, Materials 7(12) (2014) 8168-8188.

[89] C.L. Ventola, Medical applications for 3D printing: current and projected uses, Pharm. Ther. 39(10) (2014) 704.

[90] A. Emelogu, M. Marufuzzaman, S.M. Thompson, N. Shamsaei, L. Bian, Additive manufacturing of biomedical implants: a feasibility assessment via supply-chain cost analysis, Addit. Manuf. 11 (2016) 97-113.

[91] H. O, C. D, Direct fabrication of custom orthopedic implants using electron beam melting technology, in: I. Gibson (Ed.), Advanced manufacturing technology for medical applications: reverse engineering, software conversion and rapid prototyping, John Wiley & Sons, Ltd, England, 2005.

[92] G. Girasole, G. Muro, A. Mintz, J. Chertoff, Transforaminal lumbar interbody fusion rates in patients using a novel titanium implant and demineralized cancellous allograft bone sponge, Int. J. Spine Surg. 7(1) (2013) e95-e100.

[93] J. Li, S. Li, C. Van Blitterswijk, K. De Groot, A novel porous Ti6Al4V: characterization and cell attachment, J. Biomed. Mater. Res. Part A 73(2) (2005) 223-233.

[94] J. Yang, H. Cai, J. Lv, K. Zhang, H. Leng, Z. Wang, Z. Liu, Biomechanical and histological evaluation of roughened surface titanium screws fabricated by electron beam melting, PLoS One 9(4) (2014) e96179.

[95] S.C. Cox, P. Jamshidi, N.M. Eisenstein, M.A. Webber, H. Burton, R.J.A. Moakes, O. Addison, M. Attallah, D.E.T. Shepherd, L.M. Grover, Surface finish has a critical influence on biofilm formation and mammalian cell attachment to additively manufactured prosthetics, ACS Biomater. Sci. Eng. 3(8) (2017) 1616-1626.

[96] R.A. Perez, G. Mestres, Role of pore size and morphology in musculo-skeletal tissue regeneration, Mater. Sci. Eng. C 61 (2016) 922-939.

[97] P. Wu, D.W. Grainger, Drug/device combinations for local drug therapies and infection prophylaxis, Biomaterials 27(11) (2006) 2450-2467.

[98] Zimmer, Trabecular Metal™ Technology. http://www.zimmer.co.uk/medical-professionals/our-science/common/trabecular-metal-technology.html. 2018).

[99] S. Ghouse, S. Babu, R.J. Van Arkel, K. Nai, P.A. Hooper, J.R. Jeffers, The influence of laser parameters and scanning strategies on the mechanical properties of a stochastic porous material, Mater. Des. 131 (2017) 498-508.

[100] M. Revilla-León, M. Özcan, Additive manufacturing technologies used for 3D metal printing in dentistry, Curr. Oral Health Rep. 4(3) (2017) 201-208.

[101] J. Ong, M.R. Appleford, G. Mani, Introduction to biomaterials: basic theory with engineering applications, Cambridge University Press2013.

[102] Y. Oshida, Bioscience and bioengineering of titanium materials, Elsevier2010.

[103] A.A. El Sawy, M.A. Shaarawy, Evaluation of metal ion release from Ti6Al4V and Co-Cr-Mo casting alloys: in vivo and in vitro study, J. Prosthodont. 23(2) (2014) 89-97.

[104] M.M. Hanasono, N. Goel, F. DeMonte, Calvarial reconstruction with polyetheretherketone implants, Ann. Plast. Surg. 62(6) (2009) 653-655.

[105] B. Schliemann, R. Seifert, C. Theisen, D. Gehweiler, D. Wähnert, M. Schulze, M.J. Raschke, A. Weimann, PEEK versus titanium locking plates for proximal humerus fracture fixation: a comparative biomechanical study in two-and three-part fractures, Arch. Orthop. Trauma Surg. 137(1) (2017) 63-71.

[106] M. Punchak, L.K. Chung, C. Lagman, T.T. Bui, J. Lazareff, K. Rezzadeh, R. Jarrahy, I. Yang, Outcomes following polyetheretherketone (PEEK) cranioplasty: Systematic review and meta-analysis, J. Clin. Neurosci. 41 (2017) 30-35.

[107] C. Kilkenny, W. Browne, I.C. Cuthill, M. Emerson, D.G. Altman, Animal research: reporting in vivo experiments: the ARRIVE guidelines, Br. J. Pharmacol. 160(7) (2010) 1577-1579.

[108] R.G. Hauser, Here we go again—another failure of postmarketing device surveillance, N. Engl. J. Med. 366(10) (2012) 873-875.

[109] B. Goldacre, Bad pharma: how drug companies mislead doctors and harm patients, Macmillan2014.

[110] M. Syed, Black box thinking: why most people never learn from their mistakes - but some do, Penguin2015.

[111] Y. Li, K. Zhou, S.B. Tor, C.K. Chua, K.F. Leong, Heat transfer and phase transition in the selective laser melting process, Int. J. Heat Mass Transfer 108 (2017) 2408-2416.

[112] M. Fahad, N. Hopkinson, Evaluation and comparison of geometrical accuracy of parts produced by sintering-based additive manufacturing processes, Int. J. Adv. Manuf. Technol. 88(9-12) (2017) 3389-3394.

[113] P. Wang, W.J. Sin, M.L.S. Nai, J. Wei, Effects of processing parameters on surface roughness of additive manufactured Ti-6Al-4V via electron beam melting, Materials 10(10) (2017) 1121.

[114] N. Shamsaei, A. Yadollahi, L. Bian, S.M. Thompson, An overview of direct laser deposition for additive manufacturing; part II: mechanical behavior, process parameter optimization and control, Addit. Manuf. 8 (2015) 12-35.

[115] A. Fatemi, R. Molaei, S. Sharifimehr, N. Phan, N. Shamsaei, Multiaxial fatigue behavior of wrought and additive manufactured Ti-6Al-4V including surface finish effect, Int. J. Fatigue 100 (2017) 347-366.

[116] K.S. Chan, M. Koike, R.L. Mason, T. Okabe, Fatigue life of titanium alloys fabricated by additive layer manufacturing techniques for dental implants, Metall. Mater. Trans. A 44(2) (2013) 1010-1022.

[117] P. Das, R. Chandran, R. Samant, S. Anand, Optimum part build orientation in additive manufacturing for minimizing part errors and support structures, Procedia. Manuf. 1 (2015) 343-354.

[118] G. Ameta, S. Moylan, P. Witherell, R. Lipman, Challenges in tolerance transfer for additive manufacturing, ASPE Top. Meet.-Ext. Abstr., 2016.

[119] H. Hasib, O.L. Harrysson, H.A. West, Powder removal from Ti-6Al-4V cellular structures fabricated via electron beam melting, JOM 67(3) (2015) 639-646.

[120] P. Julius Bonini, K.C. Mazza, J. Morra, Cleanliness and microstructural issues related to additive layer manufactured porous surface structured titanium medical and dental implants, in: A.L. Pilchak, J.E. Allison, S. Ankem, R. Boyer, J. Christodoulou, H.L. Fraser, M.A. Imam, Y. Kosaka, H.J. Rack, A. Chatterjee, A. Woodfield (Eds.) Proc. 13th World Conf. Titan., 2016, pp. 1751-1759.

[121] A. Wennerberg, T. Albrektsson, Effects of titanium surface topography on bone integration: a systematic review, Clin. Oral Implants Res. 20(s4) (2009) 172-184.

[122] M. Fera, F. Fruggiero, A. Lambiase, R. Macchiaroli, State of the art of additive manufacturing: review for tolerances, mechanical resistance and production costs, Cogent. Eng. 3(1) (2016) 1261503.

[123] M.B. Hoy, 3D printing: making things at the library, Med. Ref. Serv. Q. 32(1) (2013) 93-99.

[124] D. Kinsel, Design Control Requirements for Medical Device Development, World J. Pediatr. Congenit. Heart Surg. 3(1) (2012) 77-81.

[125] S.J. Hollister, C.L. Flanagan, D.A. Zopf, R.J. Morrison, H. Nasser, J.J. Patel, E. Ebramzadeh, S.N. Sangiorgio, M.B. Wheeler, G.E. Green, Design control for clinical translation of 3D printed modular scaffolds, Ann. Biomed. Eng. 43(3) (2015) 774-86.

[126] J.U. Pucci, B.R. Christophe, J.A. Sisti, E.S. Connolly Jr, Three-dimensional printing: technologies, applications, and limitations in neurosurgery, Biotechnol. Adv. 35(5) (2017) 521-529.

[127] F. Prinz, T. Schlange, K. Asadullah, Believe it or not: how much can we rely on published data on potential drug targets?, Nat. Rev. Drug Discov. 10(9) (2011) 712.

Table 1 – Literature types.

Type	Number of papers	References
Case series	5	6-10
Case study	16	11-26
Clinical animal study	2	27, 28
Applied non-clinical	10	29-38
Animal study	14	39-52
Fundamental science	19	53-71
Review	18	72-89
Theoretical	1	90

Table 2 – Economic references.

Reference	Device description	Costs
[72]	• Acetabular implant	• OSSIS - £11,000 (EBM) • MOBELIFE - £13,000 (assumed to be SLM) • Zimmer (non-AM Trabecular metal; open cell foam vapour deposition) - £7000
[12]	• Custom 3d printed titanium truss cage for tibial fracture	• Trials and actual implant = $8400 12 hours outside of surgery creating model
[8]	• Craniomaxillofacial upper maxilla titanium plates	• Device costs from 500 – 1000€; average 750€
[30]	• Tool - bone reduction clamp for hand surgery • Stainless steel, SLM	• Final design $1200; $100-150 per hour for creating model (65 hours)
[37]	• Customised hip stem prostheses – Ti-6Al-4V ELI (extra low interstitials) • Comparison costs of material consumption, file preparation and manufacturing – other costs assumed the same	• 35% cheaper for EBM than traditional manufacture (conventional machining)
[91]*	• Fabrication and material costs • Custom designed titanium knee	• EBM knee $150-$200

*book chapter is original source, identified in reviewed paper[87].

1 *Table 3 – Design feature detail.*

Reference	Design feature	Detail	Justification
[26]	• Holes	---	• To avoid seroma
[25]	• Holes on surface	---	• For drainage
	• Plate thickness	• 2-3 mm	---
	• Plate weight	• 160 g	---
[21]	• Screw trajectories planned and built into implant	---	• To aid in screw placement
	---	---	• Maximum strength to support patient, but allow large central empty space for bone graft
	• Self-supporting structure	---	• Minimum support material to minimise post processing
	• Maximum sparseness	---	• Best possible postoperative imaging
	• Form	---	• Lardosis change of 6°
[19]	• Form	• Identical to anatomical structure	---
	• Fixation	• Pedicle screw inserted bilaterally from L3 to iliac; 1 screw at S1 level; metallic cables through sacral pore and iliac bone at midline	---
	• Structure	• High density at screw hole and contact surfaces	---
	• Strut surface/Internal architecture	• Rugged and porous mesh	• To accelerate bony fusion
[35]	• Form	• Mirror image of healthy side	---
	• Implant thickness	• 1.25 mm	---
	• Fixation tabs	• × 4	• Firm fixation
	• Taper screw holes	---	• Firm attachment; complete sinking of screws to enhance patient comfort
	• Sold border around meshed part of implant	• 10 mm	• For fixing of screws
	• Porous region	• Cell type - body diagonal with nodes; 49.81% porous, strut size 800 µm, pore size 700 µm	• Lighter in weight with good mechanical efficiency
[34]	• Internal lattice structure	---	• Lattice structure designed to meet stiffness of bone
	• Powder outlet	---	• Remove un-melted powder
	• Joint surface same as original bone	---	---
[17]	• Form	• Based on patient anatomy	---
	• Porous endplates	---	• Osseointegration
	• Angulation	---	• Correct sagittal balance
	• Fixation holes	• For pedicle screw	• Assist screw insertion

	•	Multiple implants	•	Of various heights and angles in 2 mm increments	• In case of intraoperative complications
[10]	•	Overlay design	---		---
	•	Mirrored	---		---
	•	Tabs with holes	---		---
	•	Mesh lattice	•	Honeycomb structure	• High strength to weight ratio; used to flat or slightly curved surface topography; avoid stress shielding
	•	Surface area	•	Mean value of 18,036 mm^2	---
[27]	•	Open cavity structure	•	Incorporate design of breathing pore	• To surround remnant of natural beak
	•	Partition in open cavity near tip	---		• Prevent infection and support weight
	•	Breathing hole	---		---
	•	Hole	---		• Manufacturing process requirement (remove powder)
	•	Fixing screw holes	•	2 rows of 3 holes	---
	•	Thickness of beak increased	---		• Space for sunken screw
	•	Bulkhead	---		---
	•	Internal hollow structure	---		• To reduce weight
[15]	•	Through holes	---		• Fixation
	•	Porous section	---		---
[8]	•	Screw holes	•	× 8 of 2 mm diameter; avoiding damage to tooth roots	• Guide fixation; many holes so alternative options if one hole fails
[7]	•	Fixation	•	2.4 mm locking system	---
	•	Mesh design	---		---
	---		---		• Provide support to orbital contents
	---		---		• Obliterate any communication between the orbit and nasopharynx
	---		---		• Reconstruct the palatal surface
	---		---		• Achieve facial symmetry and good aesthetic results
[32]	•	Large plate geometry (long × wide × thick)	•	55.7 mm × 10.0 mm × 2.5 mm	---
	•	Small plate geometry (long × wide × thick)	•	41.9 mm × 7.5 mm × 2.0 mm	---
	•	Under surface	•	Scalloped design	• To avoid compression of plate against periosteum
	•	Contour	•	Rounded	• Reduce stress concentration
	•	Screws	•	Locking screws; arrange unequally	• More resistant to screw failure; help in tension distribution
[16]	•	Pre-angled screw holes	---		• To assist correct placements
	•	Porous	---		• Osseointegration

[18]	• Porous	• Highly organised microstructure; uniformity of size and shape of pores and continuity of struts; greater pore density	• Biomechanical properties associated with less stress shielding; prevent implant subsidence; increased bone-metal interface conductive to bone in-growth
	• Proximal wings	• Contour of inferior articular surface of C1 vertebra	• Easy access for screw insertion
	• Bottom surface of device	• Tilted surface based on angulation of upper endplate	• Reduce the chance of implant subsidence
	• Anterior surface	• Zero profile	• Prevent dysphagia
[13]	• Sternal core	• Rigid	---
	• Holes in sternal core	---	• Anchoring with steel wire
	• Clamp	• Rough inner surface	• Minimise risk of migration or dislocation secondary to rib stump
	• Hole in clamp	• Insert customised titanium bolt	• To further lock to costal stump
[12]	• Form	• Volume = 45 ml; 48 mm × 46 mm × 30.5 mm	---
	• Truss design	---	---
	• Centralizer	• 14 mm diameter	• Prevent graft entering canal of cage
	• Roughened titanium	---	• Osteoblast adhesion
[11]	• Mirror of healthy side	---	---
	• Form	• Designed considering surgical approach and surrounding soft tissue	---
	• Porous scaffold	• Rigidly connected to solid plate; 70% porosity, pore size of 720 µm, solid strut thickness of 350 µm	• Reduce weight, promote bone ingrowth
	• Loading conditions of hip during gait	• Avoid high stress peaks in bone	• Finite element modelling; minimise risk of bone fractures
[29]	• Form	• Elliptical; no sharp edges	---
	• Working surface	• Specially profiled on side of insert	• Appropriate range of motion and protects from dislocation
	• Working surface of lower plate on side of insert	• 4 symmetrically spaced fixing bolts	• Smooth translational movement of insert, varied rotating axis location, better reflection of kinematics
	• Height of bolts	---	• Selected not to limit anatomical mobility of operated mobile segment
	• Recesses in insert	• Specially grooved system of small canals with shape resembling a ‘roundabout’	• Increase smoothness of flow, body fluids provide lubricating film; removes wear debris
	• Top plate	• Spherical cup	• Transfers stresses circumferentially onto insert
[14]	• Implant/bone contact area maximised	• 10 × 6 mm mini-screws	• Stable anchorage
	• Retention for glabella and lateral maxillary process	• 2 threads in centre for conventional magnetic abutments	• Sufficient retention of nasal prosthesis
	• Skin penetrating areas	• Smooth polished surface	• Optimal hygienic conditions
	• Good access	---	• Patient hygiene
[74]	• STRATOS system clips	• Resemble claws	• To attach to ribs
	• STRATOS contour	• Areas of narrower, more angled profile	• Concentration of stresses contributing to fracture
	• MatrixRIB pre-contoured plate holes	• Fastening to rib with locking screws	• To attach to ribs

	• MatrixRIB contour	• Smoother	---
	• Mesh	---	• Flexibility; permits uniform tension distribution at defect edges; limit seroma formation
[6]	• Porosity of implant-bone interface	---	• Osseointegration
	• Iliac prosthesis:		
	o Shape	o Matches inner wall of ilium	---
	o Screw holes	o × 2; plus polyaxial screw on rear	o Fixation to sacrum and acetabulum; connection to lumbar pedicle screws
	o Holes	o Several on outer and inner edges	o Attachment of soft tissues
	• Hemipelvic prosthesis:		
	o Modifications of contour of iliac	---	---
	o Modification of screw holes	---	---
	o Modification of implant-bone interface	---	---
	• Screw-rod connected hemipelvic endoprosthesis		
	o Sacral component	---	---
	o Acetabular ring	---	---
	• Linking mechanism	o Vertical section has 3 holes; inner surface is porous	o For sacral fixation and two polyaxial screws to lumbar pedicle screws
		o Angle adjustable through linking mechanism	o Angles of abduction and anteversion of acetabulum can be adjusted
		o Double axel mechanism	---

1 *Table 4 – Porosity detail.*

Reference	Details of design	Reason for porosity
[19]	Porous mesh and incorporated dense strut with rugged surface	Osseointegration (implant fixation)
[47]	Pore sizes 300, 600 and 900 µm; diamond lattice; porosity 65%; 600 µm suitable for orthopaedic - compressive strength of 42 MPa	Mechanical properties similar to human bone; facilitate bone ingrowth
[45]	High strength, fully porous femoral stems Pore size 50-800 µm, porosity >50%	Tuneable mechanical properties to reduce stress shielding
[46]	Pore size 500-600 µm, porosity 83%; open porous; stepped cylindrical shape, rod thickness 200 µm	Osteopromotive properties
[44]	Compact and porous cylinders; porous cylinders with pore size 0.45 mm and porosity 61.3%	Bone regeneration and ingrowth of osseous tissue
[56]	32, 45 and 58% porosity; *D*/*L* of 0.5, 0.6 and 0.7 where *D* and *L* are diameter and length of strut (with *L* kept at 1 mm)	Prevent stress shielding
[20]	Trabecular surface	Bone ingrowth for superior fixation
[21]	Cage	Maximum sparseness to ensure best possible postoperative imaging; empty space for bone graft whilst maintaining strength
[36]	Rhombic structures (due to space filling properties and geometric properties suitable for EBM) with cell size 3-12 mm	Tailored mechanical properties to prevent stress shielding
[57]	Reduction of modulus by 75-80% through porous design; body-centred cubic structure; designed with 4,6 and 9 mm diameter struts and 28, 44 and 70% porosity respectively; yield strength 185, 333 and 842 MPa respectively	Minimise stress shielding; improve osseointegration and long term stability
[35]	Strut size 800 µm; pore diameter 700 µm (within ideal range of 500-1500 µm); porosity 49.81% (50% ideal for bone tissue ingrowth); body diagonals with nodes	Bone formation and implant fixation through porous structure while maintaining adequate mechanical strength
[41]	Porosity 53%; pore size ranges from 800 to 1500 µm; elastic modulus of 37.9 GPa longitudinally, 18 GPa and 15.8 GPa in 2nd and 3rd directions	Bone ingrowth with loading
[10]	Reticulated mesh arrays: open honeycomb design; array of hollow cells formed between thin vertical walls; columnar or hexagonal shape cells;	Minimise amount of material; weight and costs kept to minimum; maximum strength to weight ratio; avoid stress shielding; allow firm tissue integration – prevent local infection
[54]	250 µm pore size (supports angiogenesis)	Osteoblast seeding and proliferation
[33]	Tessellated tetrahedron micro-architecture; 500 µm pore size at 70% porosity	Reduce stress shielding through tuneable mechanical properties
[16]	Porous	Osseointegration
[34]	Lattice structure	Meet stiffness of bone
[17]	Porous	Osseointegration
[48]	68% porosity; 710 µm pore size; young's modulus 2.5 GPa	Bone ingrowth and mechanical stability
[60]	65% porosity; unit cell 600 µm; 200-500 µm pore size	Permeability; bone ingrowth; mechanical integration; mechanical matching
[18]	Porous: size and shape of pore fine-tuned to achieve ultrastructural balance between dimension of struts and porosity to facilitate bone in-growth and biomechanically similar to cancellous bone	Better biomechanical stability and enhanced bone healing
[71]	Cubic scaffolds with pore width of 0.45-1.2 mm; scaffold applied to mandible	Optimal for bone ingrowth
[24]	Macrostructure generated to geometry; 0.4 mm net thickness; 3 mm hole size	Decision that net macrostructure was suitable for patient was decided by surgeon – based on similar design to traditional bendable orbital reconstruction plates
[68]	77 and 89% porosity; pore diameter of 0.66 and 1.37 mm	Trabecular structure for initial stability; maximum secondary fixation
[67]	Skin of 0.35, 1 or 1.5 mm; porous core; 35 GPa Young's modulus with skin of 0.35 mm and when core compromised 74% of volume	Mechanical match to bone
[66]	Varying hatch distance to create porosity of 88-99%; designed lattice of 65% with pore and strut size of 500 µm (optimal for bone ingrowth)	Support regeneration of critical bone defects; mechanically match bone
[51]	Diagonal pore (channel) sizes of 500, 600, 900 and 1200 µm	Osteoinductivity

[49]	SLM - 250-800 µm pore size; 63% porosity; 1500 µm thickness EBM – 350-1400 µm pore size; 49% porosity	Trabecular like implant surface; implant fixation
[64]	Pore size >100 µm; 50-70% porosity	Bone colonization; mechanical properties to match bone
[59]	17-58% porosity; pore size <800 µm with 200 µm critical size; open cellular pores	Cell ingrowth of osteoblasts
[42]	120-230 µm strut diameter; 68 and 88% porosity; dodecahedron unit cell	Vary elastic modulus with strut diameter – lower elastic modulus so more deformation of scaffold and more ingrowth
[55]	Pore size ~500 µm; porosity ~58%; strut diameter 348 µm after sintering	Stress shielding, mechanical properties – customisation of load-bearing
[6]	3d printed porous structure; pre-determined pore size and density	"Potentially" improves stability in the long-term
[11]	Porous scaffold: 70% average porosity; average pore size 720 µm; thickness of solid struts 350 µm	Highly resistant to mechanical compression, while elastic modulus is comparable to that of bone to minimize the risk of peri-implant stress shielding Promote bone in growth and provide long-term implant stability Reduce implant weight
[12]	Truss cage; open architecture	• Guide bone formation • Based on theoretical benefits not previously test in a clinical scenario
[7]	Mesh	Traditional treatment method
[15]	Porous area	Bone regeneration
[39]*	OsteoAnchor: strut diameter 0.63 mm; pore size 0.63 mm; hook height 0.58 mm; separation between anchors 1.26 mm	Improve primary fixation
[53]	Cubic cell: strut diameter 416 µm; size of cell 1215 µm; pore size 799 µm Diagonal cell: strut diameter 1448 µm; size of cell 4024 µm; pore size 797 µm Pyramidal cell: strut diameter 393 µm; size of cell 1182 µm; pore size 789 and 198 µm	Optimised designs for structural modulus of 15 GPa (in range of human cortical bone)
[40]	Open porous scaffold with rectangular strut: width 400 µm and height 800 µm	Bone formation
[58]	Triangular, hexagonal and rectangular pore shapes; 500 and 1000 µm pore size; strut size 200 µm; stiffness from 0.45 to 11 GPa	Small pores - initial cell attachment; large non-circular pores - avoid pore occlusion

*not strictly an AM porosity, but an AM feature that creates a non-solid area to improve implant stability.

Table 5 – Fabrication detail.

Method	Reference
Electron beam melting (EBM)	6, 10, 13, 15, 18-20, 35-38, 43, 44, 48, 49, 68
Selective laser melting (SLM)	7, 8, 11, 14, 22-25, 27, 29, 30, 32, 34, 39-43, 45-47, 49, 51, 54, 56-58, 60, 62-67, 70, 71, 85
Laser engineered net shaping (LENS)	59
Fused deposition modelling (FDM)	55
Not stated or generic 3d printing/rapid prototyping/free-form fabrication	9, 12, 16, 17, 21, 26, 31, 52

Table 6 – Materials detail.

Material	References
Titanium alloy	6, 18
Ti-6Al-4V	8, 11, 14, 15, 22, 27, 36, 40, 42-44, 48, 49, 55, 57, 58, 67, 70
Ti-6Al-4V ELI	10, 19, 20, 25, 35, 37, 39, 52
Co-28Cr-6Mo	29
Titanium	7, 12, 16, 17, 21, 23, 26, 38, 45, 47, 54, 59, 71
Surgical grade titanium alloy	13
Stainless steel	30
Commercially pure titanium	32, 51, 60, 62, 64, 65
Grade 2 titanium	41, 46, 68
NiTi	56, 66
TiB2	63
CoCrMo	70
Not stated	9, 34, 45

1 *Table 7 – Checklist for authors*

	Factors	Essential/ Desirable	Stated?	Consider justification
Study	Clinical measures	E		
	Technical measures	E		
	Study design (cohort number, follow up period, etc.)	E		
Manufacturing	Fabrication process	E		
	• Technology platform	D		
	• Build parameters	D		
	Post processing	E		
	• Parameters	D		
	Material	E		
	• Chemical composition	D		
	Who is responsible?	E		
Design	Feature	E		
	• Specification	D		
	Tools	D		
	Who is involved and in what context?	E		
Economics	Design costs	D		
	• Software	D		
	• Human resources	D		
	Manufacturing costs	D		
	• Machine (initial and maintenance)	D		
	• Material	D		
	• Post-processing	D		
	• Human resources	D		
Miscellaneous	Comparable conventional technique?	D		
	Aborted projects/negative results?	D		

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