Quality by Design for industry translation: Three-dimensional risk assessment failure mode, effects, and criticality analysis for additively manufactured patient-specific implants

Daniel Martinez-Marquez1 | Klemens Terhaer2 | Peter Scheinemann2 | Ali Mirnajafizadeh3 | Christopher P. Carty4,5 | Rodney A. Stewart1

1School of Engineering, Griffith University, Gold Coast, Australia
2Implantcast, Buxtehude, Germany
3Molecular Cell Biomechanics Laboratory, University of California, Berkeley, California,
4School of Allied Health Sciences and GCORE in Health Technology, Menzies Health Institute, Queensland Griffith University, Gold Coast, Australia
5Department of Orthopaedics, Queensland Children’s Hospital, Children’s Health Queensland Hospital and Health Service, Brisbane, Australia

Correspondence
Rodney A. Stewart, School of Engineering, Griffith University, Gold Coast, QLD 4222, Australia.
Email: r.stewart@griffith.edu.au

Funding information
Advance Queensland Mid-Career Fellowship; Griffith University International Postgraduate Award

Abstract
The complexity of patient-specific implants combined with the current limited expertise in reliability engineering and manufacturability in the additive manufacturing (AM) sector is posing a number of quality performance challenges. Worldwide medical device regulatory bodies are facing increasing pressure to devise adequate standards to ensure long-term patient safety and product performance. The implementation of the Quality by Design (QbD) system to titanium 3D-printed bone implants offers a proven system to ensure that products are designed and manufactured correctly from the beginning without errors. This article reports on the development of a failure mode, effects, and criticality analysis (FMECA) coupled with a 3D risk assessment approach. This integrated approach is based on a questionnaire performed with three industry firms and three university research groups with significant experience and expertise in medical device product development and/or research in this field. Research outcomes include a FMECA form containing 137 failure modes with AM materials, AM machine general, fabrication, electron beam melting machine, finishing, and design being as the most sensitive process areas in terms of product quality. We subsequently propose corresponding preventive and corrective strategies for risk mitigation. The approach forms part of the QbD system being developed by the authors specifically for additive manufactured titanium patient-specific implants.

KEYWORDS
additive manufacturing, criticality analysis, failure mode effects, patient-specific implants, quality by design
1 | INTRODUCTION

1.1 | A need for reliability

Additive manufacturing (AM) can be used to fabricate custom medical devices with complex geometries that were not previously possible with traditional manufacturing methods. As a result, there is rapid market growth in the availability of 3D-printed bone implants that offer personalized solutions for reconstruction following trauma and/or replacement of diseased bone. To gain first mover advantage, many medical device companies invest in designing complex, innovative products at the expense of long-term reliability, and manufacturing control efficiency. Consequently, defective orthopedic products such as knee and hip prostheses rank fifth in medical product recalls, of which 48% are caused by manufacturing issues and 34% by design flaws.

Rapid growth in the patient-specific bone implant market creates new risks and challenges, which in combination with insufficient investment in reliability engineering and manufacturability in AM, exposes the industry to high risk of product failure. This is because long-term product quality and performance is not yet established. Moreover, medical regulatory bodies are confronted with updating standards to enable innovation, while also ensuring long-term patient safety and product performance. Therefore, it is imperative to increase current focus on product quality by encouraging companies to adopt best practices drawing on experience from within and outside industry learning.

1.2 | Designing towards reliability

The Quality by Design (QbD) system, created by Joseph Juran and adopted by the US Food and Drug Administration (FDA), offers a systematic product development method for research and industry to develop medical devices around regulatory requirements and quality assurance strategies. The QbD system aims to carefully design quality products and accelerate their development by focusing on the early stages of the product development lifecycle. As a result, processes with less variability can be achieved to meet critical quality requirements and minimize risks and costs, thus producing high quality products.

Quality risk assessment is an important element of the QbD system and ensures that any changes in product design are understood and correctly managed to guarantee patient safety. The risk assessment process compromises three main steps: risk identification, risk analysis, and risk prioritization. Risk identification is undertaken by developing a list containing all potential failure modes (FMs) that can potentially affect the product, system, or project that is being analyzed. The risk analysis process focuses on rating of the identified risks in relation to their probability, severity, and detectability. Risk prioritization identifies the most critical risks for further risk analysis. Almost every industry has its specific risk assessment guidelines that need to be followed in order to comply with their required industry quality standards. For example, the guideline for quality risk assessment for pharmaceutical development (ICH Q9) provides a systematic approach, introducing some of the tools for effective risk-based decisions. In the case of medical devices, ISO 14971:2007 is the standard risk management procedure required by the US Food and Drug administration (FDA) and the European Commission's (EC) Medical Device Directive for medical devices. The integration of these guidelines describes the minimum risk assessment requirement to move toward implementation of QbD for complex medical devices such as patient-specific implants.

Both guidelines encourage the use of available information from different sources (eg, journal articles, international standards, customer feedback, etc.) to identify harms and hazards, and to estimate risks using techniques, such as the Fault Tree Analysis, Hazard and Operability Study (HAZOP), and the Failure Mode, Effects, and Criticality Analysis (FMECA). However, FMECA and ISO 14971:2007 approaches are rarely carried out in an integrated manner, either in theory or in practice. The FMECA is a very powerful and effective analytical tool developed by the Grumman Aircraft Corporation for the NASA Apollo Program and is widely used in different industries such as defense, shipbuilding, medical, and insurance to test system safety and the reliability of designs and processes. The FMECA documents the most critical risks of failure in a system design, determines the effect of each failure on the product, and ranks each failure according to its detectability, severity, and probability of occurrence. The FMECA thus facilitates the identification of preventive and corrective actions for risk mitigation leading to higher quality, enhanced safety, and higher reliability.
2 | PURPOSE AND OBJECTIVES

Traditional academic research focuses mainly on understanding new phenomena and the invention of technologies, with little focus on clinical translation. One of the reasons for this lack of focus on clinical translation is that it requires new ideas to be designed a priori around regulatory requirements and quality assurance strategies. 21 To date, the quality assurance of patient-specific implants has been carried out in the medical device industry without any specific standard for these products. 22 As a result, there is a critical need for research developments aimed at facilitating regulatory approval of AM for clinical translation. 21, 23 This gap in research prompted the authors to develop a comprehensive FMECA for the design and fabrication of titanium 3D-printed bone implants following the ICH Q9 guideline 12 and the American national standard ISO 14971. 24 To achieve this goal, the following objectives were set:

- Identify the most critical risks through soliciting in-depth responses from experts employed by relevant industrial firms and university research groups (ie, cases of study).
- Conduct a 3D-based FMECA with a 3D risk management approach, using data collected from case studies to assess and rate the identified risks.
- Develop appropriate mitigation and preventive strategies for the most critical risks identified in the 3D-based FMECA.

3 | SCOPE

Recently published work of the authors described the steps 5.1 to 5.3 of the QbD risks assessment procedure developed specifically for AM patient-specific bone implants and scaffolds. This prior study resulted in a comprehensive design and fabrication process flow diagram, and a risk breakdown structure (RBS) containing 86 FMs that lead to quality non-conformances and 178 potential undesirable effects on product quality. 2 The current study extends on this prior work, focusing on steps 5.4 to 5.7 of the QbD risk assessment procedure for the design and fabrication of AM patient-specific bone implants and scaffolds (Figure 1).

4 | MATERIALS AND METHODS

4.1 | Research design

To the authors knowledge there is no empirical research describing how companies in the sector of AM patient-specific bone implants deal with product quality. FMECA and ISO 14971 are seldom performed in an integrated manner. 15 Therefore, a semiquantitative exploratory investigation-based FMECA was conducted in this study. Conducting risk assessment studies requires the gathering of primary data in the form of expert judgement from key individuals such as managers, workers, and technical staff. This expert judgement is vital in the risk assessment process to evaluate the criticality of risks, to incorporate scientific data in the body of evidence on how to handle these risks with sufficient flexibility, and to consider and resolve aspects that are particularly critical in a specific case. 25 The primary data for this type of research is general gathered through interviews and questionnaires to extract expert knowledge about experiences, beliefs, or opinions. 26-28 To enhance the reliability of data collected for risk assessment research it is recommended to include the Delphi method. 10
The Delphi method helps researchers to obtain the most reliable consensus opinion of the group consulted. Furthermore, when a heterogeneous profile group is required, this method allows for the removal of biased responses within the surveyed group by avoiding direct confrontation with participants.

As a result, the research team of this study conducted semistructured face-to-face interviews combined with the Delphi method with selected firms and research groups having expertise in AM patient-specific bone implants, in order to perform the above-mentioned risk assessment steps. The nature of the data to be collected in this study is considered semi-qualitative and is reported following the consolidated criteria for reporting qualitative research (COREQ). In addition, gathered numerical data from study participants (ie, FM incidence reports) were also considered in the study but due to the infancy of the industry and insufficient sample size, are not presented in a statistical manner.

The main objectives of the in-depth risk assessment interviews were to: (1) identify the most critical FM within the design and fabrication of AM titanium patient-specific implants and (2) identify preventive and corrective actions to mitigate and control the most critical risks. A semistructured interview was designed to guide the participants through the different sections of the risk assessment questionnaire. The 86 FMs were classified into eight different groups and each participating case study organization was only requested to assess the FM groups related to their expertise.

### 4.2 Case study sample selection criteria

According to ISO 14971, the risk assessment process for medical devices requires the involvement of several representatives with expertise in different stages of the medical product life cycle. Therefore, the criteria to select the participants for this study were based on their experience and expertise in medical device product development. Specifically, the selection of case study participants required that they had to satisfy at least one of the following criteria: (1) companies that manufacture patient-specific implants and/or medical devices; (2) companies that design patient-specific implants and/or medical devices for AM; (3) research groups in the field of tissue engineering based on medical imaging; (4) research groups in the field of AM; (5) research groups in the field of 3D medical image processing; or (6) research groups in the field of patient-specific implants.

When there is limited information about the topic, a qualitative approach is more suitable to capture textual data from a few selected cases. Thus, it is noteworthy to mention that currently, the use of AM in biomedical industries is limited with a relatively small number of international companies producing titanium patient-specific bone implants. Many of these companies are not open to researchers and open sharing of knowledge due to intellectual property concerns. This study sought to extract in-depth knowledge on AM processes and practices from companies and research groups that were open to knowledge sharing. The niche size of the biomedical AM industry and the limited number of companies willing to share in-depth information necessitated that the research team focuses on a sample of comprehensive case studies. Therefore, the sample size was limited by the nature of the research field, which is characterized by small specialist firms and research groups, but with in-depth and comprehensive data collection. Taking this limitation into consideration, this study selected the snowball sampling method since it allows further study participants to be suggested or introduced from the interviewees network.

### 4.3 Data extraction and analysis

Semistructured interviews are used to gather qualitative data and enable the researcher wants to ask additional questions to thoroughly understand the answers provided. Face-to-face interviews are also known to have the highest response rate in survey research. Furthermore, face-to-face interviews capture the most detail of both verbal and nonverbal communication. This data collection method provides the opportunity to establish rapport with participants, allowing the researcher to clarify ambiguous answers during the interview. As a result, the team selected face-to-face interviews as the main data collection method for this research. These semistructured interviews were performed with experts on the previously identified list of risks in order to conduct a detailed risk assessment process.

To ensure that each interview was performed in a consistent manner, an interview guide and a protocol were developed following the COREQ. The semistructured interviews applied a three-phase Delphi method. The first phase has been previously reported and involved a systematic literature search to identify risk factors related to the design and fabrication of AM patient-specific implants. Eighty-six FM risk factors were identified that lead to quality nonconformances and 178 potential undesirable effects on product quality; these factors were categorized into a RBS.
TABLE 1  Sample extract of the FM questionnaire containing the corresponding spaces to rate each risk based on $S$, $O$, and $D$ including two cells to add their corresponding preventive and corrective actions

| Level 1 | Level 2 | Level 3 | Effect | Severity | Occurrence | Detection | Corrective action | Preventive action |
|---------|---------|---------|--------|----------|------------|-----------|--------------------|-------------------|
| 1. Method | 1. CT protocol | 1.1.2 | Slice increment is too large, or the slice thickness is too big | • Stair step effect | • Rough dissolved surface | • Fail to capture thin bone (mainly in facial structures such as orbital walls) | • Smooths out sharp corners greatly affecting the accuracy of sharp vertices or acute edges. | • Internal defects | • Undesirable porosities |
| 2. Machine | 2.7 | Laser failure | | | | | |

TABLE 2  Summary of semiquantitative scale for Severity, Occurrence and Detection adapted from References 20 and 37

| Score | Severity | Occurrence | Detection |
|-------|----------|------------|-----------|
| 10    | Hazardous | Extreme high: failure almost inevitable | Absolute uncertainty |
| 9     | Serious   | Very high  | Very remote |
| 8     | Extreme   | Repeated failures | Remote |
| 7     | Major     | High       | Very low  |
| 6     | Significant | Moderately high | Low |
| 5     | Moderate  | Moderate   | Moderate  |
| 4     | Low       | Relatively low | Moderately high |
| 3     | Minor     | Low        | High      |
| 2     | Very Minor | Remote     | Very high |
| 1     | None      | Nearly impossible | Almost certain |

The second phase consisted face-to-face interviews and a questionnaire with relevant experts belonging to the participant firms and university research groups. During each interview, the participants were asked to evaluate only those FM inherent to their areas of involvement and responsibility within the design or fabrication process of AM patient-specific implants. Each FM in the list, was ranked by each participant using three different variables: the likelihood of not detecting the failure ($D$), severity of the failure ($S$), and the frequency of failure ($O$), as shown in Table 1. A 10-point (i.e., 1 to 10) assessment scale, adapted scale, was used in this study as it is easy to interpret and provides precision and accuracy in the ranking quantification process. Moreover, due to a lack of available historical information for this relatively new AM process, the actual probability of occurrence for each risk was determined using experts’ perceptions, experience, and knowledge. This evaluation also included an open-ended section where participants added their comments about preventive and corrective actions to control and mitigate each FM (Table 1). Moreover, participants could add new FM deemed to be important. The third phase sought to resolve disagreements using the following procedure. If the numerical value fell between two adjacent numbers, the
higher number was always selected, however, if the participants provided ratings that were more than one rating category apart, the results were sent back by email to each participant for a second evaluation in order to produce risk rating consensus.

After obtaining consensus from the Delphi method, the data were used to identify the most critical FM using the 3D risk priority matrix. The goal of this stage was to determine the level of criticality in order to focus on the most important FM. The 3D risk priority matrix developed in this study (Figure 2A) is a volumetric cube composed of 10 volumetric layers, parallel to the XY plane. These volumetric layers correspond to the ranking values of $D$ from 1 to 10. Each volumetric layer creates a unique Probability and Impact (PI) Matrix according to the $D$ ranking, as shown in Figure 2B. Different types of risk matrices are currently used in industry and research. However, there is no universal or standardized approach to construct a risk matrix. The 3D risk priority matrix developed in this study is composed of four different regions that follow the Pareto principle “the vital few and the trivial many” meaning that 80% of the effects come from 20% of the causes. The four regions in the 3D risk priority matrix are represented by four colors according to the magnitude of the risk. The trivial many in the 3D risk priority matrix corresponds to the green and yellow regions, which together represent 76.8% of the total volume of the cube, as presented in Figure 2C. The green region contains risks that are low. Risks on the yellow region are moderate risks that require some consideration. The remaining 23.2% of the cube’s volume is composed of the orange and red regions. Risks within the orange region are high risks that are important to manage. Risks within the red region correspond with catastrophic risks that need special attention and a detailed risk management plan.

To identify the most critical risks, three steps need to be followed. First, it is necessary to categorize each risk according to its detectability $D$. The second step requires the allocation of each risk within its' corresponding PI matrix in order to identify its criticality in respect to both severity and occurrence, as presented in Figure 3. Each PI matrix is a simple mechanism to increase the visibility of risks based on the probable outcome of a hazardous event. For this purpose, it is necessary to calculate the risk priority number (RPN) which is obtained by multiplying the variables $D$, $S$, and $O$ (ie, $RPN = D \times S \times O$).

The RPN is a decision factor that identifies those elements that are the most likely contributors to the low quality of the final product. The resulting RPNs facilitate allocation of each FM within the PI matrices that allows these high to extreme risk priorities to be examined further, and for the level of difficulty for the risk being detected to also be considered. The relationship between RPN and risk level is presented in Table 3. The third step is the identification of the most critical FMs, which are those with RPN scores higher than 250, located in the orange and red areas of the 3D

**FIGURE 2** A, 3D risk priority matrix. B, The volumetric layers of the 3D risk priority matrix. C, The four volumetric regions of the 3D risk priority matrix distributed according to the Pareto principle.
FIGURE 3 Example of two different IP matrices with their corresponding RPNs based on S, O, and D. A, IP matrix for detection level 10. B, IP matrix for detection level 7

TABLE 3 RPN score range, risks level description and required actions

| RPN      | Risk level | Required action                          |
|----------|------------|------------------------------------------|
| 499 < RPN ≤ 1000 | Red: Catastrophic | Must be mitigated with a detailed action plan |
| 250 < RPN ≤ 499   | Orange: High   | Immediate mitigation based on research and management planning |
| 100 < RPN ≤ 249   | Yellow: Moderate | Require specific monitoring or response procedures |
| RPN ≤ 100        | Green: Low    | Acceptable, can be managed with routine procedures |

risk priority matrix. Subsequently, the results of both the risk assessment and the interviews are combined to undertake, the FMECA, which contains all the identified critical FM with their corresponding mitigation and preventive actions based on the judgement and experience of the participants in this study. Furthermore, a further analysis of the RPNs is performed to identify the most problematic activities within the design and fabrication processes of patient-specific implants. For this purpose, it was necessary to calculate the relative importance (RI) of each subprocess based on the sum of all the RPN of all FM within them. The results of the RI are then plotted in a Pareto chart to identify the most critical processes that require more attention. This process is required because each activity within the design and fabrication process of patient-specific implants has a different number of FM. Therefore, it is important to identify the subprocesses that require more attention in order to design strategies to improve the overall quality of the most critical processes.

4.4 Study participants

Twelve invitations were sent to different companies and research groups in America, Europe, and Oceania. Three companies and three research groups agreed to participate in this study, representing a response rate of 50% (Table 4). A total of 13 one-on-one interviews were performed between June 2018 and April 2019 with pertinent experts in AM, quality control, patient-specific implant design, motion capture, computational neuromuscular modelling, nanoengineered implants, and medical image processing. The interviews were performed at the headquarters of each company and university research group according to the developed protocol and the interview guide. The duration of each interview ranged from 45 to 60 minutes. At the beginning of each interview, participants provided informed consent. To protect confidentiality and anonymity of each participant’s organization, they will be referred as organization A, B, C, D, E, and F.
The participant companies A, E, and F are companies that are dedicated to the design and manufacture of patient-specific implants with AM. However, it was found that each participant company used a different AM system to produce their products. Company A is a three-year-old small company that uses their own developed AM system to produce components for different industries including patient-specific medical devices. On the other hand, company E and company F are medium size companies solely dedicated to the design and manufacture of patient-specific implants, with 6 and 5 years of experience, respectively, in the AM implant market. Company E produces their products with Arcam Q10 plus Electron Beam Melting machines, and company F uses an EOSINT M 280 direct metal laser sintering (DMLS) system.

The participant research groups B, C, and D are specialized in different fields related to patient-specific implants such as motion capture, bone biomechanics, computational neuromuscular modelling, and nanoengineered coatings for orthopedic and dental implants. The years of experience of the interviewees ranged from 4 to 23 years.

5 | RESULTS

5.1 | FMECA of AM patient-specific bone implants

The main purpose of a quality risk assessment is to identify the most critical risks in order to design corrective and preventive actions to mitigate their effects on product quality. A prior completed systematic literature review by the authors identified 86 FMs that lead to quality nonconformances, including 178 potential undesirable effects on product quality. These risks were first classified using the Ishikawa method into four main groups: (1) Methods, (2) Machine, (3) Personnel, and (4) Materials. A further risk classification using a RBS was performed based on the main activities and subprocesses required to design and fabricate patient-specific implants. During the interviews in this present study, a further of 51 new FMs (ie, 86 + 51 = 137) and three new workflow activities were identified. Using this information, the previous RBS was updated to comprise 17 activities and subprocesses where 137 FMs were allocated. The 17 activities and processes covered in this study are: materials, fabrication, AM machine general, electron beam melting (EBM) AM machine, laser-based AM machine, finishing, design, simulation and finite element analysis, CT and MRI protocol, surface coating, personnel, volumetric reconstruction, sterilization, image acquisition, marking and packaging, and image segmentation. It is noteworthy to mention the section of the RBS dedicated to AM machines was divided in three subsections. The first subsection of AM is “AM machine general”, which contains the FM related to most AM system. The second subsection is “EBM AM machine” which have only the FM related to
EBM systems. Finally, the third subsection “laser-based AM machine” contains only the FM associated with laser-based AM systems.

The new RBS was then used to identify the most critical FM based on the rating of $D$, $S$, and $O$ provided by each participant according to their knowledge and expertise. Following this procedure, a FMECA table was created containing the RPN score of each FM and their corresponding corrective and preventive measures, as presented in the Data S1.

From the FMECA, a total of 13 risks were found to be “high” or “catastrophic” representing 9.49% of the total risks (Figure 4). The remaining 124 risks were determined as being noncritical risks with 24.09% and 67.88% distributed in the yellow and green regions, respectively, in the 3D risk priority matrix (Figure 4). The distribution of the 13 most critical risks within the 3D risk priority matrix is presented in Figure 5. According to the 3D risk priority matrix (Figure 5), it can be seen that thermal and phase change effects, AM powder contamination, cross-contamination, and inadequate sand blasting were rated with a $D$ score of 10, meaning that without the proper tools and strategies their timely identification is absolutely uncertain. On the other hand, the FM AM material suppliers, process documentation, and AM machine maintenance were scored with a detectability rating ($D$) between moderately high and high, but despite their easy detectability of these risks they were found to be critical due to their hazardous and serious consequences, if they are not appropriately mitigated. The identification of the most critical risks enabled the researchers to focus on the pertinent FM risk mitigation strategies to address them. These mitigation strategies can be preventive, corrective, or both and were proposed by the interviewed experts also reported in the literature, as shown in Table 5. Furthermore, it was found that the 13 most critical risks are located within five distinct categories in the RBS. These categories are: AM materials; AM machine (divided in three subcategories: AM machine general, EBM AM machine, and Laser-based AM machine); fabrication; finishing; and design. Therefore, a further risks analysis was performed and presented in the following section.
| Code | Failure mode | Effect | Corrective action | Preventive action | RPN | Ranking |
|------|--------------|--------|-------------------|-------------------|-----|---------|
| 1.7.8 | Thermal and phase change effects | Part deformation, changes in material microstructure, and residual stresses. | Application of heat treatments such as stress relief and annealing. | Perform thermomechanical simulations to predict residual stresses and product distortion. Can be compensated enlarging the CAD model with a fixed compensation factor. Optimize process parameters like laser/electron beam power, scanning speed and scanning spacing etc. Set the machine fabrication hatch to a crossing in-fill pattern Use real-time AM process monitoring systems. | 1000 | 1 |
| 1.8.5 | Crosscontamination during blasting due to different materials used | Negative influence of component properties due to contamination (eg, unwanted interstitials). | Use micro-CT scanner to identify particles. Extraction of powder particles from cavities for example, ultrasonic cleaning. Worst case reject component. | Provide training. Develop procedure guides. | 900 | 2 |
| 4.9 | Omitting of regular powder examination due to human failure; lack of procedure definition | Negative influence of component properties due to noncompliant powder properties (oxygen pick up, humidity,…) | Perform powder examination procedure. | Use a quality management software that can provide reminders. Develop a monitoring system with defined examination intervals. Develop procedure guidelines, checklists, and powder traceability documentation. | 810 | 3 |
| 5.13 | Omitting sieving of powder | Contamination of the powder Negative influence of component properties due to contamination; | Perform sieving process Perform powder examination procedure | Provide training. Develop recycling procedure guides, checklists, and powder traceability documentation. | 810 | 4 |
| 2.1.1 | Omitting inspection of material metallizations in EBM machine chamber | Contamination of the powder; Negative influence of component properties due to contamination. Material metallizations effects on: - Rake blades - Used heat shields - Build chamber - Cone & foil | Each fabricated component should be thoroughly inspected (visual, micro-CT) to identify defects and material contamination. Perform cleaning activities. | Provide training. Develop operating procedure guide. Develop an operating checklist. Perform cleaning activities before and after each fabrication process. | 576 | 5 |
| 2.3.7 | Machine maintenance | Equipment failure. Inefficient fabrication process. | Perform maintenance Perform in-house validation of machine performance. Technical support with providers. | Provide training. Develop preventive maintenance procedure guides, checklists, and documentation. Use real-time monitoring systems. Have maintenance and extended warranty agreements with providers. | 378 | 6 |

(Continues)
| Code | Failure mode | Effect | Corrective action | Preventive action | RPN | Ranking |
|------|--------------|--------|-------------------|-------------------|-----|---------|
| 1.8.2 | Inadequate sand blasting | Inclusions of particles in porous structures (biological contamination) Geometrical deviation of parts | Use micro-CT scanner to identify particles. Extraction of powder particles from cavities for example, ultrasonic cleaning. Worst case reject component. | Provide training. Develop procedure guides. | 350 | 7 |
| 1.7.12 | Process documentation and expression of documents | Defective product Inaccurate product definition Inefficient workflow Miscommunication and difficulty to understand different terminologies from the different fields involved. | Repeat process. Develop the necessary documentation and reports. | Develop appropriate information systems and documentation. Develop process maps, workflows, checklists, guidelines for activities and processes. Develop a commonly agreed language and vocabulary for an adequate communication with staff and clients. Develop documentation containing fully defined requirements, testing results, checklists, and control diagrams to track product quality. Perform project postmortem reports containing failures and solutions to minimize duplication of effort. | 300 | 8 |
| 4.8 | Material suppliers | Poor quality. Poor supplier service and involvement. Remote geographical location. Supply chain disruption. Delay delivery. Lack of experience in suppliers’ risk management. | Select a better supplier considering all the preventive actions. | Procure powder material from AM equipment manufacturers. Select powder materials with similar properties than validated material. Select material suppliers with at least 5years of experience. Request powder certificates and material data sheets with powder material properties. Selected suppliers that have quality management programs such as ISO 9001, AS9100, or ISO 13485. | 300 | 9 |

(Continues)
| Code | Failure mode | Effect | Corrective action | Preventive action | RPN | Ranking |
|------|--------------|--------|------------------|-------------------|-----|---------|
| 2.2.5 | Omitting inspection of material metallizations in DMSL machine chamber | Contamination of the powder; Negative influence of component properties due to contamination. Material metallizations effects on: - Laser optical lens - Rake blades - Build chamber | Each fabricated component should be thoroughly inspected (visual, micro-CT) to identify defects and material contamination. Perform cleaning activities. | Provide training. Develop operating procedure guide, and checklist. Perform cleaning activities before and after each fabrication process. | 288 | 10 |
| 1.5.4 | Wrong design (surface and unit cell) | Wrong implant’s mechanical properties for soft-hard tissue contact adaptation (modulus of elasticity) | Repeat design process. Perform quality control activities for implant. | Implant surface roughness and modulus of elasticity should adapt to surrounding tissue. Use validated/certified software. Review Research. Collaborate with universities research groups to facilitate design process. Develop implant's design guidelines. | 256 | 11 |
| 2.3.9 | Machine parameters | Dimensional accuracy. Low quality parts. Unreliable mechanical properties. Negative influence of component properties due to wrong process parameters. | Perform machine validation process. Use design of experiments (DoE) methods to identify the most optimal parameters configuration. | Perform machine validation process. Use standard commercial validated machines. Use design of experiments (DoE) methods to identify the most optimal parameters configuration. | 252 | 12 |
| 5.11 | Powder handling at temperatures above 25°C, due to human failure; omitting temperature monitoring | Negative influence of component properties due to noncompliant powder properties (oxygen pick up…) | Perform powder examination procedure | Use a room for powder handling, sieving, and storage with controlled temperature and atmospheric conditions. | 252 | 13 |
5.2 Interpretation of findings

Analysis of the FMECA revealed that the majority of the critical risks were clustered in six main categories of the RBS. Therefore, a further risk analysis was performed to identify the most critical activities and subprocesses that need more attention during the design and fabrication of AM patient-specific implants. For this analysis, the RPN score of all risks belonging to each category was summed to calculate the relative importance of each category. According to our results, the categories AM materials, AM machine general, fabrication, EBM machine, finishing, and design are the most problematic areas in the design and fabrication of AM patient-specific implants, all together accounting for approximately 70% of the RPN scores identified in the FMECA (Figure 6).

5.2.1 AM materials

AM materials were identified as the most important of the 17 main activities related to the fabrication of AM patient-specific implants, having a RI rating of 18.2% (Figure 4). This section of the FMECA contains all the identified risks related to AM powder material handling, storage, properties, and recycling. The high criticality of the AM materials for medical devices is due to its influence in the mechanical, biological, and physicochemical properties of the final product. For example, powder-based AM systems such as EBM and DMLS require precise and reliable powder characteristics in order to produce high quality components with appropriate mechanical and chemical properties as well as to comply with the required standards. Therefore, according to the Pareto principle, if all the activities related to the materials used in AM are standardized and adequately controlled then 80% of the potential product quality issues can be avoided or mitigated.

The results of the FMECA show that from the 13 most critical FMs identified in this study three are located in the materials section of the RBS. These risks are: omitting material powder examination, omitting powder material sieving, and handling powder material at temperatures at above 25 °C, with RPN scores of 810, 810, and 252, respectively, as shown in Table 5. The high RPN score of these three risks is due to the fact that powder materials for AM are highly sensitive to atmospheric conditions, temperature, and recycling methods. Changes to these factors can have detrimental effect on powder quality. For example, powder titanium alloys such as Ti6Al4V can easily absorb water, oxygen, and hydrogen from the surrounding atmosphere thereby affecting the density and flow rate of the powder particles, resulting in negative effects in the chemical composition and mechanical properties of the final product. Moreover, the high acquisition cost of powder materials for medical applications makes the handling and recycling of powders key factors in governing their affordability. Consequently, powder chemical composition and physical characteristics such as flowability, apparent density, particle shape, and size need to be tightly controlled. Therefore, as a preventive action to maintain powder characteristics the participants of this study suggested that manufacturing companies of patient-specific implants should consider having a dedicated room for powder handling, sieving, and storage with controlled temperature and atmospheric
conditions. This room should also have an automated monitoring system that can be programmed to set of alarms when the required atmospheric conditions are not met. It was also recommended to use a quality management software that can provide reminders with defined examination intervals to assist the quality control process and documentation of powder use. In this way, the handling of the powder with an incorrect room temperature and omitting the sieving of recycled powder can be avoided. Moreover, it is essential that companies in this sector develop procedure guidelines, checklists, and powder traceability documentation for an appropriate powder lifecycle management and quality control.\cite{48} Furthermore, according to Du Plessis et al,\cite{49} a micro-CT scanner is a key technology to control powder characteristics, since it is the only method that can determine the real sphericity, volume, and surface areas of powder particles to ensure flowability and eventually quality of the powder bed.

The selection of material suppliers was also identified as one of the most critical risks, having an RPN score of 300. The risk of material suppliers was allocated in the FMECA table within the Personnel section, however, as this section was not identified as critical and the risk of material suppliers is also directly related to the AM material it will be discussed here. The selection of material suppliers was identified as the 10th most critical FMs, involving a variety of issues, such as poor material quality, poor supplier service and involvement, geographical location, supply chain disruption, delay delivery, and lack of experience in suppliers’ risk management.\cite{50} For example, the use of unvalidated powder for a specific AM equipment may lead to poor quality products with unpredictable mechanical properties, that may not meet medical and metal industry standards. Moreover, powder material from different providers might have different properties raising the risks of negative effects in product quality.\cite{51} Furthermore, material traceability is a key quality control factor that needs to be adequately assessed in order to acquire commercialization clearance from medical regulators such as the FDA in the USA and Medical Device Regulation (MDR) in the European Union.\cite{52,53} Therefore, as a preventive action to reduce these risks companies usually prefer to procure powder material from AM equipment manufacturers. This offers several advantages, such as established procurement routes, better support since powder has been already tested and validated with clearly define machine parameters, and the opportunity to concentrate on core skills.\cite{54} Nevertheless, some of the disadvantages are that material cost is much higher, there are limited material options, lack of traceability of manufacturing process and material source, and experimentation with new material is limited.\cite{55} Furthermore, dependency of a single supplier creates a high risk of a supply chain disruption and inhibits the acquisition of in-house expertise.\cite{56} Consequently, selecting this type of material supplier can act as a preventive action for companies with low experience and track record in AM, where the equipment/material supplier can provide valuable technical support.

On the other hand, if a company has sufficient experience in AM, with defined quality control and quality assurance systems, and is willing to embark into new alloys and materials, procuring powder material from third party suppliers or directly from powder manufacturers is a good option however, it has unique advantages and disadvantages. The advantages of using powder from validated third party suppliers are the large variety of materials and batch sizes available. Moreover, as the powder is validated there is confidence about its properties. However, this procurement option can lead to a lack of machine manufacturer support, nonstandardized machine parameters, and low traceability.\cite{55} With regard to direct manufacturers, they offer a wide range of material choices with a high level of material traceability. This option also allows the selection of powder materials produced with different manufacturing processes and different characteristics at a reduced cost.\cite{57,58} Nonetheless, in some cases using direct manufacturers to procure AM raw material may require the purchase of larger quantities of material, and the resulting risk of powder quality variation with each batch. Furthermore, there is no guarantee that the acquired material will be suitable for a specific AM machine, limiting machine manufacturer support.\cite{55} Nevertheless, regardless of who is the supplier of the powder material, to safeguard a highly consistent certified supply chain it is important to select powder materials that closely match the properties of the powder to the specific machine used to safeguard a highly consistent certified supply chain. Moreover, according to the experts interviewed, to facilitate material traceability and quality control, manufacturers of patient-specific implants should select material suppliers with at least 5 years of experience in the market, and request powder suppliers to provide certificates and material data sheets with powder material properties. In addition, according to the FDA\cite{53} and ASTM standards,\cite{42} the selected supplier must also have a recognized quality management program such as ISO 9001, AS9100, or ISO 13485.
5.2.2 AM machine general, EBM, and DMLS

We identified 13 FMs that can be related to AM powder bed fusion machines representing almost 13% of the total cumulative RPN scores, which make it the second most critical area of our FMECA. Even though most of these issues were ranked with low RPN scores, two of them being machine maintenance and machine parameters, stand out due to their high RPN score making them the sixth and the 12th most critical FMs, respectively. Poorly maintained machines can hardly produce products with consistent quality, and they frequently fail requiring more spare parts, consumables, labor, and longer downtimes, which in turn leads to loss of profit margin. Moreover, the maintenance cost of traditional manufacturing firms accounts for 15-70% of production costs. This cost can be even higher when advanced manufacturing technologies such as AM are used. Therefore, omitting and having inadequate maintenance activities of manufacturing equipment can affect an organisation's long-term profitability. For example, an inadequate maintained AM machine can lead to poor recoating performance, resulting in products with lower mechanical properties and higher quality variability, representing a potential threat to the patient and a serious financial issue to the company.

According to the interviewees' opinion, one of the most suitable maintenance methodologies for AM is called reliability centered maintenance. This is a preventive maintenance methodology that uses qualitative and quantitative data to formulate effective and optimized maintenance plans using risk management techniques, based on failure diagnosis and prediction to increase the reliability of manufacturing equipment. The qualitative and quantitative data are usually obtained using expert knowledge and computerized databases. This maintenance methodology is ideal for AM systems equipped with real-time monitoring systems capable of providing detailed postbuild reports containing vital information of each fabrication process and machine parameters. Therefore, by linking the information obtained through the report provided by the AM monitoring system with the final product characteristics it is possible to implement reliability centered maintenance in an AM environment. Moreover, to reduce the risk of inadequate maintenance the participating companies acquired machines having real-time process monitoring systems that can help to reduce maintenance activities. For example, company E retrofitted all of their EBM machines with an innovative monitoring system that automatically calibrates the machine thereby reducing the maintenance calibration procedure from 4 hours to just 15 minutes. Furthermore, the participant companies of this study also have their machines subjected to maintenance and extended warranty agreements negotiated during their acquisition. These agreements usually include one or two main maintenance procedures per year including detailed technical support when is required. Therefore, these companies are limited in providing only the daily basic maintenance to their machines before and after each fabrication process reducing the criticality of maintenance risks.

Having an incorrect set of machine parameters was identified as the 12th most critical risk in our FMECA. The high criticality of this FM relies on the fact that without the identification of the proper fabrication parameters of the AM machine used it is basically impossible to validate the fabrication process and have a reliable production. However, this FM is only critical when noncommercial machines are used or when a new experimental material is employed. In that case, it is necessary to perform a variety of systematic tests using design of experiments methods to identify optimal parameters configuration for that particular machine or material. Therefore, the interviewees agreed that the safest option to avoid this FM is to use commercial validated AM machines and materials.

5.2.3 EBM machine

As previously discussed, there are general potential issues that have to be considered for any powder bed fusion machine. However, there are some risks that are unique to each AM technology. For example, despite EBM machines having fewer mobile parts than DMLS, they are more complex and sensitive due to the electron beam, the vacuum chamber, and the elevated temperatures (600-1000 °C) used in the fabrication process. As a result, the total downtime and the number of preventive maintenance procedures per year are 50% higher than those required for a DMLS machine. Consequently, in this study it was found that the RI obtained for the AM EBM machine was two times higher than the RI of laser-based AM machines, and make it the fourth most important area to control (Figure 4). Moreover, the formation of metallizations is another common issue in AM powder bed fusion systems that can cause a variety of quality problems to the final product. In the case of EBM systems, this FM was ranked as the fifth most critical, whereas for DMLS machines this FM was ranked as the 10th most critical. The reason for this difference is that the occurrence of metallizations in EBM machines is much higher than in DMLS machines. The high occurrence of metallizations in EBM systems is due
to the combination of high temperatures and the vacuum atmosphere during the fabrication process. This causes the condensation of light alloying elements of the powder material to evaporate and sputter in different components inside the building chamber, such as heat shields and rake blades forming a metallized layer that is difficult to detect.\(^8\) There are three main problems that these metallizations can cause. First, metallizations can drastically affect the in-situ process monitoring system, which relies on high-speed infrared IR camera. This IR camera detects porosities and quantifies the beam focus size in order to determine control of the machine parameters in real time.\(^9\) Second, during the building process metallized material can peel off and fall into the melt pool and powder layer affecting the fabrication process and the material chemistry.\(^6\) Furthermore, metallizations can also cause detrimental effects on the rake blades leading to premature wear and failure of the entire building process.\(^9\) Therefore, according to the experts in AM interviewed in this study, the best preventive action is to develop appropriate operation procedures and check lists containing cleaning activities to be done before and after each fabrication process. These cleaning activities should focus on the removal of metallizations from the build chamber, start plate, sensors, heat shields, rake blades, cone, and foil. Moreover, it is vital that the machine operators receive proper training not just to operate the machine, but also to timely identify fabrication flaws and potential threats. However, if the metallizations cleaning process is omitted, any fabrication in process should be stopped, and the cleaning process should be performed. If a batch of components were already manufactured when omitting the cleaning procedure, each component should be thoroughly inspected in order to identify possible geometrical defects and material contamination.

### 5.2.4 Fabrication process

The fabrication process of patient-specific implants with powder bed fusion was identified as the second most critical process in the production line. Our results show that this activity accounts for 12.63% of the identified risks. The criticality of the AM fabrication process is due to the novelty of this technology and the lack of defined procedures and standards, including all the different process parameters that need to be set and controlled.\(^9\) To prevent the potential issues that may occur during the AM of patient-specific implants, the interviewed experts in AM recommended an annual AM validation process. This validation process should aim to challenge the AM machine to identify the worst-case scenarios and process limitations in relation to machine conditions. For this purpose, test coupons and components as representative samples should be used to challenge the complete build volume of the AM machine.\(^5\) The result of this validation process is the establishment of the final process parameters that produce consistent and repeatable products that fulfill the required specifications.

It is not by chance that the risk with the highest RPN score belongs to the AM fabrication process. With a total RPN score of 1000, the thermal and phase material changes produced during the fabrication of metallic components with AM powder bed fusion systems is the most critical FM identified in our FMECA (Table 5). During the fabrication of metal components with AM systems such as DMLS and EBM, large thermal gradients are developed due to the rapid heating and cooling cycles in the fabrication process.\(^9\) These result in residual stresses, geometrical distortions (warping), shrinkage, and changes in material microstructure and chemical composition.\(^9\) However, the criticality of these issues highly depends on the type of AM system used. For example, laser-based AM systems produce components with more residual stresses and distortion than EBM systems.\(^1\) According to the opinion of the interviewees, the most common corrective action to counteract and mitigate these issues when DMLS machines are used, is the application of different heat treatments. These heat treatments are aimed to relieve the stresses and distortions caused in the fabrication process, and to adjust the material microstructure and chemical composition of manufactured parts.\(^1\) Furthermore, to reduce warping of thin components fabricated with EBM, Tan et al.\(^8\) emphasized that by setting the machine fabrication hatch to a crossing in-fill pattern strategy to help to minimize residual stresses and distortion. Moreover, as a preventive action, some of the participants of this study used finite element software packages to run thermomechanical simulations in order to predict residual stresses and product distortion. The companies in this study also use a fix compensation factor to enlarge the CAD model to counter the shrinkage effect.\(^1\) Another preventive action to minimize component warping and changes in material microstructure is to use updated AM machines equipped with real-time process monitoring systems, which can accurately monitor and control the production process.\(^7\) Nevertheless, regardless of the real-time monitoring system used, metallic components fabricated with DMLS systems still require heat treatments at the end of the fabrication process.
5.2.5 Finishing

Finishing was identified as the fifth most critical process of AM patient-specific implants. This process comprises several steps such as blasting of powder material, removal of support structures, sandblasting, CNC machining, polishing, and cleaning. Nevertheless, if these activities are not appropriately performed, they can lead to irreversible damage and contamination of implants. For example, the second and sixth most critical FMs identified in this study can occur during the blasting process of the powder material, and during the sandblasting of AM parts. These risks are cross contamination, and part damage during blasting, having an RPN of 900 and 350, respectively. Blasting is one of the postfabrication activities necessary to reveal and remove the manufactured parts from the powder bed. Cross contamination of the powder material used for AM is a common issue that occurs in AM when impurities, foreign bodies during preprocessing and postprocessing activities get into the powder.\(^8\) Cross contamination can also occur when a machine is used to produce batches with different feedstock materials. These impurities can create interstitials in the build parts leading to alterations in the chemical composition and detrimental effects in the mechanical properties of the final product.\(^8\) On the other hand, during the sandblasting process, delicate areas of the implant can be damaged and inclusion of foreign particles within the trabecular and lattice structures of patient-specific implants can occur.\(^105,106\) The high RPN score of these two finishing processes is due to the difficulty to detect these issues when these activities are performed, including the expensive technologies required to detect them. According to the interviewees’ opinion, the most common preventive actions to reduce the probability of occurrence of these FMs are to provide adequate training for machine operators and the development of procedural guidelines for this process. One of the main technologies by the participating companies of this study is X-ray Micro-Computed Tomography scanner (micro-CT) to identify trapped particles, presence of pores, internal flaws, and to perform dimensional validation of each implant.\(^49,107\) This type of industrial analysis using micro-CT are described in detail by du Plessis et al.\(^108-110\)

This procedure is then followed by in-house developed extraction methods capable of removing powder particles up to 60% over the regulatory allowance, due to the fact that 100% extraction of particles is not yet possible. Moreover, to control the quality of the powder material different standard characterization methods are used to assess powder chemical composition. Nevertheless, Brandão et al\(^45\) state that these methods are limited for the detection of cross contamination of powder material, demonstrating that using a X-ray CT scanning procedure for the powder feedstock is an ideal complementary method to identify foreign high density particles in the powder feedstock.\(^49\)

5.2.6 Process documentation and expression of documents

Inadequate process documentation and expression of documents are identified in this study as the eighth most critical risk to affect the quality of AM patient-specific implants. Process documentation and expression of documents are interrelated activities that are part of the knowledge management of an organization. Knowledge and expertise are some of the main factors of organization’s competitive advantage,\(^111\) especially in intensive collaborative environments, such as in projectized organizations, where the risk of knowledge loss is a significant issue.\(^112\) According to several studies, 90% of an organization’s knowledge is mainly retained by its employees.\(^113\) However, companies usually overlook this issue\(^114\) leading to the risk of losing valuable knowledge, good practices, and lessons learnt when a valuable employee moves on.\(^115\) Moreover, in project-oriented businesses with crossdisciplinary activities, such as organizations dedicated to the design and fabrication of patient-specific implants, it is vital to have a smooth flow of knowledge and information to ensure a close cooperation between engineers and clinicians.\(^116,117\) Therefore, as a preventive action in this type of organizations it is very important to promote information and knowledge sharing through an adequate used of information systems and documentation.\(^118\) Process documentation is a key success factor for businesses to achieve consistent quality, and to facilitate standardization and reengineering.\(^119,120\) Standardized procedures and processes help to transform activities into routine defined tasks, increases consistency and efficiency, and facilitates process control.\(^113,121\) Processes documentation requires the development of process maps, workflows, checklists, guidelines, and commonly agreed language and vocabulary.\(^120\) Which in turn help to reengineer and simplify processes by facilitating process understanding, and identification of value and nonvalue adding activities.\(^120,122\) Moreover, to acquire commercialization approval of medical devices from regulatory bodies, companies are required to establish procedures with documentation containing fully defined requirements, testing results, checklists, and control diagrams to track product quality variations at each stage of the production cycle.\(^96\) This also facilitates the product validation process and conformance with corresponding standards. Furthermore, project postmortem reports are highly recommended at the end of each project, which document
particular failures and solutions to minimize duplication of effort, improve future projects, and create process documents. These postmortem reports enable companies to master the project learning cycle and save considerable costs.\textsuperscript{112,113,119}

### 5.2.7 Implant design

The aim during the design of additively manufactured patient-specific bone implants is to mimic the unique porous structure of bone and match the anatomic shape of the injury site or optimize joint function. However, the different biological, physicochemical, mechanical, dimensional, and functional factors that need to be considered during the design process make the design of patient-specific implants a difficult task. Therefore, according to the participants' opinion, the design process is one of the most critical areas to consider during the workflow of additively manufactured patient-specific bone implants, thus it is not surprising that this activity obtained the sixth place with a RI of 8.42 in the FMECA (Figure 4).

The properties of porous bone implants are influenced by their porosity and pore shape.\textsuperscript{123} The porosity of natural bone is important for vascularization, diffusion of cell nutrients and metabolic waste, and cell migration,\textsuperscript{124} and in a similar way important for metallic bone implants. Moreover, porosity and pore shape are considered as the main parameters affecting the stiffness of the implant, which is vital to reduce the stress shielding effect. Stress shielding occurs when there is a stiffness mismatch between the implant and surrounding bone and can cause inflammation and the need for revision surgery.\textsuperscript{125} During the design of patient-specific implants with porous structures, porosity and pore shape are directly controlled with the selection of the unit cell, which is used to imitate the bone structure. However, according to the interviewees, currently there are no medical standards or regulations to guide the design of fully porous patient-specific implants. Furthermore, the large variety of unit cells (more than a 1000) and design methods to create porous/lattice structures can make the implant design process difficult.\textsuperscript{126-132} As a result, all the participants in this study unanimously agreed that an inadequate selection of the unit cell is one of the most critical subactivities during the design of patient-specific implants, placing this subactivity 11th place in the list of critical risks. To control and mitigate the risks associated with this activity, the clinical engineers recommend leveraging the design process with collaboration agreements with universities research groups. This type of collaboration between industry and university provides access to specialized knowledge and innovative technologies that can assist the design of innovative patient-specific implant, giving a competitive advantage to both parties.\textsuperscript{133-135} In this way, the development and clinical testing of patentable medical designs can be facilitated.\textsuperscript{136,137}

However, it is important to consider that a university-industry collaboration is a complex relationship due to the different objectives, interest and constrains of both parties.\textsuperscript{138} Therefore, to overcome these differences, universities and industry partners need to develop appropriate strategies to build trust and facilitate communication.\textsuperscript{139}

### 6 DISCUSSION

Risk assessment is a well-established process, necessary to comply with the minimum regulatory requirements of any medical device. However, risks are time and circumstantial dependent entities that change and evolve based on a variety of factors unique to each project. Risks are usually more difficult and expensive to control when they move forward in the product development process. Therefore, at the beginning of any biomedical engineering product development process, it is very important to uncover all of the possible ways that the product could fail. This allows a product industry and its development companies to gain in-depth insight into the types of tests and technologies that should be used to validate the product and its manufacturing process. In this way, risks and cost can be kept to their minimum.

The infancy of the AM patient-specific implant industry and the lack of defined quality standards prompted this present study to apply FMECA and ISO 14971:2007 approaches in an integrated manner with a 3D risk assessment approach. Consequently, in this study, a comprehensive risk assessment and associated strategies were formulated for the initial stages of the development process of AM patient-specific implants. It is noteworthy to mention that FMECA is an ongoing process that should be updated throughout the entire product development process when more risks, and new strategies to mitigate them, are uncovered and need to be managed. During the FMECA, it became clear that AM materials, AM Machine general, fabrication, EBM machine, finishing, and design are the most sensitive process areas in terms of product quality. Nonetheless, one of the main reasons of project failure is the lack of senior management
commitment. Therefore, leadership is the most crucial ingredient for an adequate implementation of any quality management system. Overall, the primary contribution of this research is the identification of the most critical risks that can impact the quality of patient-specific implants during their design and fabrication process. Moreover, to facilitate the visualization of critical risks a new 3D risk priority matrix was developed in this study. This 3D risk priority matrix is a robust and simple tool that can be easily used in any industry setting. This matrix provides a more accurate graphic representation of the three different factors used for risks rating, thus facilitating the presentation of risk assessment analysis to different stakeholders.

The study had some limitations. First, it was not possible to articulate detailed risk mitigation strategies for all of the risks identified by participants due to the uniqueness of the observed companies’ products and their manufacturing methods. Moreover, the strategies proposed in this study represent a collection of individual experiences and knowledge from a relatively small group of industry experts and researchers. However, despite these limitations, the herein developed novel risk identification procedure and the list of FMs provided in the Data S1 can be used as a guide to companies seeking to create high quality AM patient-specific Ti implants. Further research is required to address study limitations and to foster high quality performance in this rapidly growing industry. For example, future research can use this study as a foundation to focus on the strategic planning of quality assurance and control methods that can help to prepare this new industry for future changes in MDRs. This includes more detailed risk assessment and quality control strategies that consider time and cost constraints in different scenarios and different AM systems. Moreover, it is known that currently the different medical regulatory organizations such as the FDA (USA) and the TGA (Australia) are working together to create a regulatory scheme for personalized AM medical devices. Therefore, there is an urgent need for engineering management research that focuses on regulatory models that foster innovation and are capable of covering the technical considerations for designing, manufacturing, and testing such medical devices. Taking this into consideration, we believe that the integration of our previous work coupled with the 3D risks assessment method proposed in this study can serve as a basis for a new regulatory model for additively manufactured patient-specific bone implants.

7 | CONCLUSIONS

This study utilized a FMECA coupled with a 3D risk assessment approach to better understand and manage critical risks associated with the design and fabrication of AM titanium patient-specific implants. The 3D risk priority matrix developed in this study was used to categorize the criticality level of the identified FM considering the detection difficulty ($D$), the potential severity of damage ($S$), and likelihood of occurrence ($O$) of the FM. The 3D risk priority matrix was constructed emphasizing detection difficulty ($D$) due to the uniqueness of each patient-specific implant, thus facilitating the visualization of critical risks. The risk assessment process was performed using the Delphi method with 13 experts from six different companies and research institutions across related fields such as quality management, AM, and clinical engineering. A total 137 FMs categorized into 17 groups were evaluated with semistructured interviews with participants. The novel risk evaluation procedure identified 13 critical FM within six risk critical groups. The six most critical groups identified in this study were AM materials, AM machine general, fabrication, EBM machine, finishing, and design. Pertinent preventive and corrective actions, based on expert opinions and literature, were proposed to mitigate the effects of the most critical FM and to control the quality of the most critical processes and activities within the design and fabrication workflow of such medical products.

Companies dedicated to the fabrication of patient-specific implants with AM full-melt powder bed fusion such as EBM, and DMLS have to strongly rely on two main quality control technologies to accurately monitor and control several aspects of the production process. The first quality control technology is micro-CT scanner. This technology is vital for the identification of trapped particles, presence of pores, internal flaws, and for dimensional validation. Moreover, micro-CT scanners can also be used to control of power particles characteristics and powder cross-contamination. The second vital technology is real-time process monitoring systems for AM machines. This quality technology is critical to guarantee that the reliability of the AM process in order to produce high quality parts with consistent mechanical properties, chemical composition, and accurate geometries. Nonetheless, to mass produce high-performance patient-specific implants with reliable characteristics and competitive costs there is a need of AM machines integrated with smarter real-time monitoring systems and micro-CT scanners.

Overall, this study seeks to accelerate the maturity of AM in the biomedical industry by presenting the implementation of a FMECA coupled with a 3D risk assessment approach as a pragmatic tool to tackle long-term patient safety and product performance. Therefore, we believe that this research may serve as a guide for the implementation of QbD in start-ups,
small, and medium-sized companies as well as part of the new medical regulatory standards for additively manufactured patient-specific implants.

ACKNOWLEDGEMENTS
The authors gratefully acknowledge the input of the case study firms and research institutes and their respective participants of the semistructured interviews.

CONFLICT OF INTEREST
The authors have declared that no competing interests exist.

AUTHORS CONTRIBUTIONS
Daniel Martinez-Marquez contributed to the conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, validation, visualization, and writing of the original draft, review, and editing. Klemens Terhaer contributed to the data curation, validation, and writing of the review and editing. Peter Scheinemann contributed to the data curation, validation, and writing of the review and editing. Ali Mirnajafizadeh contributed to the project administration, supervision, and writing of the review and editing. Christopher Carty contributed to the funding acquisition, project administration, supervision, and writing of the review and editing. Rodney Stewart contributed to the formal analysis, methodology, project administration, supervision, and writing of the review and editing.

ETHICS STATEMENT
The authors confirm that consent has been obtained by all the participants of this study. Moreover, the protocol and procedures employed in this study were reviewed and approved by the Griffith University Human Research Ethics Committee under the Ref No: 2017/217.

ORCID
Daniel Martinez-Marquez https://orcid.org/0000-0001-7326-1015
Christopher P. Carty https://orcid.org/0000-0002-8969-5181
Rodney A. Stewart https://orcid.org/0000-0002-6013-3505

REFERENCES
1. Morrison RJ, Kashlan KN, Flanagan CL, et al. Regulatory considerations in the design and manufacturing of implantable 3D-printed medical devices. Clin Transl Sci. 2015;8(5):594-600.
2. Martinez-Marquez D, Mirnajafizadeh A, Carty CP, Stewart RA. Application of quality by design for 3D printed bone prostheses and scaffolds. PLoS One. 2018;13(4):e0195291. https://doi.org/10.1371/journal.pone.0195291.
3. FDA U. Understanding Barriers to Medical Device Quality. Silver Spring, MD: US Food and Drug Administration; 2011.
4. Martinez-Marquez D, Mirnajafizadeh A, Carty CP, Stewart RA. Facilitating industry translation of custom 3D printed bone prostheses and scaffolds through quality by design. Procedia Manuf. 2019;30:284-291.
5. Thompson MK, Moroni G, Vaneker T, et al. Design for additive manufacturing: trends, opportunities, considerations, and constraints. CIRP Ann. 2016;65(2):737-760. https://doi.org/10.1016/j.cirp.2016.05.004.
6. Martinez-Marquez D, Jokymaiyte M, Mirnajafizadeh A, Carty CP, Lloyd D, Stewart RA. Development of 18 quality control gates for additive manufacturing of error free patient-specific implants. Materials. 2019;12(19):3110. https://doi.org/10.3390/ma12193110.
7. Yeong WY, Chua CK. A quality management framework for implementing additive manufacturing of medical devices. Virtual Phys Prototyping. 2013;8(3):193-199. https://doi.org/10.1080/17452759.2013.838053.
8. Juran JM. Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services. New York: Simon and Schuster; 1992.
9. Little TA. Essentials in quality by design. BioProcess Int. 2014;12:3.
10. Huang S-M, Chang I-C, Li S-H, Lin M-T. Assessing risk in ERP projects: identify and prioritize the factors. Ind Manag Data Syst. 2004;104(8):681-688.
11. Hudson P. Applying the lessons of high risk industries to health care. BMJ Qual Saf. 2003;12(suppl 1):i7-i12.
12. ICH Harmonised Tripartite Guideline. Guidance for industry. Q9 quality risk management. ICH Steering Committee, Step. 2006.
13. Lincoln JE. Product risk management under ISO 14971:2007. J Valid Technol. 2009;15(4):10.
14. ISO E. 14971:2009. Medical Devices—Application of Risk Management to Medical Devices (ISO 14971: 2007, Corrected Version October 1, 2007). Brussels, Belgium: CEN/CENELEC; 2009.
15. Chan S, Ip W, Zhang W. Integrating failure analysis and risk analysis with quality assurance in the design phase of medical product development. Int J Prod Res. 2012;50(8):2190-2203.
53. FDA. Technical considerations for additive manufactured medical devices: guidance for industry and food and drug administration staff. In: Services USDoHaH, ed. U.S Food & Drug Administration; 2017.
54. Mellor S, Hao L, Zhang D. Additive manufacturing: a framework for implementation. Int J Prod Econ. 2014;149:194-201.
55. Dawes J, Bowerman R, Trepleton R. Introduction to the additive manufacturing powder metallurgy supply chain. Johnson Matthey Technol Rev. 2015;59(3):243-256.
56. Blome C, Henke M. Single versus multiple sourcing: a supply risk management perspective. Supply Chain Risk. 2009;124:125-135.
57. Mellor I, Grainger L, Rao K, et al. Titanium powder production via the metalysis process. Titanium Powder Metallurgy. Oxford: Elsevier; 2015:51-67.
58. Despeisse M, Ford S, eds. The role of additive manufacturing in improving resource efficiency and sustainability. Paper presented at: IFIP International Conference on Advances in Production Management Systems; 2015: Springer.
59. Karuppuswamy P, Sundararaj G, Elangovan D. Application of computerised maintenance management system coupled with risk management techniques for performance improvement of manufacturing systems. Int J Bus Perform Manag. 2006;9(1):7-21.
60. Popovic VM, Vasic BM, Rakicevic BB, Vorotovic GS. Optimisation of maintenance concept choice using risk-decision factor – a case study. Int J Syst Sci. 2012;43(10):1913-1926. https://doi.org/10.1080/00207721.2011.563868.
61. Ruffo M, Tuck C, Hague R. Cost estimation for rapid manufacturing-laser sintering production for low to medium volumes. Proc Inst Mech Eng B J Eng Manuf. 2006;220(9):1417-1427.
62. Hopkinson N, Dicknes P. Analysis of rapid manufacturing—using layer manufacturing processes for production. Proc Inst Mech Eng C J Mech Eng Sci. 2003;217(1):31-39.
63. Park KS, Han S. TPM—total productive maintenance: impact on competitiveness and a framework for successful implementation. Hum Factors Ergon Manuf Serv Ind. 2001;11(4):321-338.
64. Jelis E, Hespos M, Groeschler SL, Carpenter R. L-PBF of 4340 low alloy steel: influence of feedstock powder, layer thickness, and machine maintenance. J Man Eng Perform. 2018;28(2):693-700. https://doi.org/10.1007/s11665-018-3739-2.
65. Hrgarek N, Bowers K-A. Integrating six sigma into a quality management system in the medical device industry. J Inform Org Sci. 2009;33(1):1-12.
66. Chang D. Internalizing the external costs of medical device preemption. Hastings LJ. 2013:65:283.
67. He D. Engineering quality systems: cost of quality. Mod Appl Sci. 2010;4(5):102-104.
68. Bettayeb B, Bassetto SJ, Sahnoun M. Quality control planning to prevent excessive scrap production. J Manuf Syst. 2014;33(3):400-411. https://doi.org/10.1016/j.jmsy.2014.01.001.
69. Hamedi A. Bayesian networks in additive manufacturing and reliability engineering [master's thesis]. Tempere University; 2019.
70. EOS. EOSTATE System: control over all production-relevant data in the 3D printing process. 2019 [cited 2019 Jan 4]. https://www.eos.info/software/monitoring-software/eostate-system.
71. EOS. EOS Software for Additive Manufacturing Krailling. Germany: EOS; 2019 [cited 2019 Jan 4]. https://www.eos.info/systems_solutions/software.
72. Fuchs L, Eischer C. In-process monitoring systems for metal additive manufacturing. EOS Electro Optical Systems; 2018.
73. EOS. EOSTATE PowderBed: recording every coating and exposure phase. 2019 [cited 2019 Jan 4]. https://www.eos.info/software/monitoring-software/eostate-powderbed-control.
74. Foster B, Reutzel E, Nasar A, Hall B, Brown S, Dickman C, eds. Optical, layerwise monitoring of powder bed fusion. Paper presented at: Solid Freeform Fabrication Symposium; 10–12 August 2015; Austin, TX.
75. EOS. Technical Description EOSINT M280. 2010 [cited 2019 Jan 4]. https://webbuilder5.asiannet.com/ftp/2684/TD_M280_en_2011-03-29.pdf.
76. Gibson I. The changing face of additive manufacturing. J Manuf Technol Manag. 2017;28(1):10-17.
77. Berumen S, Bechmann F, Lindner S, Kruth J-P, Craeghs T. Quality control of laser-and powder bed-based additive manufacturing (AM) technologies. Phys Procedia. 2010;5:617-622.
78. GE-additive. Electron Beam Melting (EBM) machines. 2019 [cited 2019 Jan 3]. https://www.ge.com/additive/additive-manufacturing/machines/ebm-machines/arcam-ebm-q10plus.
79. Arcam AB. Process Validation Tools. 2019 [cited 2019 Jan 3]. http://www.arcam.com/technology/electron-beam-melting/process-validation-tools/.
80. Petetel M, ed. Additive Manufacturing: In-Situ Process Monitoring, Defect Detection and Control. Materials Science & Technology. Columbus, OH; 2015.
81. Lindemann C, Jahnke U, Moi M, Koch R, eds. Analyzing product lifecycle costs for a better understanding of cost drivers in additive manufacturing. Paper presented at: 23th Annual International Solid Freeform Fabrication Symposium—An Additive Manufacturing Conference; 6-8 August 2012; Austin, TX.
82. Cloots M, Spierings A, Wegener K, eds. Assessing new support minimizing strategies for the additive manufacturing technology SLM. Paper presented at: Solid Freeform Fabrication Symposium (SFF); August 2013; Austin, TX.
83. Spierings A, Levy G, Wegener K, eds. Designing material properties locally with additive manufacturing technology SLM. Paper presented at: Solid Freeform Fabrication Symposium 2012; 2014; ETH-Zürich.
84. Xu D, Cheng F, Zhou Y, Matalaray T, Lim PX, Zhao L, eds. Process optimization: internal feature measurement for additive-manufacturing parts using x-ray computed tomography. Paper presented at: Tenth International Symposium on Precision Engineering Measurements and Instrumentation; 2019; International Society for Optics and Photonics.
116. Sabherwal R, Becerra-Fernandez I. An empirical study of the effect of knowledge management processes at individual, group, and organizational levels. Decis Sci. 2003;34(2):225-260.

117. Arntzen AAB, Leguy C. A model of knowledge sharing in biomedical engineering: challenges and requirements. J Bus Chem. 2007;4(1):21-32.

118. Rinkus S, Walji M, Johnson-Throop KA, et al. Human-centered design of a distributed knowledge management system. J Biomed Inform. 2005;38(1):4-17.

119. Clarke A. A practical use of key success factors to improve the effectiveness of project management. Int J Proj Manag. 1999;17(3):139-145.

120. Ungan M. Towards a better understanding of process documentation. TQM Mag. 2006;18(4):400-409. https://doi.org/10.1108/09544780610671066.

121. Ferreira F, Faria J, Azevedo A, Marques AL. Product lifecycle management in knowledge intensive collaborative environments: an application to automotive industry. Int J Inform Manag. 2017;37(1):1474-1487.

122. Gardan N. Knowledge management for topological optimization integration in additive manufacturing. Int J Manuf Eng. 2014;2014:1-9.

123. Suska F, Kjeller G, Tarnow P, et al. Electron beam melting manufacturing technology for individually manufactured jaw prosthesis: a case report. J Oral Maxillofac Surg. 2016;74:1706.e1-1706.e15.

124. Dorozhkin SV. Calcium orthophosphate-based bioceramics. Materials. 2013;6(9):3840-3942.

125. Oh I-H, Nomura N, Masahashi N, Hanada S. Mechanical properties of porous titanium compacts prepared by powder sintering. Scr Mater. 2003;49(12):1197-1202. https://doi.org/10.1016/j.scriptamat.2003.08.018.

126. Cheah C, Chua C, Leong K, Chua S. Development of a tissue engineering scaffold structure library for rapid prototyping. Part 1: investigation and classification. Int J Adv Manuf Technol. 2003;21(4):291-301.

127. Sun W, Starly B, Nam J, Darling A. Bio-CAD modeling and its applications in computer-aided tissue engineering. Comput Aided Des. 2005;37(11):1097-1114. https://doi.org/10.1016/j.cad.2005.02.002.

128. An I, Teoh JEM, Suntornnond R, Chua CK. Design and 3D printing of scaffolds and tissues. Engineering. 2015;1(2):261-268.

129. Chantarapanich N, Puttawibul P, Sucharitpwatskul S, Jeamwatthanachai P, Inglam S, Sitthiseripratip K. Scaffold library for tissue engineering: a geometric evaluation. Comput Math Methods Med. 2012;2012:1-14.

130. Wettergreen M, Bucklen B, Starly B, Yuksel E, Sun W, Liebschner M. Creation of a unit block library of architectures for use in assembled scaffold engineering. Comput Aided Des. 2005;37(11):1141-1149.

131. Yoo D. New paradigms in hierarchical porous scaffold design for tissue engineering. Mater Sci Eng C. 2013;33(3):1759-1772.

132. Afshar M, Anaraki AP, Montazerian H, Kadkhodapour J. Additive manufacturing and mechanical characterization of graded porosity scaffolds designed based on triply periodic minimal surface architectures. J Mech Behav Biomed Mater. 2016;62:481-494.

133. Philbin S. Process model for university-industry research collaboration. Eur J Innov Manag. 2008;11(4):488-521. https://doi.org/10.1108/14601060810911138.

134. Davey SM, Brennan M, Meenan B, McAdam R. Innovation in the medical device sector: an open business model approach for high-tech small firms. Technol Anal Strat Manag. 2011;23(8):807-824.

135. Lyu LC, Wu WP, Hu HP, Huang R. An evolving regional innovation network: collaboration among industry, university, and research institution in China’s first technology hub. J Technol Transf. 2019;44(3):659-680. https://doi.org/10.1007/s10961-017-9620-x.

136. Rochford L, Rudelius W. New product development process: stages and successes in the medical products industry. Indus Market Manag. 1997;26(1):67-84.

137. Lee YS. The sustainability of university-industry research collaboration: an empirical assessment. J Technol Transf. 2000;25(2):111-133. https://doi.org/10.1023/A:1007895322042.

138. Okamuro H, Nishimura J. Impact of university intellectual property policy on the performance of university-industry research collaboration. J Technol Transf. 2013;38(3):273-301.

139. Dan MC. Why should university and business cooperate? A discussion of advantages and disadvantages. Int J Econ Pract Theor. 2013;3(1):67-74.

140. TGA. Proposed regulatory changes related to personalised and 3D printed medical devices. In: Administration DoHTG, ed. Version 1.0, November 2017 ed. Woden, Australia: Therapeutic Goods Administration; 2017.

141. TGA. Consultation: proposed regulatory scheme for personalised medical devices, including 3D-printed devices. In: Administration DoHTG, ed. Woden, Australia; 2019.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Martinez-Marquez D, Terhaer K, Scheinemann P, Mirnajafizadeh A, Carty CP, Stewart RA. Quality by Design for industry translation: Three-dimensional risk assessment failure mode, effects, and criticality analysis for additively manufactured patient-specific implants. Engineering Reports. 2020;2:e12113. https://doi.org/10.1002/eng2.12113