New Knee Implant Variants Under the Medical Device Regulation: A Bayesian Approach to Estimate Their Performance

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Abstract

The new Medical Device Regulation (MDR) addresses patient safety by mandating supporting clinical evidence for the sale and clinical use of medical devices. However, it places pressure on medical device manufacturers to supply regulators with robust clinical evidence to obtain regulatory approval of new devices they develop. Regulatory compliance is therefore more stringent, requiring more effort on part of both regulators and manufacturers. This thesis project explored the possibility of developing a new method to be used as a regulatory decision-making tool for the approval of newly developed knee implants. A Bayesian probabilistic method was developed and proposed. This method utilises existing arthroplasty registry and arthroplasty registry annual report data to determine if a newly released implant variant is “good”, where a “good” implant is one which meets standard regulatory thresholds in term of revision risk. This method was implemented on two datasets which were selected based on conditions of granularity, measures of implant performance, and accessibility for the thesis project. Some advantages and limitations of this method as a regulatory tool were proposed, the limitations being based on a clinical appraisal framework. Based on this it was concluded that the method indeed showed potential as such a regulatory tool, but needs further improvement due to considerations of reliability, precision, and the probabilistic nature of the results it yields. Both surgeons and patients can also potentially stand to benefit from this method. Aside from the regulatory context, also, the method has limitations in the fact that it does not account for other factors that may be responsible for complications related to knee arthroplasty surgery. Overall, however, this thesis presents a novel approach towards estimating the performance of knee implants from existing clinical data.

Chapter 1 | Introduction

1.1 Context

Total Knee Arthroplasty (TKA) remains one of the most effective treatments for end stage osteoarthritis today (Kini, 2022). It boasts high patient satisfaction rates, effectively restoring knee function and alleviating pain. Throughout the last decade, the TKA, as a surgical intervention, has undergone significant change in both surgical technique and implant design and performance (Pande & Dhatrak, 2021). Implant design itself has evolved from the initial hinged and Guépar prostheses to modern variants of cruciate retaining (CR) and posterior stabilised (PS) implants (Saragaglia et al., 2019). This has led to many different prosthesis products in the market, offered by many different manufacturers. Their models vary in design, material, and parts. More so, a single brand can have multiple designs and implant types. These are called *variants* as defined in the section *Variants in the Thesis Context*.

A brand could consist of many models with different sub-components, materials, and designs which can be considered separate implants in their own right. These are called variants (Phillips & Tucker, 2021). Variants can be regarded as individual knee prostheses having a unique combination of characteristics. A list of seven characteristics described in the section *Variants in the Thesis Context* helps uniquely identify an implant variant, distinguishing it from other similar variants even if they share a common brand name. This approach of looking at implant variants individually differs from that used by registry reports, literature studies and rating agencies which group many variants under a single brand name.

Registries, clinical studies, and independent agencies study implant performance, safety and efficacy. After all, knee replacement is a major surgical procedure and poor implant quality can significantly increase the risk of surgical complication. Once implanted in the body, any subsequent operation due to problems with the knee implant is difficult and carries a higher risk of complication (Dennis et al., 2011; Fitzpatrick et al., 2012; Jenny et al., 2008). It also poses a significant clinical burden on the patient and financial burden on the healthcare system (Khan et al., 2016). Therefore, it is important that knee implants perform as intended the first time they are implanted within the body and hence the need for properly gauging an implant's performance. Implant performance in the context of this thesis is defined entirely in terms of revision risk in section *Defining Implant Performance*.

Studied implants are rated on this basis and assign performance metrics such as the revision risk, which is the probability of a patient needing revision surgery within a specified time period of follow-up. Many variants may be studied, and metrics for each of them may be published in sources like registry reports and medical research. Naturally, implant performance, safety and efficacy can vary significantly based on the variant used. It is known that some implants generally come with a higher risk of revision and a lower performance, whereas others have a stellar track record with low rates of revision. This can be the case even for close variants: those sharing a common brand name, such as in the case mentioned by Keohane et al., 2020, 2022 for the Nexgen LPS implant and its variants.

Differences between implant performance of close variants with a common brand name can result in Camouflage (Haddad, 2021a; Phillips & Tucker, 2021; Wilton et al., 2023a). Camouflage is the association of a brand with only good performing variants, overshadowing underperforming variants. Variants with stellar metrics of revision, safety and efficacy may paint a good picture of the whole brand. In this process, other variants with the same brand name may be associated with the same performance metrics, even if they underperform. In some cases, the good picture of a brand has masked the presence of variants with known safety concerns (Keohane et al., 2020, 2022; Wilton et al., 2023b).

If each new variant is properly vetted with supporting clinical evidence before release for open use in surgical contexts, camouflage can be reduced drastically. Underperforming variants would be used with caution and would not be overshadowed by the good performance of other, more popular variants with the same brand name. To a certain extent, this vetting of new variants has been taken up by regulators with the new Medical Device Regulation (MDR). Up until recently, regulatory authorities approved the use of knee implant variants based on the performance of near variants under the same brand name. This is mentioned in the “similar device” clause in the Medical Device Directive (MDD) Directive 93/42/EEC (Official Journal of the European Communities, 1993). However, due to a series of clinical failures as described in section *The MDR in the Knee Arthroplasty Context*, the new Medical Device Regulation (MDR) has taken effect from 2017. The MDR mandates manufacturers to provide evidence for individual variants even if it is similar to an already-approved implant in terms of prosthesis characteristics.

Although this reduces the likelihood of camouflage and has positive implications for patient safety, this new system puts an immense amount of pressure on manufacturers to supply appropriate clinical evidence to regulators for the release of new implant variants (Wilkinson & van Boxtel, 2020). This burden is further exacerbated when manufacturers release new variants frequently in short innovation cycles. Typically, when this happens, new variants closely resemble other already-approved variants. Implant characteristics are similar, with changes from an older variant to a newer one being incremental. Implants may need to be re-approved from scratch despite the presence of clinical evidence from a near variant which has already been approved. Previous clinical and surgical evidence associated with a near variant may be completely ignored in this process of generating evidence from scratch.

This thesis explores the possibility of using this evidence from known, tested and regulated variants to new ones which enter the market. In other words, it looks at the possibility utilising existing evidence to make informed estimations on the performance of new variants with similar characteristics. This could serve as a foundational effort benefiting both regulators and manufacturers in the field of knee implants. A probabilistic Bayesian method is found ideal for achieving this objective.

1.2 Problem Statement

The current regulatory framework for medical devices like knee implants, the MDR, mandates supporting clinical evidence for the regulatory approval of each new implant variant created by manufacturers for subsequent sale and surgical use. The MDR, in doing so, addresses concerns of patient safety and Camouflage, where underperforming variants are overshadowed by high-performing ones within the same brand. However, this introduces new issues. New implant variants now need to be supported by robust clinical evidence for obtaining regulatory approval. This places pressure on manufacturers to supply such clinical evidence for each implant variant they create because new variants may be frequently released only with incremental changes as compared to their predecessor variants. Additionally, it is typically more challenging, costlier, and time consuming to obtain clinical evidence for medical devices like knee implants compared to medicinal products like drugs. Therefore, there is a need to identify a new method that assists this regulatory approval process by providing an initial estimate of new implant variants that manufacturers release, even if it may be an incremental improvement from a predecessor variant. This method would assist this regulatory decision-making process by providing an initial estimate of a new variants' potential performance during clinical use. This method would need to be predictive, using available clinical data, because at the regulatory approval stage there may be little clinical data associated with the variant in question. Thus, general clinical evidence from literature and arthroplasty registries would need to be utilised in the method.

1.3 Research Objectives and Question

1.3.1 ***Research Objectives***

OBJ ①
Examine data from arthroplasty registries, studies of regulated knee implants and other clinical data and identify suitable sources of information to develop a method to estimate knee implant variant performance.

OBJ ②
To identify an approach for developing a method to estimate the revision risk performance of knee implant variants using existing arthroplasty registry and literature on regulated knee implants (medical literature)

OBJ ③
Develop a method to estimate knee implant variant performance leveraging evidence from arthroplasty registries or clinical data.

OBJ ④
Evaluate the method to determine its applicability in regulating knee implant variants.

1.3.2 ***Research Question***

RQ ①
What method can use existing clinical data from arthroplasty registries and studies of regulated total knee implants to estimate the revision risk performance of implant variants?

Sub-research question

RQ ②
What methods can regulators of medical devices use to improve decision-making on the approval of new knee implant variants?

1.4 Literature Overview

This brief literature review section aims to analyse existing research on total knee implant variants, focusing mainly on their performance and regulatory implications. It synthesises existing research with the overall goal of highlighting the importance of individual variant assessment in enhancing patient safety and clinical outcomes in the context of this thesis project.

1.4.1 ***Literature Search***

A small set of studies curated by one of the supervisors served as motivation for the literature search. These included three studies exposing a phenomenon called “camouflage” in the context of knee arthroplasty (Haddad, 2021b; J. R. A. Phillips & Tucker, 2021; Wilton et al., 2023b) and one on the necessity of more thorough evaluation of medical devices (Fraser et al., 2021; Lübbeke et al., 2023a). This paved the way for a deeper investigation on this topic with the help the Google Scholar. Besides this, studies from the Bone and Joint Journal were also included because of its specialisation in arthroplasty. However, due to difficulties in searching for articles in this database and the presence of this journals’ papers in Google Scholar, searching on this database was avoided.

Research on similar articles to those provided by the supervisor revealed many articles on medical device regulation (Ben-Menahem et al., 2020; Bowers & Cohen, 2018; Vasiljeva et al., 2020a; Wagner & Schanze, 2018) and cases of disastrous failure of implants such as metal-on-metal hip implants (Cohen, 2012; Heneghan et al., 2012). This phase of the literature review indicated that current regulation on medical devices was more stringent that a few years before, and more evidence vetting the safety of new devices was necessary before regulatory approval (Nüssler, 2023). This was predominantly motivated by medical device failures that affected scores of patients (Shatrov & Blankart, 2022). The new regulation also proved beneficial in the context of knee arthroplasty because of cases of recent implant failures (Keohane et al., 2020, 2022; Wilton et al., 2023b). This new regulatory environment for medical devices, however, introduced new challenges. More stringent rules for regulatory compliance burdens manufacturers to provide enough clinical evidence when bringing new medical devices into the market vetting their safety and efficacy (Ben-Menahem et al., 2020; Wagner & Schanze, 2018). Clinical evidence is not easy to obtain and requires significant time and financial investment. Other methods which assess implant safety and performance are mostly retrospective and require clinical evidence to make properly measure implant safety and performance. Although there exists significant research on such methods and ways to generate, synthesise and analyse clinical evidence, literature is lacking on predictive methods measuring implant safety and performance. Some articles do develop methods to predict the outcomes following knee arthroplasty surgery (Andersen et al., 2021; Aram et al., 2018; Devana et al., 2021; Fernandes et al., 2017; Hinterwimmer et al., 2022; Huber et al., 2019; Navarro et al., 2018; Twiggs et al., 2019), but they do not focus on implant performance alone, rather also take surgical factors and patient characteristics into account. They seek to predict patient outcomes instead of the performance of particular implants. Many of them put forth multivariate and machine learning models.

1.5 Scientific Contributions

This thesis project presents a novel mathematical method to estimate the performance of new knee implant variants using existing clinical data, which is also relevant in the current medical device regulatory context. In literature, some studies have attempted to predict surgical complications post knee surgery such as revision, do not predict the revision risk of implant variants (El-Galaly et al., 2020; Fernandes et al., 2017). Additionally, techniques such as machine learning are preferred (Devana et al., 2021; Fernandes et al., 2017; Hinterwimmer et al., 2022; Twiggs et al., 2019), and Bayesian probabilistic methods have not been used.

Chapter 2 | Background

2.1 Knee Implant Variants

Total knee implants usually consist of various individual prostheses, each distinguished by unique characteristics (Smith et al., 2023) These prostheses serve as components within the knee implant, and these can vary widely in type, make, brand, model, material, and design. These components articulate with each other to form a complete total knee implant

A knee implant brand often includes multiple knee implants that share some major physical characteristics but differ in minor physical characteristics. These differences often involve variations in design and the types and combination of components used in the implant. Therefore, one single brand can cover a wide range of distinct knee implants. Wilton et al., 2023b refer to this range of implants under one common brand name as "variants." For example, the Genesis II knee implant brand, manufactured by the company Smith & Nephew, highlights the many variants that can fall under one brand. The Genesis II knee implant is the most frequently used knee implant in the Netherlands as of 2022 (de Reus et al., 2023b). It is not a single implant but a brand name consisting of a many implant variants that can differ in design, material composition, and the type and combination of components. One variant may incorporate a particular version of a component, while another might utilise a different material altogether. According to the Genesis II surgical guide (*Genesis II DCF Surgical Technique*, 2022), there are over 80 variants possible.

2.1.1 *Characterising Knee Implant Variants*

Seven implant characteristics can help distinguish variants and differentiate one from another. Four of these characteristics are based on the components as mentioned above. The type, make brand, model, and design of these four components partly help distinguish one variant from another. Two of these components can be considered “major”: the femoral and tibial components. The femoral component attaches to the femur of a human knee while the tibial component attaches to the tibia of the human knee, both ultimately replace the femorotibial articulation in the knee. In addition to these two components, knee systems have the “insert” and “patellar” components to support the two major components. The insert functions as a surface for the smooth motion of the femoral component, supporting and stabilising the joint while minimising friction on knee bending. The patella is a bony structure which is part of normal human anatomy. It is often augmented with a component fitting its underside to further support knee function. Patellar resurfacing, as this augmentation is called, is a controversial procedure in surgical practice, and it is often skipped in total knee arthroplasty (Fu et al., 2011). For all purposes within this report, the “patellar component” refers to this augmented patellar structure. Ultimately, these four components can help partly characterise a knee implant variant, setting it apart from other variants.

Besides these four components, implant variants also have three other characteristics. These are not physical components of the knee implant, but rather elements implant design. These includes the 1) type of attachment method to bone (also called cement or fixation), 2) the bearing type, and 3) whether it replaces the posterior cruciate (PC) ligament. These introduce 3 new characteristics of a knee prosthesis: the cement, bearing and ligament. The four components along with these 3 characteristics results in a total of 7 prosthesis characteristics, as shown in Table 1 *Implant characteristics*. As shown, each characteristic can also be of many different types.

Characteristic	Types
Femoral	Brand, material
Tibial	Brand, material
Insert	Brand, material, HF, DD, etc.
Patella	Brand, shape, etc.
Fixation	Cemented, cementless, hybrid
Bearing	Mobile bearing, fixed bearing, rotating, hinged
Ligament	Cruciate retaining (CR), minimally stabilised (MS), cruciate sacrificing (CS) or posterior stabilised (PS)

Table 1 Implant characteristics

Using these seven characteristics, variants can be distinguished from each other. Each variant may have a different combination of characteristics setting it apart from other variants of the brand. An example of two variants which are quite similar but differ based on one of the characteristics (in bold) is shown in *Table 2 Two knee prostheses, Implant 1 and Implant 2 which could be considered variants*. Two knee prostheses, *Implant 1* and *Implant 2* which could be considered variants having a common brand name “Genesis II” from the company Smith & Nephew are shown (*Smith+Nephew Medical Devices and Advanced Wound Care | Global*, n.d.). Both these implants have a high chance of being referred to collectively as the brand “Genesis II” in registry reports, literature studies etc. as was the case in the Landelijke Registratie Orthopedische Interventies (LROI) annual registry report (de Reus et al., 2023, p. 131). Combining them as a single implant in a report like that of the LROI can have some ill consequences, as discussed in the following sections.

Characteristic	Implant 1	Implant 2
Femoral	Genesis II femoral component	Genesis II femoral component
Tibial	Genesis II tibial component	Genesis II tibial component
Insert	**Deep Dished insert**	**CR High Flex insert**
Patella	No patella	No patella
Fixation	Cemented	Cemented
Bearing	Fixed	Fixed
Ligament	CR	CR

Table 2 Two knee prostheses, Implant 1 and Implant 2 which could be considered variants

2.2 Camouflage because of Implant Variants

Knee implants are medical devices extensively studied in the field of arthroplasty. Consequently, there is a substantial body of medical literature on their use. Published refereed journals like the Bone & Joint Journal (BJJ), the Clinical Orthopaedics and Related Research (CORR), and The Journal of Bone and Joint Surgery (JBJS) among other feature extensive medical research on knee arthroplasty. A significant portion of this literature focusses on evaluating the safety of different knee implants and their effectiveness in treating arthritis and traumatic injury (such as by Asokan et al., 2021a and Broberg et al., 2022). Unfortunately, these studies only consider knee implants at the brand level and overlook detailed analyses of specific variants (Wilton et al., 2023a). Thus, their findings are more relevant to the overall brand and not individual variants. Each brand may consist of many individual variants having distinct safety or effectiveness profiles which may be different from published results. Therefore, highly safe and effective “star” variants can sometimes overshadow potential safety issues and low effectiveness of other variants within the same brand. This phenomenon is called "Camouflage" by Wilton et al., (2023b). It is also discussed by Phillips & Tucker, 2022.

In medical literature and studies from published refereed journals, the safety and effectiveness of knee implants are covered by the loose umbrella term "performance." Performance is essentially a measure of the outcome of knee implantation surgery and can refer to:

1. **A measure of joint function** following knee implantation surgery (Mizner et al., 2011; Stratford & Kennedy, 2006).
2. **Patient-reported outcomes** following knee implantation surgery such as knee pain(Mizner et al., 2011; Stratford et al., 2003).
3. **Surgical outcome** such as length of hospital stay (Mohammed et al., 2022) and the chance of surgical complications like infection and re-surgery (Blom et al., 2004; SooHoo et al., 2006).
4. **Implant function**: how well an implant functions as expected after surgery such as by resisting wear and tear, remaining intact within the body (Koh et al., 2019) and the chance of implant failure.

Revision Risk as a Measure of Performance

Performance is often expressed in terms of *revision risk* which can be considered a measure of both surgical outcome and implant function. The revision risk, also called cumulative percent revision or cumulative failure rate is defined as:

$$100 \times [1 - S(t)]$$

Where $S(t)$ is the survivorship probability estimated by the Kaplan-Meier method for the proportion of patients who have not yet experienced a defined censoring event at time t (Smith et al., 2023, p. 455-456). Censoring events can include patient mortality, loss of the patient to follow-up, revision, or closure of data collection. Here revision refers to revision total knee surgery. Revision total knee surgery is a surgical procedure that involves replacing a previously implanted knee replacement with a new implant, a re-surgery. Revision total knee replacement is often required after surgical complications like infection or implant failure (such as implant loosening or implant instability). A higher revision risk suggests a greater likelihood of a patient requiring revision surgery with a specific knee implant, indicating lower performance compared to an implant with a lower revision risk, where the likelihood of revision surgery would be lower.

Both Wilton et al., 2023b and Phillips & Tucker, 2022 define Camouflage in terms of this definition of revision risk: Camouflage is the masking of poor revision risk performance in some implant variants by the better performance of others within the same brand. Poorly performing variants may have a higher revision risk, but this may be overshadowed by the lower revision risks of high-performing variants.

Defining Revision Risk in This Thesis Context

The above definition of revision risk is not suitable for this thesis, as it implies the use of a time-based survival analysis methodology, which is not suitable in this context as the focus is more cross-sectional with discrete follow-up periods. A modified version of the revision risk is used in this manuscript. **The revision risk R_t is defined as the total number of knee implants which have been revised for a specified time period of follow-up t divided by the total number implanted within this period** (S. J. Kim et al., 2020). Specific time periods used in this thesis are 1, 3, 5, 10, 15, and 20 years of follow-up. This revision risk R_t is considered an attribute of a knee implant variant. Each variant may will have a distinct value of R_t revealing its revision risk performance. This definition of revision risk as a measure of implant performance will be used to define "good" implant variants in the next chapter.

$$R_t = \frac{Number\ of\ implants\ revised\ within\ follow-up\ period\ t}{Total\ number\ implanted\ in\ follow-up\ period\ t}$$

$$Here, R \in [0,100]\ if\ expressed\ in\ percentage$$

Equation 1 Revision risk defined as a probability

2.2.1 *The Repercussions of Camouflage*

Camouflage in knee implants is a serious problem. It can create significant risks for patients and introduce new challenges for healthcare providers. When problematic knee implants are mislabelled as performing as well as the high-performing ones under the same brand, both surgeons and patients can be misled. Surgeons might unknowingly choose these underperforming or problematic implants, putting patients at risk without their informed consent. This situation is unfair to patients, who may be implanted with potentially unsafe implants without proper knowledge of its side effects and risks. This happened in the case of the Nexgen LPS implant variant, where patients were implanted with faulty implants that led to surgical complications (Brown et al., 2021; Keohane et al., 2020, 2022). This issue was only with one implant variant under the Nexgen brand, and other variants displayed good performance according to many surgeons (Wilton et al., 2023a), making it a clear case of Camouflage. Some other severe consequences of Camouflage can also include implant recalls, safety alerts, and increased costs for healthcare organisations and society (Vasiljeva et al., 2020a; Wilton et al., 2023b).

2.2.2 *The Impact of the Medical Device Regulation (MDR) on Camouflage*

The new Medical Device Regulation (MDR) mandates thorough scrutiny of medical devices, especially those classified as “high risk” devices like knee implants, before they can be used for knee surgery or total knee arthroplasty (Fraser et al., 2021). The MDR is a successor regulation to the Medical Device Directive (MDD), which initially set the policy framework for regulating knee implants. Under the MDD, knee implant variants could be approved based on the performance of another variant with similar characteristics, without necessarily requiring clinical evidence on their performance for regulatory approval and subsequent surgical use.

However, unlike the MDD, the MDR now requires manufacturers to provide clinical evidence for all variants of knee implants. This means that manufacturers must provide clinical evidence for each implant demonstrating its performance before it can be approved for surgical use (Ecker, 2023). By mandating clinical evidence at the variant level, the MDR reduces the likelihood of the Camouflage effect, where high-performing variants may overshadow those with poorer performance within the same brand. As elaborated in the next section, however, the MDR also introduces some new issues despite its benefit of reducing Camouflage.

2.3 The Medical Device Regulation (MDR)

The Medical Device Directive (MDD) was in force until 2017. However, due to several adverse events in the use of medical devices, the MDD began to be considered outdated and insufficient (Nüssler, 2023). The scandalous cases of metal-on-metal hip implants (Cohen, 2012) and Poly Implant Prothèse breast prostheses (Greco, 2015) spurred on the introduction of the new Medical Device Regulation (MDR) of the EU. This is officially called the “Regulation 2017/745 of the European Parliament and of the Council of 5 April 2017” (Shatrov & Blankart, 2022).

The core difference between the MDD and the MDR is the determination of the benefit-risk profile of a medical device (Wilkinson & van Boxtel, 2020). It includes a new definition of "clinical benefit” and a detailed description of intended clinical benefit during testing. It also mentions clinical benefit in definitions of “clinical performance,” “clinical evaluation,” and “clinical evidence” which is not included in corresponding definitions in the MDD (Wilkinson & van Boxtel, 2020). Overall, the new MDR and its focus on clinical benefits was to ensure “smooth functioning of the internal market” and “high standards of quality and safety to meet common safety concerns.”

2.3.1 *The MDR in the Knee Arthroplasty Context*

Both the MDD and MDR are applicable to implantable medical devices like knee prostheses too. For the MDD, the Council Directive 93/385/EEC (Directive, 1990) specifically looked at active implantable devices like knee prostheses. However, it did not always require rigorous testing for all implantable devices, including knee implants. In some cases, approval could be given to a knee system based on literature evidence associated with a “similar device” (Directive 93/42/EEC) (Official Journal of the European Communities, 1993). Here, a “similar device” could also mean a variant of an implant which already has market presence. Consequently, this resulted in Camouflage as discussed in the previous sections. Several devices or variants were released claiming to have equivalence to previously tested devices in the EU and international markets (Vasiljeva et al., 2020a). Consequently, many failed, some quite catastrophically, such as metal-on-metal hip implants (Carr, 2017).

One striking case of camouflage is that of the NexGen LPS knee system by Zimmer Biomet. NexGen had a portfolio of highly successful components and models. However, it had many variants consisting of different combinations of its subcomponents in total knee systems. Some had different femoral components, whereas some had different tibial components. One such combination had a tibial component from having a "flex" design and without the standard polymethylmethacrylate (PMMA) coating. This variant had alarmingly high revision rates due to the loosening of the tibial component after surgery. This issue only garnered attention when clinical and registry evidence signalled possible cause for concern with this variant (Keohane et al., 2020, 2022; Wilton et al., 2023b). In other words, the performance of this variant was "camouflaged" because surgeons earlier reported good outcomes. It had already received necessary regulatory approval because it was in use at the time alarms were raised.

The Medical Device Regulation (MDR), therefore, is an apt response to this concern of camouflage. It does not completely eliminate the possibility of unpredictable or catastrophic events like that of metal-on-meal hip implants, but does put systems in place for:

1. The minimisation of such a risk of such catastrophic events.
2. The assigning of responsibility, mitigation measures, and regulatory netting if it does take place.

2.4 New Issues

However, this new regulatory framework introduces new issues as well. The MDR increases the regulatory and clinical burden on the manufacturer (Wilkinson & van Boxtel, 2020). In fact, the burden of providing:

1. Plan of clinical evaluation
2. Clinical evidence
3. Creating technical documentation
4. Post-market surveillance plans

Even if manufacturers have the necessary resources to carry out this long process, there are no standard tools and methodologies that they can use. The "gold standard" (just like knee arthroplasty is the "gold standard" for end stage knee osteoarthritis) for obtaining clinical evidence in medical science is the randomised clinically controlled trial (RCT). They are used extensively in the case of drugs in the pharmaceutical industry for the approval of new drugs. However, RCTs may not be possible or appropriate for the case of medical devices (Wilkinson & van Boxtel, 2020), especially knee systems. Some reasons for this are the impracticality of an active control group, the risk of not receiving a treatment, and extended follow-up periods (Wilkinson & van Boxtel, 2020). Further implant variants may only be incrementally different, for example just a difference in a coating material for a certain component. This, in most cases, does not warrant another full clinical trial for the whole device.

There are also concerns that the new MDR will hinder innovation in this segment of medical devices. Manufacturers may reduce their product portfolios and reduce incremental innovation that leads to the birth of new variants. Instead, they may focus on compliance with new regulations (Ben-Menahem et al., 2020). This is especially true for small and medium sized manufacturers who have lesser resources than players with a larger market capitalisation (Wagner & Schanze, 2018).

2.5 The Necessity of a New Approach

Initial clinical evidence provided by manufacturers may be sufficient for regulatory approval of knee implants, but this evidence rarely provides a complete picture of the variant's performance. Robust clinical evidence, which does provide this complete picture, typically emerges over time through clinical use and subsequent patient observation. Moreover, variants often lack any external clinical evidence at the time of regulatory approval (Lübbeke et al., 2023b). Consequently, during the regulatory approval process, most stakeholders have limited knowledge of the implant variant's performance beyond the evidence provided by the manufacturers.

Registries also play a part in building a body of evidence surrounding knee implants. They collect, maintain and analyse patient-level arthroplasty information at a national level (Baker et al., 2023a; Hegde et al., 2023). This data is then utilised for tracking implant performance, identifying factors associated with higher revision risks, and facilitating post-market surveillance of certain implants (Hegde et al., 2023; Pijls, 2023). Annual reports published by registries highlight general trends in the field of arthroplasty and report implant performance of selected implants. However, such annual reports are retrospective and rarely cover the performance of all implant variants. Rather, they focus on underperforming variants instead of providing granular information on every implant variant (NJR Implant Scrutiny Committee, 2018). Often, registries analyse implant variants at the brand level, and a brand can contain multiple variants. This leads to Camouflage.

2.5.1 *Limitations of Current Methods for Estimating the Performance of Implant Variants*

Traditionally, a variety of analytical techniques have been used to assess implant performance in the context of knee arthroplasty. These techniques essentially transform clinical data into measurable performance markers such as revision risk. Some of these are survivorship analysis and competing risk techniques like the Cox proportional hazards analysis, etc. (Jonkergouw et al., 2016). Such techniques are extensively used in registry annual reports and other clinical studies assessing implant performance. As such, they are seen as a standard in this context. Most registries' annual reports feature some form of survival analysis (Foster et al., 2020).

These methods, however, are not predictive. They suffice in transforming raw clinical information into measurable metrics like revision risk and as such can be very useful in determining the performance of variants which have extensive associated clinical evidence. If a new variant is released into the market for sale and surgical use, however, these methods cannot be evoked to determine performance because of little associated evidence at the time of release (Pietzsch et al., 2004). Yes, the performance of close variants in terms of characteristics which have some associated evidence can be used to determine the performance of such a new variant using these methods. This has been done before. Implants have been regulated based on the performance of close variants under the Medical Device Directive (MDD) (see sections *The MDD and MDR*, *The MDR in the Knee Arthroplasty Context*). However, doing so results in Camouflage and could generate misleading results about the performance of certain implants, as seen in the section *The Repercussions of Camouflage*.

This calls for a methodology which can estimate the performance of new variants at the time of regulatory approval when clinical evidence related to the variant is seldom available. This would be of immense benefit to the various stakeholders in the approval process and serve as a valuable guide for those who may be unfamiliar with the new implant. Additionally, any existing evidence, be it from a registry report or a clinical study can be incorporated into this estimate to increase its likelihood of displaying the variant's true performance.

Chapter 3 | Methodology

3.1 Research Design

The research question, RQ1, is exploratory in nature. It aims to identify a method for estimating the revision risk performance of knee implant variants using existing clinical data from arthroplasty registries and studies of regulated total knee implants.

According to literature search results, no existing method predicts the revision risk of knee implants based only on the implant and its characteristics. Instead, studies such as those by Devana et al., (2021) and Fernandes et al., (2017) develop predictive techniques for specific outcomes of knee arthroplasty, such as pain, function, and surgical complications like infection, rather than revision risk (Hinterwimmer et al., 2022). These studies also incorporate additional factors such as the surgical method and the patient age (Hinterwimmer et al., 2022; Smith et al., 2023).

Therefore, to address the research question RQ1 and all objectives, this thesis develops a new method to estimate the revision risk performance of knee implant variants under the assumption that the implant itself is the primary factor responsible for revisions in total knee arthroplasty. While other causes of revision exist, this method considers only the impact of the implant's characteristics on revision rates. This assumption is further discussed in the Discussion (Discussion on the Bayesian Method as a Standalone Approach, Beyond the Regulatory Context) and Limitations (Future Work and Limitations) chapters. This methodology section also prioritizes method development over data collection, entry, coding, and exploratory and descriptive statistical methods. This primary focus on developing and implementing a new methodology contrasts with standard quantitative methods outlined by Mertens et al., (2017) and Sekaran & Bougie, (2016) which emphasize data collection and analysis using statistical techniques to test hypotheses. Three objectives help structure this chapter:

1. **OBJ1:** Examine existing data and identify suitable sources of information for developing the method.
2. **OBJ2:** Identify a problem-solving approach for method development such as probabilistic, deterministic, frequentist or a Bayesian approaches. This approach should fulfil certain criteria for the method to be theoretically relevant, as mentioned below.
3. **OBJ3:** Develop and iteratively improving the method by applying the identified approach and respecting the criteria mentioned below.
4. **OBJ4:** Evaluate the method to determine its applicability in regulating knee implant variants.

Criteria to Incorporate Theoretical Context

To ensure that the developed method is both theoretically relevant and addresses the limitations of current methods of estimating implant performance as discussed in the previous chapter, it must meet the following criteria shown below. These criteria are addressed in OBJ3, through elements of them are present across all three objectives.

1. Must use existing information as identified by OBJ1 and must not require the collection or generation of clinical evidence.

2. Must make distinct estimates of revision risk for each implant variant. This ensures that the method is based on the specific characteristics of each variant, allowing for distinct estimates of revision risk and prevent Camouflage.
3. Must be predictive and must make predictions on the performance of any knee implant variant, even a new hypothetical variant which has not been created. This would enable it to potentially be used as a tool during the regulatory approval process for new implant variants, even when clinical evidence for the variant is not yet available.

3.1.1 *Structure of the Methodology Section*

The section *Data Collection* addresses OBJ1, sections *Problem Analysis to Method Development* and *The Bayesian Method for Method Development* address OBJ2. OBJ3 and OBJ4 are addressed in the next chapter. The following figure outlines the general steps taken in this thesis.

3.2 Data Collection

3.2.1 *Selection of Data*

The first objective OBJ1 calls for examining data from arthroplasty registries and studies of regulated knee implants measuring implant performance. This reveals three potential sources of data that could be used for the methodology: 1) Arthroplasty registry data, 2) Registry annual report data, and 3) Medical literature from published refereed journals. The utility and relevance for this thesis are discussed in separate sections. For “examining data” as per OBJ1, some important criteria for the selection of suitable data are put forth below. These criteria can also pave the way for answering RQ1, showing how existing clinical data from arthroplasty registries and studies of regulated knee implants can be used to estimate the performance of implant variants. Criteria:

1. **Adequate granularity** featuring two or more implant characteristics from the total seven characteristics as defined in the section *Characterising Knee Implant Variants*. More characteristics would potentially prove important for developing a method to estimate the performance of implant variants which can be completely defined on the basis of these 7 characteristics.
2. **Implant performance in terms of revision risk**. There are other methods of measuring implant performance like the Knee Society Score (KSS) (Knee Society Score (KSS) for Total Knee Replacement | APTA, n.d.), the Hospital for Special Surgery Scoring system (HSS Hip and Knee Replacement, n.d.), and radiological line analysis but these are highly surgical focussing more on outcomes of knee arthroplasty surgery rather than implant performance. Moreover, assessing the outcome of knee arthroplasty surgery in such a way requires clinical evidence and follow-up with patients, which is not within scope of this thesis.
3. **Feasibility and accessibility** for this thesis project. Obtaining and using this data should fit within thesis timelines and scope.

Arthroplasty registries are organisations that collect surgical information about joint replacements: information about patients, techniques and implants with the goal of monitoring and improving arthroplasty surgery outcomes (Romanini et al., 2021). They include information on hip, knee, shoulder, ankle, wrist and finger arthroplasties (de Reus et al., 2023a; Malchau et al., 2018; Smith et al., 2023). Registries can function at different levels: national, hospital, or regional. National registries, which function at a national or country level, are the most frequently cited in arthroplasty-related studies in literature. This is mostly due to their comprehensive coverage of surgical techniques, implant characteristics, and patient risk factors on a national scale. The data collected at the national level presents a significant advantage: it reflects nationwide patterns in policy, institutional practices, and surgical methods (Baker et al., 2023b). Although this data is detailed and patient-specific, it is obtained from the same population, minimizing the impact of potential differences in ethnicity, culture, and clinical practices on surgical outcomes (J. Liu & Chow, 2002).

Although data from arthroplasty registries are potentially excellent data sources for this methodology due to their granularity and comprehensive coverage (Graves, 2010), most registry data is proprietary and not publicly accessible. This is primarily because the data may contain confidential patient information. Access to such data typically requires a detailed application process which is not feasible within the thesis timeline. One of the first sources of data that was scoped for potential use in this thesis was proprietary registry data from the Dutch Arthroplasty Register, called the Landelijke Registratie Orthopedische Interventies (LROI) in Dutch. The Dutch Arthroplasty Register is the official arthroplasty register of the Netherlands and records, stores, and analyses information about patient-level orthopaedic interventions in the country (Wat Is de LROI?, n.d.). This dataset is owned by the LROI and, like other registry datasets, is not publicly accessible. An application needs to be made along with a research proposal to the Wetenschappelijke adviesraad (WAR) advisory committee of the LROI, and only on approval can this data be used for research. Due to thesis deadlines and potential delays in obtaining this proprietary data, the application was not made arthroplasty registry information was not used in this way.

However, another dataset provided by one of the supervisors also showed great utility for the methodology. It was a proprietary dataset that contained information about different implants used for arthroplasty surgery in the Netherlands aggregated by prosthesis characteristics. In fact, this dataset is quite similar to the dataset that would have been obtained by application to the WAR from the LROI. It fulfils all criteria for this thesis: great granularity with 6 prosthesis characteristics, accessibility and performance is expressed in terms of revision risk. Therefore, this dataset has been selected and used for developing and implanting the methodology.

Registry Annual Report Data

Another important potential source of data are registry reports published by various registries of the world. Registry annual reports are valuable sources of arthroplasty information and are effectively reported outcomes of analyses carried out with the data the registries collect and possess. Annual reports from different registries vary a lot in terms of the variables they collect, the analyses conducted, and the presentation of results in the report (Serra-Sutton et al., 2009). For use in this methodology, an annual report with adequate granularity had to be selected. Some reports were highly granular and reported outcomes of many different prostheses by characteristics, whereas others were not and only general or aggregate results. The Australian National Report was identified as one of the most detailed registry reports by country (Smith et al., 2023) featuring the granularity of two prosthesis characteristics–the femur and tibia components. It fulfilled the other two criteria as well: accessibility because this report is publicly available and implant performance being measured in terms of revision risk. Another potential option was the National Joint Registry (NJR) Annual Report of the UK and Wales (Reed et al., 2023) which also fulfilled all criteria. However, the Australian report was preferred because importing data from this report was more convenient, and it was a good first choice for the methodology. Unfortunately, the Dutch Annual Report (de Reus et al., 2023a) is not granular enough and was not used in the method.

Medical Literature

Medical literature was not used for this thesis because most studies measuring implant performance were not granular enough. Additionally, many studies focussed on other performance measures like the KSS, HSS, etc. more than the revision risks.

Final Selection of Datasets

This method was finally developed using two datasets:

1. Data from the Australian National Registry Annual Report 2023 (Smith et al., 2023). This report contains aggregate information on knee, hip, shoulder, wrist, and ankle arthroplasty surgeries in Australia. This dataset is referred to as the "AOANJRR dataset" henceforth.
2. A proprietary dataset from one of the supervisors. This is knee arthroplasty data from the Netherlands. This is henceforth called the LROI dataset.

As such, data collection from people, patients, or medical personnel is not required and because information from both these datasets will be used, and sampling is not required.

3.2.2 *About the AOANJRR and LROI datasets*

The AOANJRR dataset is in the form of a report published by the Australian National Registry. The Australian National Registry itself collects and owns patient-level information for arthroplasty surgeries in Australia (Home - AOANJRR, n.d.). The owned data is quite granular: it contains details of each surgery with patient information, surgical details, prosthesis characteristics, among others (Smith et al., 2023). As of 2023, there were over 880.000 primary total knee replacements in the country recorded since 2000. The registry therefore maintains a record of these 880.000+ surgeries in its database. Other countries also maintain such arthroplasty databases with the help of their own national registries. These databases are almost always proprietary because they contain confidential patient information (Banerjee et al., 2014).

Registries, with the help of this highly granular, patient-level information, can choose to do a variety of analysis to generate insights on arthroplasty surgeries in the country. Such insights can be about the performance of particular prosthesis variants, about the success of specific surgical techniques, or the consequence of using certain tools during surgery. They later publish these insights in their annual registry reports. This is the case for the AOANJRR registry as well (Smith et al., 2023). Because the registry reports contain the results of the analyses and not patient level information, information contained in these annual reports is at a coarse, super-aggregate level. This contrasts with the datasets possessed by the registries themselves, which is extensive and granular (Rubinger et al., 2023). However, despite its coarse nature, information from the AOANJRR annual report can be used for the Bayesian method developed below.

Figure 1 Granularity of different datasets

The proprietary LROI dataset provided by the supervisors differs from the AOANJRR dataset. Unlike the super-aggregate level of annual report data, this LROI dataset contains information at a finer level of granularity, although it is not at the finest level of granularity as contained in registry databases. Essentially, it is LROI registry data aggregated by prosthesis characteristics. As such, no patient level information can be identified in this dataset. Hence it can be considered a "medium"-aggregate dataset.

3.2.3 *Structure of the AOANJRR Dataset*

The Australian registry has one of the most detailed annual reports in the world. Data is contained within 52 tables within the report covering many different aspects of total knee arthroplasty. As seen in the section *Implementing the Bayesian Method with AOANJRR Data*, tables KT9, KT10 and KT11 and the data contained within them will be used in the developed Bayesian Method. Truncated versions showing the first three rows of tables KT9, KT10 and KT11 are shown below. All three of these consist of 10 columns. The first two columns show two prosthesis characteristics: the femur and tibia name. Two other columns show the number of implants used and the number of implants revised. The others show revision risks along with lower and upper 95% confidence intervals (in brackets) for 1, 3, 5, 10, 15 and 20 years of follow-up. Since these tables only contain two prosthesis characteristics—the femoral and tibial components—implant variants cannot be fully defined. However, there is more granularity compared to implants defined at the brand level. The combination of the femoral and tibial components in the first two columns of the AOANJRR report tables can further subdivide an implant brand into roughly defined implant variants, defined only with the femur-tibia combination. Additional subdivision based on other characteristics could lead to fully defined variants, but this dataset does not allow for that as it only includes two implant characteristics.

1. **Femoral component:** The femoral component that features in the knee implant. This usually includes the brand name.

2. **Tibial component:** The tibial component that features in the knee implant. This usually includes the brand name.
3. **N Total:** The total number of implants that have been used since the inception of the Australian national registry (AOANJRR).
4. **N Revised:** The total number of implants that were revised after primary total knee arthroplasty surgery since the inception of the Australian national registry (AOANJRR).
5. **<X> Yr. Revision (%):** This is a percentage and an indicator of performance. It denotes the mean value of revision risk for an implant with a particular femur-tibia combination. The revision risk is the percentage of implants that underwent revision after primary knee arthroplasty surgery within <X> years of follow-up or those that were lost to follow-up within this period. Here revision refers to revision total knee arthroplasty, where the implant is surgically replaced or removed in its entirety in case of surgical complications, implant failure or poor surgical outcomes like excessive pain and little functional improvement.
6. **Lower and Upper 95% Confidence Intervals:** The lower and upper confidence intervals accompany the mean value of revision risk for each femur-tibia combination. The confidence interval specifies a set having a specified probability of containing the true value of revision risk within it (Smith et al., 2023, p. 455).

Femoral Component	Tibial Component	N Revised	N Total	1 Yr. Revision (%)	3 Yr. Revision (%)	5 Yr. Revision (%)	10 Yr. Revision (%)	15 Yr. Revision (%)	20 Yr. Revision (%)
ACS	ACS Fixed	24	769	1.6 (0.9, 2.8)	2.8 (1.8, 4.3)	3.4 (2.3, 5.1)	No data	No data	No data
ACS	ACS Mobile	43	1492	1.0 (0.6, 1.7)	2.1 (1.4, 3.1)	3.4 (2.5, 4.8)	4.3 (3.1, 5.9)	No data	No data
Active Knee	Active Knee	131	3516	0.9 (0.6, 1.3)	2.6 (2.1, 3.2)	3.5 (2.9, 4.3)	5.4 (4.4, 6.4)	7.4 (5.1, 10.7)	No data

Table 3 Table KT9 of the AOANJRR Annual Report Showing Cumulative Percent Revision Along with Lower and Upper 95% Confidence Intervals of Cemented Primary Total Knee Replacement by Prosthesis Combination

Femoral Component	Tibial Component	N Revised	N Total	1 Yr. Revision (%)	3 Yr. Revision (%)	5 Yr. Revision (%)	10 Yr. Revision (%)	15 Yr. Revision (%)	20 Yr. Revision (%)
ACS	ACS Fixed	55	1171	1.6 (1.0, 2.5)	3.9 (2.9, 5.2)	4.6 (3.5, 6.1)	6.0 (4.6, 7.9)	No data	No data
Active Knee	Active Knee	588	4896	1.4 (1.1, 1.7)	4.0 (3.4, 4.5)	5.6 (5.0, 6.3)	9.6 (8.8, 10.5)	13.4 (12.3, 14.5)	16.3 (14.8, 17.9)
Apex Knee CR	Apex Knee	28	508	2.3 (1.3, 4.1)	5.2 (3.5, 7.6)	5.6 (3.9, 8.2)	6.2 (4.3, 8.9)	No data	No data

Table 4 Table KT10 of the AOANJRR Annual Report Showing Cumulative Percent Revision Along with Lower and Upper 95% Confidence Intervals of Uncemented Primary Total Knee Replacement by Prosthesis Combination

Femoral Component	Tibial Component	N Revised	N Total	1 Yr. Revision (%)	3 Yr. Revision (%)	5 Yr. Revision (%)	10 Yr. Revision (%)	15 Yr. Revision (%)	20 Yr. Revision (%)
ACS	ACS Fixed	68	1528	1.3 (0.8, 2.0)	3.8 (2.9, 4.9)	4.5 (3.5, 5.8)	No data	No data	No data
Active Knee	Active Knee	165	2324	0.6 (0.4, 1.1)	2.8 (2.2, 3.5)	3.8 (3.1, 4.7)	6.8 (5.7, 8.0)	10.4 (8.8, 12.4)	No data
Advance	Advance II	24	428	0.7 (0.2, 2.2)	2.4 (1.3, 4.4)	3.4 (2.0, 5.7)	5.3 (3.4, 8.1)	6.8 (4.5, 10.3)	No data

Table 5 Table KT11 of the AOANJRR Annual Report Showing Cumulative Percent Revision Along with Lower and Upper 95% Confidence Intervals of Hybrid Primary Total Knee Replacement by Prosthesis Combination

3.2.4 *Structure of the LROI Dataset*

The LROI dataset is nothing but patient level information from the LROI aggregated by prosthesis characteristics: femur name, tibia name, stability method used, mobility, patella use, and stability. This dataset does not contain any patient information and as such no such information can even be deduced with it. It is the same information as contained in the LROI registry database which is used to produce LROI annual reports, albeit older and with patient characteristics removed. The first three rows of this dataset are shown in Table 6.

The dataset itself consists of multiple rows and 13 columns. Each row represents an implant variant that has been utilised for knee arthroplasty surgery in the Netherlands. The first six columns consist of implant characteristics while the other columns provide information on the number of implants used since the start of the registry data collection, along with the mean and standard deviation of revision risks for each variant at 3, 5, and 10 years of follow-up.

7. **Femur:** The femoral component that features in the knee implant variant. This usually includes the brand name.
8. **Tibia:** The tibial component that features in the knee implant variant. This also typically includes the brand name.
9. **Fixation:** The type of fixation used in the knee implant variant. The types of fixation are cemented, uncemented and hybrid.
10. **Mobility:** This refers to the type of bearing design that the knee implant variant uses. It can be of types fixed bearing, mobile bearing, and rotating platform.
11. **Patella Usage:** This refers to if a patella has been used in the knee implant variant.
12. **N Implants:** The total number of variants that have been implanted since the inception of the Dutch national registry (LROI).
13. **<X> Year Revision:** This is a percentage and an indicator of performance. It denotes the mean value of revision risk for a particular implant variant. The definition of revision risk and revision remains the same as for the AOANJRR dataset.
14. **<X> Year SD:** This is also a percentage. It is the standard deviation of the revision risk specified above within <X> years of follow-up.

Femur	Tibia	Fixation	Mobility	Patella Usage	Stability	N implants[1]	3 Yr. Revision (%)	3 Yr. SD[2] (%)	5 Yr. Revision (%)	5 Yr. SD (%)	10 Yr. Revision (%)	10 Yr. SD (%)
ProsF 1	**ProsT 2**	Cemented	Fixed[3]	No patella	MS[4]	522	3.5	0.6	4.9	0.5	6.1	0.6
ProsF 1	**ProsT 2**	Cemented	Fixed	Patella present	MS	252	1.7	1.1	4.2	2.2	3.8	2.2
ProsF 1	**ProsT 2**	Cemented	Fixed	No patella	MS	15	25	30.6	60	33.9	No data	No data

Table 6 The LROI dataset in raw form (truncated and some terms have been abbreviated), DUMMY DATA ONLY

[1] N Implants: Number of Implants used
[2] SD: Standard Deviation
[3] Fixed: Fixed Bearing design
[4] MS: Minimally Stabilized

3.3 Problem Analysis to Method Development

The preceding section identified the AOANJRR and LROI datasets for method development, contributing to the achievement of OBJ1. This section addresses both OBJ2 and OBJ3 by identifying a suitable problem-solving approach for method development and then applying this approach to develop the method. The criteria for incorporating the theoretical context in the has also been used.

3.3.1 *Initial Considerations for Method Development*

Incorporation of Implant Characteristics into the Method

Variants were also defined by seven implant characteristics. The combination of these characteristics differentiates one variant from another, even within the same brand. Incorporating these characteristics into the method would yield distinct performance metrics for each variant. This approach is essential for progressing further, beyond the Camouflage effect, where a single performance metric represented an entire brand of implants. Additionally, manufacturers often develop and create implants with incremental improvements compared to their predecessors, resulting in new implant variants that are closely related to already regulated ones, sharing many similar characteristics (Ahmad et al., 2015; Williams et al., 2010). Therefore, incorporating these characteristics into the method can be of advantage as it ensures that new variants reflect their own, distinct performance metric, even if it differs from that of other variants within the same brand. This method would address RQ2 and assist decision-making at the regulatory stage for new variants by estimating their potential performance without the need for clinical evidence. If the method cannot differentiate between variants, it would revert to the limitations of the MDD regulation, where implant variants were approved based on the performance of similar variants.

Definition of "Good" Implant Variant Performance

RQ2 calls for methods to support decision-making for the approval of variants in a regulatory context. To develop such a method addressing RQ2, it is necessary to define "good" variants according to regulatory specifications. An implant variant is considered "good" if its revision risk remains below threshold values of revision risk commonly accepted by regulators, surgeons, and the arthroplasty field in general. If this threshold value for a period of follow-up t is τ_t, then an implant variant is considered good if:

$$R_t < \tau_t$$

Threshold values specified by the Orthopaedic Data Evaluation Panel (ODEP) (Methodology for Total Knees, 2020) can be used because they are commonly used in the field of arthroplasty as a measure of implant performance in the (Hoogervorst et al., 2024; Malviya et al., 2017). The ODEP is an organisation which rates implants based on clinical evidence from registries and that submitted by manufacturers (Hoogervorst et al., 2024). Benchmarks set by the ODEP are often used for the monitoring of various implants (Samaniego Alonso et al., 2018). For an implant variant to achieve the A* rating from ODEP, it needs to have a revision risk less than 3.5% at 3 years of follow-up. Mathematically, this is $(R_t < \tau_t)$ and $t = 3$ years. According to the criteria ODEP A* total knee implants each value of t has a particular value of τ as shown in Table 7.

Years t	Associated τ (%)
1	3.00
3	3.50
5	4.00
10	5.00
15	6.50
20	8.00

Table 7

If the method can reveal, in its results, whether the revision risk of a variant is less than this ODEP threshold for a period of follow-up, it can effectively indicate whether this variant would be good enough for use in a surgical context according to regulators, surgeons and patients alike.

A binary variable Y_t will be used to denote good performance associated with a knee implant variant for a period of follow-up t. A value of 1 would indicate that the implant variant displays good performance, whereas a value of 0 would indicate that the implant underperforms as per ODEP thresholds. This is shown below:

$$Y_t = \begin{cases} 1 & if \quad R_t < \tau_t \\ 0 & if \quad R_t \geq \tau_t \end{cases}$$

Equation 2 Binary Variable Defining Good Implant Variant Performance

3.3.2 *The Argument for a Non-Deterministic Method: Uncertainty*

An implant variant has been defined as the combination of seven characteristics, and an appropriate inference about the performance of an implant variant would be how its revision risk compares to a threshold value. This is given by Y_t as per Equation 2. The method to be developed should yield such an inference while incorporating these seven characteristics. It is assumed that implant characteristics impact whether an implant meets regulatory thresholds, and specific combinations of characteristics may determine if an implant meets or fails to meet these thresholds in terms of revision risk. If meeting regulatory thresholds is considered an event, any deterministic statement would suggest that certain combinations of characteristics would always lead to this event, and the same combinations would consistently produce similar outcomes (Soltani & Moayyeri, 2007). However, this is not the case.

There is considerable uncertainty involved in the revision risk of an implant, with many other factors influencing this risk beyond the implant's characteristics (Zhang et al., 2016). Here inductive reasoning can be suitable for explaining implant performance, as it can demonstrate that the presence of particular characteristics makes the occurrence of the event highly likely with high inductive probability, and not certainty. Uncertainty is inherent in the context of surgery and knee arthroplasty because one there could be many interacting factors that could influence implant performance (Hunink et al., 2001; Jacob, 2000). The degree of uncertainty can be expressed in terms of probability to quantify this uncertainty (Soltani & Moayyeri, 2007). Implant variant performance can therefore be defined in terms of probability making the result of the methodology non-deterministic. The method that will be developed should yield the probability of the revision risk meeting regulatory thresholds at specific periods of follow-up:

$$P(Y_t = 1)$$

3.3.3 *The Argument for a Bayesian Probabilistic Method*

Probabilistic methods can be classified as either frequentist or Bayesian (Pek & Van Zandt, 2020a). Frequentist methods interpret probabilities as the long-term frequency of events occurring across repeated independent trials. Conversely, Bayesian approaches interpret probabilities as the degree of belief in an event based on the available information (Vallverdú, 2008). In evaluating performance as the probability of revision falling below specific thresholds, a Bayesian approach is more appropriate. This is because Bayesian methods treat the revision risk as a random variable that can change with new evidence, rather than as a fixed but unknown parameter (Winkler, 2001). New evidence, such as prosthesis characteristics, can be incorporated into the Bayesian method, allowing for the inclusion of multiple characteristics. Prior information from datasets can also be effectively integrated into a Bayesian approach, which is not possible with a frequentist approach which tend to disregard such evidence (Gleason & Harris, 2019). Frequentist approaches are traditionally used with techniques like hypothesis testing which result in robust, specific conclusions from a large body of evidence (Bendtsen, 2018) such as meta-analyses (Howard et al., 2015). Rather than deriving such concise, specific conclusions about variant performance, this thesis attempts to leverage a Bayesian approach to provide a comprehensive, more generalisable interpretation of implant variant performance given evidence from the two datasets.

3.4 Bayesian Approach for Method Development

A Bayesian approach has been selected as the probabilistic method. In the section *Bayesian Methods: A General Overview*, some concepts of Bayesian thinking are put forth.

3.4.1 ***Bayesian Approach in the Context of Knee Arthroplasty***

The Bayesian approach is a set of statistical techniques helpful in the interpretation of probabilities. As seen in the previous section, it is different from the frequentist approach, a more traditional form of probability reasoning (Kan et al., 2016). While frequentist approaches usually look at the long-term frequency properties of events over repeated trials, Bayesian strategies incorporate prior information and update probabilities as new data becomes available (Pek & Van Zandt, 2020b; Zyphur & Oswald, 2015). This probabilistic approach involves representing quantities with probability distributions. Quantities, also called variables, are essentially the mathematical representation of events related to the subject of the study. These can be both events that are to be estimated or predicted (dependent variables) or other events related to the subject of the analysis. In the case of total knee arthroplasty and this thesis, the subject of analysis is the revision risk performance of knee implant variants given by Y_t. Bayesian methods express values in terms of probabilities making this term $P(Y_t = 1)$.

Bayesian thinking also allows the conditioning of unknown events on other known events. These "unknown" events can be phenomena for which there is little information available; those which are "hidden" or "unobservable" (Grover, 2012, p. 59). Known events serve as evidence which can help make informed estimations of the unobservable events. Bayesian approaches have been used extensively in both medical and pharmacological sciences. It has many applications: from the planning and analysis of clinical trials (Chow et al., 2012; Edwards et al., 2024a; J. P. Liu et al., 2002; Schmidli et al., 2014a, 2014b; Schnell-Inderst et al., 2017; Tsou et al., 2012; Weber et al., 2019) to effective clinical diagnosing (Athanasiou & Darzi, 2011, p. 156).

The Bayes Theorem in the form of *Equation 5 Bayesian Equation for the Performance of a Total Knee Implant* results in a $posterior$ which reflects an updated belief on the performance, in light of the implant characteristics. Initial belief about implant performance is reflected in the prior assumption, an initial belief as to how the implant will perform. The posterior, therefore, is just the prior which has been updated in light of new "evidence" of known implant characteristics. Since the performance is defined in terms of the implant's revision risk meeting regulatory thresholds, the $prior$ is the probability that the implant meets regulatory limits, and the $posterior$ is the probability that the implant meets regulatory limits *given* its characteristics. The $posterior$ is calculated according to the Bayes' Theorem (Equation 4). Each term on the right side of the equation is calculated in order to obtain the posterior: the prior, the likelihood and the denominator (henceforth called normalising constant).

The core engine of the Bayesian approach is Bayes' Theorem, which is universally applicable regardless of context. Bayes' theorem consists of the four terms: the prior, posterior, likelihood, and normalizing constant. The posterior is the output of the Bayesian method representing a final belief about the quantity to be estimate in terms of a probability distribution (Edwards et al., 2024b; Schmidli et al., 2014c). In this context it would represent an *updated estimate* of $P(Y_t = 1)$ by incorporating information from the two datasets. This is the probability of whether an implant variants' revision risk meets the regulatory threshold at a specific period of surgical follow-up. The calculation of the posterior requires the determination of each of the other terms in Bayes' Theorem: the prior, likelihood and the normalising constant while also integrating the information from the two datasets, ensuring that the posterior reflects the performance of the implant variant. The prior, in contrast to the posterior, represents an initial belief about the variable to be estimated (Edwards et al., 2024b; Schmidli et al., 2014c). This belief can be expressed again as a probability distribution, representing a range of probable values for the variable and the likelihood of each value (Held & Bové, 2020). Initially, both the prior and the posterior are assumed to be a single point estimates, but as the method is refined, they evolve into a Beta distributions.

3.4.2 *Informative Priors: from Probability to Probability Distribution*

A point estimate is a variable that takes a single value. In the Bayesian method, both priors and posteriors are initially treated as point estimates. This approach is later refined to a distribution as the Bayesian method is iteratively developed, with the variable changing from Y_t, a point estimate, to just the revision risk of a variant R_t, which is a distribution. Unlike a point estimate, a distribution assumes the variable to be a continuous random variable, representing a Probability Density Function (PDF). If the revision risk is a random variable R_t with its own distribution, it allows for the incorporation of more information into the method, making the posterior more informative, ultimately providing a broader understanding of the performance and revision risk of implant variants. The chosen distribution here is the Beta distribution, which ranges from 0 to 1. A Beta-distributed variable (R_t in this case) has a fixed probability of taking any sub-range of values within the distribution, as indicated by the area under the curve (Thomopoulos et al., 2018). The Beta distribution, as demonstrated later, can help incorporate certain aspects of the datasets, such as confidence intervals. However, the Bayesian method initially uses point estimates and only later evolves iteratively to incorporate distributions.

3.4.3 *The Bayes' Theorem*

Bayes' Theorem is key to the Bayesian approach. It is the core engine for the computation of the posterior with the help of other Bayesian terms. It essentially allows the update of priors to obtain the posterior (Edwards et al., 2024b; Zyphur & Oswald, 2015). The Bayes' theorem is shown below:

$$P(A|B) = \frac{P(B|A) \cdot P(A)}{P(B)} \; where \; P(B) \neq 0$$

Equation 3 Bayes' Theorem

$$posterior = \frac{likelihood \times prior}{normalising \; constant}$$

Equation 4 Bayes' Theorem in General Form

Here $P(A|B)$ refers to the probability of event A given that event B has already occurred. It is also called conditional probability. $P(B|A)$ refers to the probability of event A happening given even B and is also called the likelihood. $P(A)$ and $P(B)$ refer to the probabilities of these individual events.

In this context the event A can be the event of a knee implant variant displaying good enough performance given by $P(Y_t = 1)$. Event B can be new information related to the implant from the datasets. In this case, this new information is taken to be one or more implant characteristics. Fixation, for example, is an implant characteristic which specifies the method by which prosthetic components are fixed to a patient's bone during total knee arthroplasty surgery. Types of fixation can be cemented fixation, uncemented fixation and hybrid fixation. This can be represented by $F_{cemented}$, $F_{uncemented}$ and F_{hybrid} respectively. If the event B represents the event of an implant having a particular fixation type F, events A and B become:

$$A: P(Y_t = 1)$$

$$B: F$$

Therefore, the Bayesian equation becomes:

$$P(Y_t = 1 \mid F) = \frac{P(F \mid Y_t = 1) \cdot P(Y_t = 1)}{P(F)}$$

Equation 5 Bayesian Equation for the Performance of a Total Knee Implant with One Characteristic, the Fixation Type

For an implant variant with a cemented fixation type and at a follow-up period of 3 years, $F = F_{cemented}$ and $t = 3$ years. The Bayesian equation then becomes:

$$P(Y_3 = 1 \mid F_{cemented}) = \frac{P(F_{cemented} \mid Y_3 = 1) \cdot P(Y_3 = 1)}{P(F_{cemented})}$$

3.4.4 *Developing the Bayesian Method*

The next chapter *The Bayesian Method Implemented* finally develops the Bayesian Method and obtains $posteriors$ with the help of information from the two datasets. This section also refines this Bayesian method in stages: An initial method is first developed and implemented with the AOANJRR dataset. This method is then iteratively refined by making small enhancements that help make the results (in the form of the $posterior$) more meaningful. Assumptions made are also modified. Enhancements are described in the sections themselves. The sections which show this iterative refinement are linked below:

1. *Operationalisation*
2. *Implementing the Bayesian Method with the AOANJRR Dataset*
3. *Bayesian Method Using Upper Limit Values and AOANJRR Data*
4. *Bayesian Method Using Mean Values and LROI Data*
5. *Bayesian Method Using Upper Limit Values and LROI Data*
6. *Bayesian Method Using Mean Values, LROI Data, and Two Implant Characteristics*
7. *Bayesian Method Using Mean Values, LROI Data, and Three Implant Characteristics*

These sections will provide a step-by-step account of the iterative improvements made to the Bayesian method, highlighting how each enhancement contributes to more accurate and meaningful posterior calculations. From the fourth iteration confidence intervals have been incorporated. This is accompanied by a slight change in the definition of implant variant performance and the results produced by posterior calculations.

Chapter 4 | The Bayesian Method Implemented and Results

4.1 Operationalisation

In this implementation, as mentioned in the previous section, the posterior is calculated by evaluating each prior, likelihood, and the normalising constant. This section operationalises using generic calculations without the datasets. Later, the datasets are introduced, and results are obtained based on the calculations in this section.

4.1.1 *Terms of the Bayesian Equation*

The calculation for each of the Bayesian Equation terms is shown below for an implant with one characteristic: the fixation type F at a period of follow-up t.

1. **The *posterior*** is given by the term $P(Y_t = 1 \mid F)$. This term is the result of the Bayesian method, and it can be calculated using Equation 5.

2. **The *prior*** is given by the term $P(Y_t = 1)$. It is an initial estimate of whether the variant meets the regulatory threshold for t years of follow-up and is calculated without using the datasets. Since it is a probability, it is simply the ratio of implants meeting this regulatory threshold (for which $Y_t = 1$) and the total number of implants considered. This is given by:

$$prior = \frac{Count(Implants\ with\ revision\ risk < threshold\ at\ follow-up\ period\ t)}{Count(Total\ number\ of\ implants\ considered\ at\ follow-up\ period\ t)}$$

Equation 6 Prior Calculation

3. **The *likelihood*** is expressed by $P(F \mid Y_t = 1)$ and is the probability of an implant variant having a particular method of fixation given that its revision risk meets regulatory the regulatory threshold at t period of follow-up. Out of the total number of variants considered, the likelihood is the number of variants which meet the regulatory threshold *and* have the particular method of fixation at t follow-up period divided by the total number of implants considered. Mathematically the likelihood term can be expanded using the rule of conditional probability:

$$likelihood = P(F \mid Y_t = 1) = \frac{P(F \cap (Y_t = 1))}{P(F)}$$

$$= \frac{Count(Implants\ with\ fixation\ F\ AND\ having\ revision\ risk < threshold\ at\ t)}{Count(Total\ number\ of\ implants\ considered\ at\ t)}$$

Equation 7 Likelihood Calculation

4. **The *normalising constant* (NC)** is the probability of the implant variant having a particular method of fixation out of all the implant variants considered.

$$P(F = cemented) = \frac{Count(Implants\ with\ Fixation\ F\ at\ t)}{Count(Total\ number\ of\ implants\ considered\ at\ t)}$$

Equation 8 Normalising Constant Calculation

4.2 Implementing the Bayesian Method with the AOANJRR Dataset

The Bayesian Method has been implemented using the AOANJRR dataset in this section. This method yields the probability of an implant variant with a particular method of fixation meeting regulatory thresholds at 1, 3, 5, 10, 15, and 20 years of follow-up. Only the mean values will be taken into account for the calculation of each of the Bayes' Theorem terms. In tables KT9 to KT11, the mean value is the decimal number outside of the brackets in each cell. Additionally, missing data from these tables is not considered. For now, only one the implant characteristic fixation has been used.

The total number of implants considered were all the implants featured by distinct prosthesis characteristics (femur and tibial components) in tables KT9 to KT11. There were a total of 390 cemented implants, 177 uncemented implants, and 204 hybrid implants.

$$Total\ number\ of\ implants\ considered = Total\ number\ of\ implants\ given\ in\ tables\ KT9\ to\ KT11$$

4.2.1 *Calculating the Prior*

The prior is calculated according to Equation 6 for six values of t: 1, 3, 5, 10, 15, and 20 years of follow-up. Since the prior does not depend on the fixation, it remains the same for all fixations.

4.2.2 *Calculating the Likelihood*

The likelihood is calculated according to Equation 7 for all six values of t.

4.2.3 *Calculating the Normalising Constant*

The NC is obtained using Equation 8.

4.2.4 *Obtaining the Posterior*

The result, the $posterior$, is obtained using Equation 8 using all the values of the prior, likelihood and NC. The results are shown in Table 7.

4.2.5 *Posterior*

Years t	Threshold (%) τ	Fixation type	Prior (%)	Likelihood (%)	NC (%)	Posterior (%)	Posterior – Prior (%)
1	3.00	Cemented	98.18	51.85	51.82	98.25	0.07
3	3.50	Cemented	75.23	56.1	52.29	80.7	5.47
5	4.00	Cemented	63.81	62.69	53.33	75	11.19
10	5.00	Cemented	45.68	64.86	49.38	60	14.32
15	6.50	Cemented	50	48	44	54.55	4.55
20	8.00	Cemented	39.13	55.56	52.17	41.67	2.54
1	3.00	Uncemented	98.18	20.37	20.91	95.65	-2.53
3	3.50	Uncemented	75.23	14.63	21.1	52.17	-23.06
5	4.00	Uncemented	63.81	8.96	20	28.57	-35.24
10	5.00	Uncemented	45.68	13.51	25.93	23.81	-21.87
15	6.50	Uncemented	50	16	24	33.33	-16.67
20	8.00	Uncemented	39.13	11.11	21.74	20	-19.13
1	3.00	Hybrid	98.18	27.78	27.27	100	1.82
3	3.50	Hybrid	75.23	29.27	26.61	82.76	7.53
5	4.00	Hybrid	63.81	28.36	26.67	67.86	4.05
10	5.00	Hybrid	45.68	21.62	24.69	40	-5.68
15	6.50	Hybrid	50	36	32	56.25	6.25
20	8.00	Hybrid	39.13	33.33	26.09	50	10.87

Table 8 Posterior for the Bayesian Method with the AOANJRR Dataset

4.2.6 *Results of this Iteration of the Method*

This method, when implemented with the AOANJRR dataset, generates results as the probability of the implant being "good". This is the first iteration, and this method will be refined in further iterations. The posteriors in

Years t	Threshold (%) τ	Fixation type	Prior (%)	Likelihood (%)	NC (%)	Posterior (%)	Posterior – Prior (%)
1	3.00	Cemented	98.18	51.85	51.82	98.25	0.07
3	3.50	Cemented	75.23	56.1	52.29	80.7	5.47
5	4.00	Cemented	63.81	62.69	53.33	75	11.19
10	5.00	Cemented	45.68	64.86	49.38	60	14.32
15	6.50	Cemented	50	48	44	54.55	4.55
20	8.00	Cemented	39.13	55.56	52.17	41.67	2.54
1	3.00	Uncemented	98.18	20.37	20.91	95.65	-2.53
3	3.50	Uncemented	75.23	14.63	21.1	52.17	-23.06
5	4.00	Uncemented	63.81	8.96	20	28.57	-35.24
10	5.00	Uncemented	45.68	13.51	25.93	23.81	-21.87
15	6.50	Uncemented	50	16	24	33.33	-16.67
20	8.00	Uncemented	39.13	11.11	21.74	20	-19.13
1	3.00	Hybrid	98.18	27.78	27.27	100	1.82
3	3.50	Hybrid	75.23	29.27	26.61	82.76	7.53
5	4.00	Hybrid	63.81	28.36	26.67	67.86	4.05
10	5.00	Hybrid	45.68	21.62	24.69	40	-5.68
15	6.50	Hybrid	50	36	32	56.25	6.25
20	8.00	Hybrid	39.13	33.33	26.09	50	10.87

Table 8 indicate the probability of revision risk being below the threshold value given that they have the particular characteristic F.

Overall, the posterior probabilities generally reduce for increasing years of observation. This is true for all cemented, uncemented, and hybrid. Highest probabilities are for $t = 1$ year of follow-up. Interestingly, for uncemented implants the probability that revision risk below the threshold falls dramatically from 1 to 3 years. The difference between the posterior and prior is positive for cemented implants, negative for uncemented implants, and generally positive for hybrid. Its magnitude, however, is generally the greatest for uncemented implants.

4.3 Bayesian Method Using Upper Limit Values and AOANJRR Data

In the AOANJRR data, like in most registries, there is a confidence interval specified along with mean values. They include two terms: an upper and a lower confidence interval, creating a set of possible values for a summary measure (Smith et al., 2023). The true value of the measure has a fixed probability of being inside this set. Usually, this probability is 95% (Lettin et al., 1991; Nelissen et al., 1992). Confidence intervals are used extensively in registry reports such as the Dutch Arthroplasty Annual Report (LROI) (de Reus et al., 2023b) and that of the UK and Wales (Reed et al., 2023). The 95% confidence interval is also standard in literature studies of knee arthroplasty, such as that used by (Bae et al., 2012) and has statistical roots (Lettin et al., 1991; Nelissen et al., 1992).

The International Society of Arthroplasty Registries recommends a “superiority approach” based on the upper limits of confidence intervals to select benchmarked prostheses with the lowest rates of revision (International Prosthesis Benchmarking Working Group Guidance Document, 2018; Smith et al., 2023). Implementing the Bayesian method with upper limits provides a different set of results in accordance with this superiority approach. The results of the implementation of this method using upper limits are shown below.

Improvement from the previous method

The upper limit values have been used instead of the mean values from the AOANJRR dataset tables.

4.3.1 *Posterior*

Years t	Threshold (%) τ	Fixation type	Prior (%)	Likelihood (%)	NC (%)	Posterior (%)	Posterior - Prior (%)
1	3.00	Cemented	88.18	52.58	51.82	89.47	1.29
3	3.50	Cemented	52.29	64.91	52.29	64.91	12.62
5	4.00	Cemented	43.81	65.22	53.33	53.57	9.76
10	5.00	Cemented	29.63	50	49.38	30	0.37
15	6.50	Cemented	32	37.5	44	27.27	-4.73
20	8.00	Cemented	34.78	50	52.17	33.33	-1.45
1	3.00	Uncemented	88.18	18.56	20.91	78.26	-9.92
3	3.50	Uncemented	52.29	12.28	21.1	30.43	-21.86
5	4.00	Uncemented	43.81	10.87	20	23.81	-20
10	5.00	Uncemented	29.63	20.83	25.93	23.81	-5.82
15	6.50	Uncemented	32	25	24	33.33	1.33
20	8.00	Uncemented	34.78	12.5	21.74	20	-14.78
1	3.00	Hybrid	88.18	28.87	27.27	93.33	5.15
3	3.50	Hybrid	52.29	22.81	26.61	44.83	-7.46
5	4.00	Hybrid	43.81	23.91	26.67	39.29	-4.52
10	5.00	Hybrid	29.63	29.17	24.69	35	5.37
15	6.50	Hybrid	32	37.5	32	37.5	5.5
20	8.00	Hybrid	34.78	37.5	26.09	50	15.22

Table 9 Posterior for the Bayesian Method with the AOANJRR Dataset Using Upper Limit Values

4.3.2 *Results of this Iteration of the Method*

This method uses the upper limit of the 95% confidence interval from the dataset instead of the mean. It generates results in the same form as the previous iteration of the method in the form of a probability of the implant being “good” and results are consistent with that of the previous iteration.

The posterior probabilities are lesser than that of the method using mean values (section *Implementing the Bayesian Method with AOANJRR Data*). Otherwise, many of the results follow similar patterns as those in the last section, like the reducing posterior magnitude for increasing years of follow-up. Additionally, similar to the previous method, there is an unusual drop in values from 1 year to 3 years of follow-up for both uncemented and hybrid implants. The difference between the prior and the posterior is largely the same but are more mixed than that in the previous method. For example, the cemented implants show a reduction in the posterior compared to the prior at 15 and 20 years of follow-up which was not the case in the previous method.

4.4 Bayesian Method Using Mean Values and LROI Data

In this section, the Bayesian method is implemented with the LROI dataset as well first with mean values, as in this section and later with upper limit values. Mean values given in the columns 3yearrevision, 5yearrevision, and 10yearrevision are used for obtaining the posterior.

Improvement from the previous method
The LROI dataset is used for this iteration with mean values.

4.4.1 *Posterior*

Years t	Threshold (%) τ	Fixation type	Prior (%)	Likelihood (%)	Normalising constant (%)	Posterior (%)	Posterior - Prior (%)
3	3.50	Cemented	63.81	54.98	56.63	61.95	-1.86
5	4.00	Cemented	58.41	57.07	58.41	57.07	-1.34

Table 10 Posterior for the Bayesian Method with the LROI Dataset Using Mean Values, REDACTED

4.4.2 *Results*

The posteriors for the implants show much less variation in magnitude and in the pattern of increase or decrease compared to the AOANJRR dataset. Whether the posterior increases or decreases relative to the prior remains generally consistent across all years for cemented, uncemented and hybrid implants. However, in contrast to the previous method, the posterior for cemented implants generally decreases, while for uncemented and hybrid implants, they generally increase. For the AOANJRR dataset, the posteriors for cemented implants decreased and for uncemented implants, they increased relative to the prior.

4.5 Bayesian Method Using Upper Limit Values and LROI Data

As done with the AOANJRR dataset, the posterior in this next iteration is calculated using the upper limit values instead of mean values. The LROI dataset contains data in the form of mean (μ) and standard deviation (σ) values instead of confidence intervals for each variant (row) in the dataset. Lower and upper limit values for each t is deduced by making a normal assumption using the following formula:

$$lower\ limit = \mu - 2\sigma$$

$$upper\ limit = \mu + 2\sigma$$

The lower and upper limits are obtained for each row in the LROI dataset and for each value of t. Bayesian calculations with the upper limit are then done using the same method as that for the AOANJRR dataset.

Improvement from the previous method

The LROI dataset is used for this iteration with upper limit values.

4.5.1 *Posterior*

Years t	Threshold (%) τ	Fixation type	Prior (%)	Likelihood (%)	Normalising constant (%)	Posterior (%)	Posterior – Prior (%)
3	3.50	Cemented	53.59	51.55	56.63	48.78	-4.81
5	4.00	Cemented	46.18	53.64	58.41	42.41	-3.77

Table 11 Posterior for the Bayesian Method with the LROI Dataset Using Upper Limit Values, REDACTED

4.5.2 *Results*

The difference between the posterior and the prior follows largely a similar pattern as the method with the LROI dataset and mean values, but the magnitude of this difference is larger for all characteristic types. The posteriors for cemented implants decrease relative to the prior, while they increase for uncemented and hybrid implants.

4.6 Bayesian Method Using Upper Limit Values, LROI Data and Two Implant Characteristics

The LROI dataset allows for the incorporation of multiple characteristics. The Fixation type was used as a characteristic in all the previous methods. In this method, a new characteristic, Mobility (M) is incorporated along with Fixation (F). The Bayesian equation and each terms' calculation change to include the new characteristic M for each t. This means that the posterior is an updated estimate of the revision risk after the incorporation of both the Fixation and Mobility characteristics of a variant. The prior remains the same, but "new information" of two implant characteristics is used to condition it. There are 27 different combinations of characteristics F, M and time t, evident in the posterior.

Improvement from the previous method

The LROI dataset is used for this iteration with upper limit values, but with two characteristics.

1. **The *posterior*** is given by the term $P(Y_t = 1 \mid F, M)$. This term is the result of the Bayesian method, and it can be calculated using Equation 5.

2. **The *prior*** is given by the term $P(Y_t = 1)$, and remains the same as the method iterations above.

3. **The *likelihood*** is expressed by $P(F, M \mid Y_t = 1)$ and is the probability of an implant variant having a particular combination of Fixation and Mobility types given that its revision risk meets regulatory the regulatory threshold at t period of follow-up. Mathematically the likelihood term can be expanded using the rule of conditional probability:

$$likelihood = P(F, M \mid Y_t = 1)$$
$$= \frac{P\big(F \cap M \cap (Y_t = 1)\big)}{P(F \cap M)}$$
$$= \frac{Count(Implants\ with\ Fixation\ F\ and\ Mobility\ M\ AND\ having\ revision\ risk\ <\ threshold\ at\ t)}{Count(Total\ number\ of\ implants\ considered\ at\ t)}$$

4. **The *normalising constant*** **(NC)** is the probability of the implant variant having a particular method of fixation and mobility out of all the implant variants considered.

$$P(F = cemented) = \frac{Count(Implants\ with\ Fixation\ F\ and\ Mobility\ M\ at\ t)}{Count(Total\ number\ of\ implants\ considered\ at\ t)}$$

4.6.1 *Posterior*

t	τ (%)	Fixation	Mobility	Prior (%)	Likelihood (%)	NC (%)	Posterior (%)	Posterior – Prior (%)
3	3.5	Cemented	Fixed	53.59	30.93	37.02	44.78	-8.81
3	3.5	Cemented	Mobile	53.59	3.09	3.31	50	-3.59
3	3.5	Cemented	Rotating	53.59	17.53	16.3	57.63	4.04

Table 12 Posterior for the Bayesian Method with the LROI Dataset Using Upper Limit Values and Two Characteristics, REDACTED

4.6.2 *Results*

Adding the Mobility characteristic introduces more nuance into the posterior. The prior changes differently for different combinations of Fixation and Mobility. In this case, for instance, there are 9 rows each for cemented, uncemented, and hybrid characteristic types to account for these different combinations. For each Fixation and follow-up t, there are now three associated Mobility characteristics Fixed, Mobile and Rotating with different (Posterior – Prior) values for each. Cemented and Fixed implants show a reduction in the posterior relative to the prior as with in the last method with the cemented characteristic. However, cemented implants with mobile and rotating characteristics generally show an increase in the posterior which contrasts with results from the previous method. For uncemented Fixation implants, there is an increase in the posterior for fixed and rotating characteristics, but a decrease for mobile generally. Most hybrid implants show an increase in the posterior.

4.7 Bayesian Method Using Upper Limit Values and LROI Data and Three Implant Characteristics

The Bayesian Method is next implemented with three characteristics and the posterior is shown below.

Improvement from the previous method

The LROI dataset is used for this iteration with upper limit values and three characteristics.

t	*τ* (%)	F	M	S	Prior (%)	Likelihood (%)	NC (%)	Posterior (%)	Posterior – Prior (%)
3	3.50	Cemented	Fixed	MS	53.59	15.98	14.09	60.78	7.19
5	4.00	Cemented	Fixed	MS	46.18	18.54	14.98	57.14	10.96
10	5.00	Cemented	Fixed	MS	38.39	22.09	16.52	51.35	12.96

Table 13 Posterior for the Bayesian Method with the LROI Dataset Using Upper Limit Values and Three Characteristics, REDACTED

4.7.1 *Results*

There are now 45 different rows for each Fixation characteristic, accounting for different combinations of Mobility and Stability characteristics. Cemented, fixed and posterior stabilised implants show similar results to cemented and fixed implants from the previous method (posterior decrease compared to the prior), but with greater decrease from the prior to the posterior. The difference between the posterior and prior for the cemented, mobile and posterior stabilised implants is also negative. Cemented, fixed and minimally stabilised implants on the other hand, show an increase in the posterior relative to the prior unlike the previous method. If implant combinations with zero likelihoods and NCs are ignored, uncemented implants generally show an increase in the posterior irrespective of Mobility and Stability characters. Hybrid implant combinations generally show mixed results, unlike the previous method where all hybrid implant combinations showed an increase in the posterior relative to the prior.

Chapter 5 | Discussion, Future Work and Limitations

5.1 Key Results of the Bayesian Method: Arthroplasty Literature Perspective

This section discusses some key results of the developed Bayesian method and its alignment to both medical literature and the context of this thesis.

5.1.1 *Results From the Method with AOANJRR Data*

Reducing Priors and Posteriors for Increasing Years of Follow-up for the Method with Point Estimates and the AOANJRR Dataset

One of the first findings of the Bayesian method with point estimates and the AOANJRR dataset are decreasing posterior magnitudes over increasing years of follow-up. This trend is consistent when the method is applied with both the mean values and the upper limits of the 95% confidence interval, and it holds true for all fixation methods: cemented, uncemented, and hybrid. This indicates a decreasing likelihood of an implant with a particular fixation method meeting the regulatory threshold over longer follow-up periods. For example, the probability of a cemented prosthesis having a revision risk below the set threshold is generally lower at 5 years than at 3 years of follow-up. The priors also exhibit a similar trend, decreasing in magnitude with increasing follow-up years.

This result is generally consistent with literature.

One reason could be that more years of follow-up up enable a prosthesis to display its true performance and unfortunately, not many prosthesis *truly* perform as expected. During the initial periods of follow-up like 1 and 3 years, the true performance of a prosthesis may be masked by the quality of surgery, palliative, and post-operative care. Even if the implant underperforms and does not function as expected, this quality of care may delay or prevent revision surgery at these periods. Quality may also include factors like proper patient selection, accurate implant positioning, and optimising modifiable risk factors. These have been directly shown to reduce the incidence of revision and the readmission of patients (Roman et al., 2022; Urish et al., 2020). However, with larger periods of follow-up such as at 5 and 10 years, the actual performance of the implant has a larger effect on the chance of revision. Time since primary knee arthroplasty is an important factor in predicting some outcomes of primary knee arthroplasty like revision, and more time (or a larger follow-up period) leads to worse outcomes for revision (Gandhi et al., 2010).

5.1.2 *Results From the Method with the LROI Dataset*

Large (Unexpected) Linear Deviation for Cemented Implant Variants

The posterior distributions of cemented implant variants deviate significantly from their prior distributions, leading to an increase in the posterior revision risk estimate for these implants. This suggests that a variant with a cemented fixation is less likely to be considered "good" compared to those with uncemented or hybrid fixation. Additionally, the peaks of the posterior distributions for cemented implants are much lower than their prior peaks and are more spread out. In contrast, the peaks for uncemented and hybrid implants are closer to their prior peaks and more concentrated. This indicates a broader potential range of revision risk for cemented implants compared to uncemented and hybrid ones. A higher number of cemented implant variants have a revision risk outside the threshold values than variants with other modes of fixation.

This result is opposite to those obtained from the AOANJRR dataset but proves that this Bayesian method can produce distinct results on the basis of data used and can be used with various data sources. As see below, the results, although surprising, are generally consistent with literature.

These findings are surprising. While numerous systematic reviews and studies show mixed outcomes regarding the revision risk associated with cemented, uncemented, and hybrid implants, none suggest that cemented implants are likely to perform worse than uncemented or hybrid implants (Batailler et al., 2020; Irmola et al., 2020; Y. H. Kim et al., 2014, 2021; Nugent et al., 2019; Stempin et al., 2018). In fact, in the Netherlands, cemented implants are still regarded as the "gold standard" for knee arthroplasty, with the lowest associated revision risks for implants using cemented fixation methods (de Reus et al., 2023a; Humez et al., 2024). There is a dominance of cemented total knee arthroplasty in the Netherlands at 90% of the primary total knee arthroplasty surgeries being cemented (Humez et al., 2024). A higher number of cemented implants would also result in a higher total number of revisions, increasing the revision risk estimate. More so, given this dominance of cemented arthroplasties in the Netherlands, there could be an increased revision risk for cemented implants because of the reasons below:

1. Better quality of uncemented implant surgery and uncemented implants themselves, reducing revision risk of such implants more than cemented ones. Uncemented and hybrid knee arthroplasty is technically more complex than cemented knee arthroplasty, requiring more precise surgical process in the form of accurate bone cuts and implant position (Newman et al., 2020). If performed by inexperienced surgeons such as residents, there is a higher chance of implant and surgical failure (van Es et al., 2022), necessitating revision. However, in the Netherlands, Theelen et al., 2018 have highlighted that both experienced surgeons and residents achieve comparable outcomes for knee surgery in terms of implant positioning and revision risk.
2. Confounding effects of other characteristics like Bearing and Mobility: Implants with the "posterior stabilised (PS)" type of "Ligament" characteristic are known to have a higher revision risk with cemented fixation (van Es et al., 2022). Since nearly half of all knee surgeries in the Netherlands involve PS-type implants and around 90% of these are cemented, this combination of characteristic types increases the revision risk for cemented knee implants.

3. Infection rates, which can necessitate revision, tend to be higher for cemented implants (Nakama et al., 2012; Quispel et al., 2021), thus increasing their revision risk. Even when accounting for debridement, antibiotics, and implant retention (DAIR), which is the process of treating an infection, the revision risk for cemented implants can still be overestimated.

Method with Three Characteristics: Lower Posteriors for PS Implant Variants

Posterior Stabilised (PS) implants, irrespective of other characteristics in the method, consistently show reduced posteriors for almost all combinations of characteristics except uncemented fixed PS and uncemented rotating PS variants. These results are expected and in line with literature. Both Porteous & Curtis, (2021) and Spekenbrink-Spooren et al., (2018) found a greater revision risk for PS implants in the Netherlands. Spekenbrink-Spooren et al., (2018) mention that surgeons' choice of PS or CR implants for patients is largely on the basis of personal preference and training, and greater emphasis on patient characteristics is needed. This might still be the case. The greater incidence of revision for PS knees was more prominent for younger patients, typically less than 60 years of age for a mid-term follow-up period of 8 years. This can explain the increase in the posterior for the uncemented species of PS implants, which is opposite to that of all other PS variants. Uncemented knee implants are often preferred for younger patients because they are thought to last longer and withstand greater mechanical stress, which is more suitable for an active lifestyle (Chen & Li, 2019). Mid-term follow-up for younger patients and uncemented PS variants, therefore, may be better than cemented PS variants, resulting in an increase in the posterior probability that the variants will be "good".

This result is consistent with literature and highlights the advantage of the method with multiple characteristics. This method can make distinct posterior estimates for combinations of characteristics which define a variant, providing more insightful estimates showing how the interplay of characteristics impacts variant performance. More on this line of reasoning is highlighted in the next section.

5.1.3 *Comparison of Dutch and Australian Dataset Results*

Contrasting Posteriors for Cemented, Uncemented and Hybrid Variants

Results of the method with the AOANJRR and LROI datasets can be compared for the method with one characteristic (Fixation) and upper limits. Cemented and hybrid implants show an increase from the prior to the posterior probabilities while uncemented ones show a decrease for the AOANJRR dataset. On the other hand, for the LROI dataset, uncemented and hybrid implants show an increase of the posterior relative to the prior while cemented implants show a decrease.

Dutch arthroplasty circles, including surgeons, often use ODEP ratings and thresholds for the selection of implants, especially hip implants (Poolman et al., 2015; Van Dooren et al., 2024). ODEP ratings for implant influence choice of implant for surgery and making policy decisions such as criteria set by the Dutch Orthopaedic Association (NOV) (Poolman et al., 2015). In the selection of knee implant variants, surgeons may choose those with "good" ODEP ratings which have associated revision risks below the ODEP thresholds. For instance, a surgeon deciding on choosing a variant for a patient, might favour ODEP rated A* over others. A* implant variants already have an associated revision risk below the thresholds used in this method. Therefore, for the Dutch data, it is to be expected that all types of Fixation, variants should show an increase in the posterior, indicating a higher chance that the variant used will meet ODEP thresholds. This is the case for uncemented and hybrid implants which show an increase in the posterior. Cemented implants, conversely, show a decrease. This can be explained by the fact that cemented implants account for around 55% of the number individual variant types recorded in the LROI dataset. For cemented variants, there are many available options for variants, many of which do not meet the thresholds, but are still used, albeit less frequently. However, they are given equal weight in the method. This reveals an option to incorporate the number of implants used as weights in the Bayesian method, which would potentially alter the results.

For Australia, ODEP benchmarking thresholds are not as commonly used as the UK and western Europe (Wyatt et al., 2021). Different systems are in place such as the Australian superior clinical performance programme (Prostheses Cover under Private Health Insurance, 2020). Results of the method may reflect general, overall implant performance, favouring cemented implants. Cemented knee implants historically have had a lower associated revision risk, and again, are still considered the gold standard for knee arthroplasty (Asokan et al., 2021b; Hannon et al., 2023; Irmola et al., 2000). The Australian registry is also known to be skewed towards cemented implants, which could explain some of the results (Gupta et al., 2020).

Again, this result is valid, explained with literature as below. This section shows how the Bayesian method produces distinct results for different datasets from different countries, highlighting potential differences in surgical practice and regulatory and institutional policy.

5.1.4 *Overall Results*

Overall, the results generated by the Bayesian method is consistent with literature. More so, it produces distinct results based on the datasets of two countries, which highlight differences in surgical practice, and regulatory and institutional policy. The method with multiple characteristics and results yielded by it are highly relevant in a regulatory context.

5.2 The Bayesian Method in a Regulatory Context

This section further delves into the thesis context by directly addressing research questions and objectives.

The developed method yields results as the probability of an implant variant being "good" by assessing if its revision risk meets ODEP thresholds. The following section discusses the method itself and examines how its results align with the regulatory background and overall context, especially that of the MDR, addressing OBJ4 and RQ2. It discusses whether the method can be utilized during regulatory approval to assist regulators in approving new implant variants for surgical use and for subsequent post-market surveillance. It will also explore if this method can alleviate the burden on manufacturers to provide new clinical evidence and assess the advantages and disadvantages for stakeholders like patients, surgeons, industry, and authorities like regulatory bodies.

5.2.1 *Potential Benefits of Implementing the Method for Regulating Variants*

A tool like the Bayesian Method would have many advantages for patients, surgeons, regulators and manufacturers alike.

- There is speculation that increased regulatory compliance requirements specified by the MDR may discourage innovation of new medical implants (Vasiljeva et al., 2020b). However, discouraging innovation may also affect patient safety by not allowing potentially safer materials to be made available in the form of new implants (Bernasconi, 2019; Kjaersgaard-Andersen, 2019). Here, the Bayesian method can, if used to make decisions on the approval of new variants, may streamline this regulatory approval process by providing an initial estimate about the performance of a new variant, thereby striking a balance between innovation and patient safety.
- The MDR mandates Post-Market Follow-up (PMCF) for knee implants that lack long-term clinical follow-up (Gerbers & Nelissen, 2024). The Bayesian method can enhance this process by continuously analysing data collected from the surgical use of the implant to identify underperforming variants. Registry datasets, which are periodically updated with new information, can be a valuable source of data for use with the method. Regularly analysing this data can help promptly identify and report potential underperforming variants. This approach is also supported by Wilton et al., (2023b) who call for regular analysis of registry data to quickly detect and address underperforming knee implant variants.

5.2.2 *Critical Evaluation and Potential Limitations of Implementing the Bayesian Method for Regulating Variants*

In the section below, the developed Bayesian method is critically evaluated as a potential tool to assist regulators in approving and regulating new implant variants for surgical use. Besides using context from previous sections, aspects of the Critical Appraisal Skills Programme (CASP), which provides frameworks for evaluating various studies in healthcare, is also incorporated. "Critical appraisal" is a method for assessing the methodological quality of studies (Jayaraman et al., 2018; Munn et al., 2019), involving a thorough and systematic evaluation of a study's trustworthiness, quality, and rigor (Booth et al., 2021; Tod et al., 2022). The CASP is particularly relevant for knee arthroplasty and its outcomes, with numerous studies utilizing it for evidence synthesis, meta-analysis, and systematic and scoping reviews (Moutzouri et al., 2017; Nisar et al., 2022; Pryce et al., 2024; van der Sluis et al., 2021). The CASP provides many checklists for appraising different types of studies (CASP Checklists - Critical Appraisal Skills Programme, 2024).

Specifically, the clinical Prediction Rule Checklist ("CASP Clinical Prediction Rule Checklist," 2023) will be used to assess the method. This is because if the method is used in a regulatory context, it will be used as a predictive tool to estimate the performance of implant variants at the time of regulatory approval. Although this checklist is designed for patient evaluation, parts of it can still be applied to assess the method itself. This CASP Checklist has yes/no questions, some of which are relevant to discussing the Bayesian method. These questions are not answered directly but are used as starting points for a discussion on the suitability of the method for regulatory decision-making on the approval of new variants for clinical use.

Reliability of Method Results

Question 9: Would the prediction rule be reliable and the results interpretable if used?

If the Bayesian method is to be used for the approval of new variants, it must be reliable and produce interpretable results. It should be applicable to all implant variants, including new ones. However, new implant variants may not conform to the seven implant characteristics that define each variant. Changes in design and new technologies (such as a new implant material, for example, which is not included in the implant characteristics defining a variant) or the introduction of potential new implant characteristics could affect the method's applicability in this regulatory decision-making context. Consequently, the Bayesian method must be adaptable and account for such new implant variants and ensuring that it remains effective and applicable even as new implant variants and innovations emerge (Behan et al., 2017; Garretsen, 2017). Additionally, the method must first be refined to reliably estimate revision risks for implant variants that are fully defined by the seven characteristics. This means that the method must also be developed to include multiple characteristics instead of just one as demonstrated in the method implementations in the previous sections.

Definition, Relevance and Precision of the Predictive Method Outcome

Question 1: Is the method clearly defined?
Sub question 1: Is the outcome relevant and is it clinically reasonable (the outcome can be expressed as a probability or as a course of action)?
Question 8: How precise was the estimate of treatment effect?
Sub question 8: Is the rule robust, has there been any attempt to refine it?

The Bayesian method produces a probability that indicates the likelihood of a variant meeting standard threshold values for revision risk. By considering the "treatment effect" as the revision risk, this method can predict a variant's performance with high precision, as it generates a single estimate based on the characteristics defining the variant. Also, through iterative refinement, the robustness of this method has been increased. Consequently, its precision and robustness can make it a valuable tool for supporting regulatory decision-making in the approval of new variants.

The MDR requires manufacturers to actively monitor regulated variants which are in surgical use and identify previously unknown risks that could not be detected before regulatory approval. This is called post-market surveillance (M. Fink & Akra, 2020). Incorporating data from post-market surveillance into the method can lead to more robust estimates of variant performance, but only in the post-market surveillance phase which occurs after the regulatory approval phase.

The Probabilistic Nature of the Method's Results: Insufficiency for Regulatory Decision-making

The method yields the *probability* of a new implant variant being "good", rather than a binary result indicating whether the implant will be good or not. Bayesian approaches are already favoured for decision-making by regulatory agencies (Bonangelino et al., 2011). However, this method's results offer a limited view of knee implant performance, which is insufficient for regulatory decision-making that requires consideration of multiple factors such as overall patient safety, safety for the intended population, patient preferences, innovation, and overall economic policy (Aftab, 2022; Bonangelino et al., 2011; Broekhuizen et al., 2015; Ho et al., 2015; McDermott & Kearney, 2024). Therefore, this method should only be used alongside other methods, such as benefit-risk analysis often employed by regulators (Broekhuizen et al., 2015), and not as a standalone method to determine an implant's performance for regulatory approval.

5.2.3 *Other Considerations*

The Bayesian method can use existing data to effectively estimate the revision risk of implant variants based on their characteristics, even when considered outside the regulatory context. This section discusses the method as a mathematical solution to the problem of estimating the revision risk of variants and its effectiveness.

Choice of Datasets: The Dependence of Method Implementation and Results on Input Data Quality

Two datasets were selected to develop and implement the method: the AOANJRR and LROI datasets. Initially, three potential data sources were identified for method development: arthroplasty registry data, registry annual report data, and medical literature. Ultimately, only arthroplasty registry data (LROI dataset) and registry annual report data (AOANJRR dataset) were chosen based on criteria of granularity, the expression of implant performance in terms of revision risk, and the feasibility of obtaining the data for this thesis project. Medical literature was rejected as a source of data due to inadequate granularity and the use of outcome assessment methods other than revision risk.

The nature of the dataset influences the posterior outcomes and, consequently, the results of the method. When the method was applied to the AOANJRR and LROI datasets, the method produced different results, despite the method itself remaining the same with both datasets. This difference comes from the nature of the two datasets: the AOANJRR is a registry report, while the LROI is detailed, raw data aggregated from individual patient surgical records by the Dutch registry organisation, the LROI. Essentially, the LROI annual report data is more detailed and direct, whereas the AOANJRR data is a summarized version of patient information, analysed by the Australian registry (Smith et al., 2023). This is why the LROI dataset contains more implant characteristics than the AOANJRR dataset.

Differences in data granularity can affect the implementation and results of the method. Granularity has been known to introduce confounding factors in the analysis of joint arthroplasty registry data (Cahue et al., 2019). Similarly, in this analysis, varying levels of granularity could lead to confounding factors that might distort the results and their interpretation. For example, it is known that a cemented implant has a higher revision risk when it is posterior stabilized (van Es et al., 2022). Including this characteristic in the input data could skew the results of the Bayesian method. The LROI dataset includes this posterior stabilized characteristic, whereas the AOANJRR dataset does not, which means that the estimates of revision risk for cemented implants could be different for these two datasets because of their granularity. This was indeed the case: revision risk estimates for cemented implant variants with the LROI dataset were unexpectedly different compared to results using the AOANJRR dataset. This anomality is discussed in the next section.

The Complexity of Predicting the Revision Risk as a Surgical Outcome: Other Factors Influencing Surgical Outcomes Besides Implant Characteristics

Predicting general surgical outcomes like revision is inherently complex due to the many potential causes of revision (El-Galaly et al., 2020). Causes of revision can be many and may range from pain and implant failure to infection (Inui et al., 2023). This method, however, treats revision as an independent outcome, attributing it solely to the characteristics and nature of the implant itself, without investigating the underlying reasons for revision. It operates on the assumption that the characteristics of the implant are the primary factors responsible for revision and does not consider other potential causes that may not be related to the implant.

Arthroplasty registry annual reports, such as the AOANJRR report, highlight many diagnosed causes of revision (Smith et al., 2023, p. 248), as given below:

1. Infection
2. Loosening
3. Instability
4. Pain
5. Patellofemoral pain
6. Patella erosion
7. Arthrofibrosis
8. Fracture
9. Malalignment
10. Tibial insert wear
11. Lysis
12. Incorrect sizing
13. Metal related pathology (such as metal allergies)

14. Other

For each complication other than infection, there can be various reasons for revision, other than issues with the implant itself. For instance, inadequate component alignment during arthroplasty surgery can lead to instability and pain, which may not be attributable to a fault with the implant (Inui et al., 2023). The AOANJRR annual report identified several additional factors that can influence revision risks, such as age, comorbidities, and the use of computerized surgical methods, suggesting that these factors may also play a role in implant revision (Smith et al., 2023).

Considering all these factors is not feasible with the developed method and may remain challenging even with further refinement. Accounting for variables such as age, surgical methods, and other factors would require more detailed datasets and could be explored in future work. If these factors are incorporated, the method could yield more well-rounded, comprehensive results. Currently, by focusing solely on implant characteristics, the method can be seen to produce results for “aseptic revision”, meaning revision for causes which are not related to infection (Okafor et al., 2021). Implants themselves are generally not considered to cause infections in patients undergoing total knee arthroplasty (Matar et al., 2010).

The Value of the Method with Multiple Characteristics

The method with multiple characteristics is what the Bayesian method is envisioned to be: a method that can estimate the performance of a full variant on the basis of all its characteristics. The development of the method with the LROI dataset from one characteristic to three characteristics shows the value of adding more characters into it. Moving from one characteristic Fixation to two characters Fixation and Mobility introduces more nuance to the results. The posterior moves differently for different combinations of characters resulting in different estimates of whether an implant variant is “good”. For example, in the method with LROI data and one characteristic, cemented implants show a decrease in the posterior relative to the prior. Adding the Mobility characteristic shows that only cemented and fixed implants show a reduction in the posterior, but cemented and mobile and cemented and rotating show an increase. This level of nuance was not possible in the method with only one characteristic. This goes to show that the interplay of different characters also results in distinct posterior estimates for each combination.

Camouflage was also an important issue discussed in the previous chapters. The current framework of the MDR strongly discourages Camouflage by calling for each novel implant variant to be clinically tested before surgical use. This method with multiple characteristics, because it makes distinct estimates for each combination, also separates variants from each other in terms of performance. It does not group variants into brands. As a result, this approach is unlikely to lead to a regression to the previous status quo.

As seen in the method with three characteristics, however, there are certain zero values in the posterior where the method fails. This tends to occur more frequently for a larger number of characters. The incorporation of confidence intervals into the method may prove beneficial in capturing larger uncertainty and accounting for the possibility of zero values in the method. This is explored in Appendix B.

5.3 Application for Regulatory Decision-making

Here, some practical considerations for the implementation of the Bayesian Method as a regulatory decision-making tool are put forth.

As mentioned in the previous section, the method yields results in the form of a probability that the implant is “good”. A prior assumption about implant performance is made, which after conditioning on implant characteristics results in an updated, posterior estimate of the implant being “good”. This update can either be an increase, decrease or no change of the prior into the posterior probability. For any implant variant, an increase from the prior to the posterior can signify that conditioning on one or more of the variant’s implant characteristics results in a higher probability of its revision risk meeting thresholds, a higher chance that the variant is “good” than the prior assumption. A reduction from the prior to posterior probabilities can indicate that the variant with that particular set of characteristics may have a lesser chance of being “good” than the prior assumption. The magnitude of such an increase or decrease can indicate the strength of influence of the variant’s characteristics. This inference of results can be of benefit in the regulatory context, as highlighted below.

5.3.1 *Increase and Decrease of the Prior Probabilities as Eligibility for Making a Clinical Equivalence Claim*

The main objective of the regulatory framework of the MDR is to maintain a high level of patient safety and health while supporting innovation for medical devices (M. Fink & Akra, 2023). In the case of knee implant variants, regulators strive to ensure the performance, safety and quality of new devices (Wadhwa et al., 2019). Regulatory assessment of knee implants, therefore, must translate to these objectives of performance, effectiveness, safety and quality. If this method is used as a regulatory tool for the approval of new knee implant variants, its results must align with the decision-making process during regulatory approval.

This report proposes that the “clinical equivalence” clause of the MDR be based on the results of this method as a support for regulatory decision-making on the approval of new knee implant variants. In this way, it would not be used for making direct decisions on the regulation of novel knee implant variants, but still impact this process of regulation positively without compromising overall patient safety. Using the method directly for regulatory decision-making may have negative consequences for patient safety especially in light of the critique of the method as put forth above. It might also negate the MDR’s regulatory rigour and emphasis on patient safety. Using the method for eligibility in equivalence claims can strike the fine balance between overall patient safety and preventing catastrophic implant failures, and medical device innovation.

If a new variant pending regulatory approval shows a sufficient increase in the prior when tested with this method, it is proposed that the manufacturer of a novel knee implant can claim "clinical equivalence" to another implant variant if required by them. "Equivalence" in the context of knee implants and the MDR is an alternative to clinical trials for obtaining approval for surgical use (Overgaard et al., 2023). It is the degree of similarity of an implant variant to another regulated variant in clinical use (Davies & Davies, 2021). Making an equivalence claim allows a new variant to be approved for surgical use without requiring pre-market clinical trials (Overgaard et al., 2023), which are difficult, expensive and time-consuming to do. Although the concept of equivalence was present in the previous MDD as well, the MDR mandates a stricter policy for manufacturers to make an equivalence claim for the release of new variants. This includes demonstrating technical, biological and clinical equivalence of a new variant to an already-approved variant in surgical use. This report proposes that manufacturers should be allowed to make a clinical equivalence claim if the results indicate a higher probability of the variant being "good".

The concept of equivalence may have been exploited in the past by manufacturers to obtain regulatory approval for the clinical use of implant variants (Fraser et al., 2021). Subpar implant may have been introduced for clinical use. Using the method as part of making equivalence claims may help a manufacturer skip the high time and monetary investment of conducting clinical trials for every variant they release, ultimately helping strike a balance between manufacturer-led innovation and patient safety.

In case, however, the posterior is less than the prior, equivalence claims can be barred for the variant from its manufacturer. A reduction in the prior could imply that the combination of characteristics has resulted in a lesser chance that the variant will meet thresholds. This is reflected in the Bayesian calculation. When the posterior is lesser in magnitude than the prior, the likelihood is lesser than the normalising constant, meaning that the particular combination of characteristics has resulted in a greater percentage of variants which do not meet the thresholds. Therefore, the variants with these characteristics may have a greater chance of not performing as expected. This warrants greater scrutiny of such variants. For the approval of such a variant, clinical investigation must be conducted in accordance with the MDR, Annex XV (Directive 2017/745).

The magnitude of the posterior probability of a variant should also be sufficiently high to make its manufacturer eligible for making a clinical equivalence claim. Some work has been conducted to quantify uncertainty in a regulatory and medical context such as by Vreman et al., (2020) and Stern, (2017). However, due to the novel nature of this thesis, interpretation of probabilities for making binary regulatory decisions on approval is difficult. Therefore, this report proposes a purely statistical value of 70%. This thesis recommends further work in the interpretation of probabilistic results for making regulatory approval decisions, which are binary in nature, especially in a medical device context. To further incorporate uncertainty into the Bayesian method, statistical confidence intervals can be used in the method itself. Confidence intervals are used extensively in the knee implant context, such as those used for revision risks in the AOANJRR annual report (Smith et al., 2023). Confidence intervals provide bounds between which true values can lie. This can be of help in the interpretation of results in a binary regulatory decision-making context. Such an improvement of the Bayesian method with confidence intervals is suggested developed in Appendix B.

5.3.2 *Final Recommendation*

Although there are advantages of using the Bayesian method for regulatory decision-making, the method would need to be refined further before use. At this stage, it can only serve as a supplement to strong clinical evidence and cannot be used independently to fully gauge the safety or effectiveness of a new variant for regulatory approval. Therefore, it has been suggested that the possibility of Clinical Equivalence be based on the results of this method.

5.4 Ethical Issues

This method, if used as intended in the last section as an aid to regulatory decision-making, may have consequences for patient safety, surgical and regulatory practice, the medical industry, and society. Some core ethical issues in the context of the developed method are elaborated below.

5.4.1 *The Paradox of Innovation and Patient Safety*

As previously discussed, innovation in knee implants can introduce better and potentially safer variants to the market (Bernasconi, 2019; Kjaersgaard-Andersen, 2019), positively impacting patient safety. However, this process may also compromise patient safety if new implants are tested on patients: medical devices, including knee implants, are largely tested during clinical use and a limited amount of clinical evidence is available before introduction into the market for surgical use (Pietzsch et al., 2004). Consequently, implant testing and clinical use are not separate (Vinck et al., 2011), making patients susceptible to adverse events of implant failure associated with some new, untested knee implants. This presents an ethical dilemma concerning the release of new knee implant variants, and more ethical discourse is needed. Ethical debate is particularly important when the distinction between implant testing and clinical practice is blurred, because there may be limited reviews by ethics committees in such a case (Garretsen, 2017).

Here, the developed method can be useful. Implants deemed "good" by the method can be used and tested as they are, while those deemed not "good" may receive more attention through a stepwise introduction for surgical use and testing. This stepwise approach reduces health risks for patients during testing (Neyt et al., 2017; Sauerland et al., 2014).

5.4.2 *Transparency of Clinical Data for Patients and Surgeons*

Unlike medicinal products, clinical data on medical devices that have been obtained from clinical trials, is not publicly available (Hulstaert et al., 2023). There is a lack of transparency of clinical data on medical devices like knee implants preventing 1) Patients from making fully informed decisions about their intervention and treatments (Garretsen, 2017) and 2) Surgeons from having more detailed information about the performance of implant they may choose to use in practice. This is because surgeons are responsible for choosing implants with the best long-term survival and function and need to remain updated about trends in usage and survivorship of different implants (Porteous & Curtis, 2021a).

As previously mentioned, surgeons can also use the Bayesian method to make more informed decisions about the implants they use in surgical practice. This approach allows them to better understand the potential performance of the chosen implant and be in a better position to explain their choice to patients. Involving patients in surgical decision-making process on treatment options has been shown to lead to better surgical outcomes. (Charles et al., 1997; O'Neill et al., 2007).

Interestingly, there have been developments in the transparency of clinical data with the introduction of the MDR. Both the MDD and the MDR prioritize the confidentiality of clinical data over public disclosure (Garretsen, 2017; Hulstaert et al., 2023). With the new MDR, although clinical data is still not fully accessible to the public, efforts are being made to inform the public about important safety and performance aspects of medical devices through the European Database on Medical Devices (EUDAMED). EUDAMED, as part of the MDR, aims to maintain a comprehensive record of all medical devices in the EU and to increase transparency of clinical studies on medical devices (European Database on Medical Devices, 2021). However, it is still unclear how much information will be available in this database.

5.4.3 *Stakeholder Impact*

Manufacturers and Regulators

The above recommendation would not affect manufacturers in any way because they would still have to comply to all regulatory rules. For regulators, however, the method can influence decision-making on the approval of new implants. While it would not replace the entire approval process due to the wide scope of regulatory decision-making, it could provide an overview of implant performance for implant variants in the regulatory approval process, especially for non-medical stakeholders.

Surgeons and Patients

This method could be highly beneficial for surgeons, who typically have the final say in implant choice and make final decisions on implant characteristics, components, and surgical methods (Porteous & Curtis, 2021; Wilton et al., 2023b). By using the Bayesian method, surgeons can make more informed decisions about the variants they choose to use in practice and better understand the expected outcomes in terms of revision risk. They will also be in a better position to explain the choice of implant to the patient using this method's results. Involving both patient and surgeon in the decision-making process is often considered the best approach to surgical decision-making (Charles et al., 1997). Decision-making aids like this method used along with the patient could improve the decision process of selecting implants, thereby keeping patients informed and potentially enhancing surgical outcomes (O'Neill et al., 2007).

5.5 Future Work and Limitations

This section outlines potential directions for future work, inspired by some limitations faced during the thesis project.

1. **Core Assumptions**: This thesis considers only the implant characteristics as factors influencing its revision risk. This is a limitation because, revision can result from many causes, and not only from implant failure. Other surgical complications like infection and pain can also result in revision surgery, increasing the revision risk of the implant used. This has been addressed in the section *The Complexity of Predicting the Revision Risk as a Surgical Outcome: Other Factors Influencing Surgical Outcomes Besides Implant Characteristics*.
2. **Data Selection**: Two sources of data were identified, the AOANJR arthroplasty registry annual report and the proprietary LROI dataset. Medical literature was rejected as a potential source of data.
    a. **Other data in the AOANJR annual report**: The AOANJRR contains, in other tables, revision risk estimates for knee implants by factors like age, surgical technique, patient obesity. These have not been incorporated into the method and as they do not fall under implant characteristics. Incorporating this revision risk data into the method can be a direction of future work.
    b. **Medical literature data**: Medical literature can be a potentially wide source of information but cannot be incorporated into the Bayesian method currently due to inadequate data granularity. However, this source of information can be explored in future work as well.
3. **Probabilistic Bayesian Method**: A probabilistic Bayesian approach has been chosen for the method due to the uncertainty associated with an implant's revision risk. This approach allows the revision risk to be updated with new evidence, rather than being treated as a fixed parameter. Here, machine learning (ML) methods can also be explored for use due to its advantage of detecting non-linear relationships in datasets (Cabitza et al., 2018), which can potentially be used to make better predictions on revision risk for knee implants.
4. **Obtaining Information for the Prior**: An informative prior is obtained from the datasets by taking a weighted average of both the mean and standard deviation. This is a stopgap approach to restrict the thesis to its scope and is a limitation. Other methods of making an initial estimate of an implant's performance for the prior distribution may be explored in future work.
5. **Choice of Prior, Likelihood and Posterior Distributions**: The prior is assumed to be a Beta distribution which is a conjugate prior for the likelihood, which is a Bernoulli distribution. This makes an analytical solution to the Bayesian equation possible, and the posterior is also a Beta distribution. The effect of using different kinds of distributions is outside the scope of this thesis and may be explored in further work.
6. **Incorporating Confidence Intervals**: Confidence intervals can be incorporated into the Bayesian method to accommodate larger uncertainty in the method and allow for better interpretation of the posterior results.
7. **New Characteristics in New Variants**: New variants can have characteristics which are outside of the defined 7 characteristics. This could make the method less robust. Further work could explore the possibilities of defining a variant in terms of greater than these 7 characteristics.

Chapter 6 | Conclusion

This thesis began with the goal of identifying a method to predict the revision risk performance of new knee implants using data from arthroplasty registries and studies of regulated total knee implants. The effectiveness of such a method as a regulatory decision-making tool for approving new knee implants was also to be explored. However, no such method could be found in the literature. Therefore, a new method was developed from basic mathematical concepts. To retain the regulatory and knee arthroplasty context, three criteria were defined for the new method. A probabilistic Bayesian method was developed using specifically chosen datasets: the AOANJRR and the LROI datasets.

The method was evaluated in a two-fold manner 1) On the basis of its results with the two datasets and 2) In a regulatory context. The results of the method were largely consistent and aligned with medical literature in the field of knee arthroplasty. In the regulatory context, the developed method's benefits and limitations were examined, with the limitations evaluated using the CASP Predictive Rule Checklist. Although the method has benefits striking a balance between innovation and patient safety, limitations include probabilistic nature of the methods results, dependency on the choice of datasets, and the confounding effects of other factors influencing revision. Taking these benefits and limitations into account, a final recommendation was made: to use the Bayesian method for determining eligibility for clinical equivalence in the regulatory approval of novel knee implant variants. This approach strikes a balance between overall patient safety and innovation in the field of medical devices. Following this, directions for further work were suggested, inspired by the limitations encountered: exploring more characteristics to define variants, incorporating confidence intervals, and the use of other data sources like medical literature as wider information sources. Incorporating confidence intervals shows promise in quantifying the uncertainty in the method so that its results may be better suited for regulatory decision-making. Appendix B shows the development of the method while incorporating confidence intervals and may serve as a starter for future work.

In conclusion, this thesis demonstrates the potential of a probabilistic Bayesian method for predicting knee implant revision risk, especially in the current medical device regulatory setting. Despite this, however, the method requires further refinement to address identified limitations and incorporate broader influencing factors. By doing so, this method could be used as a regulatory tool, addressing issues with the current regulatory environment, positively impacting surgeons, patients, regulators and the medical industry.

Chapter 7 | Bibliography

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Chapter 8 | Appendix A

8.1 Supplementary Material: Code

The code for the Bayesian Method and all its iterations along with the AOANJRR dataset used has been uploaded to the repository:

https://github.com/Shounak-Paul/Master-Thesis/

Chapter 9 | Appendix B

9.1 Incorporating Confidence Intervals in the Bayesian Method

As seen in the developed method, a 95% confidence interval was also present for each value of revision risk in tables KT9 to KT11 in the AOANJRR registry. These intervals can be fully incorporated into the Bayesian method, rather than only using the upper limit values. This approach is similar to the "superiority" method used in survival analysis to define "good" implant performance: according to this method, the upper limit of the 95% confidence interval must be less than the benchmark revision risk value for the group of implants (Smith et al., 2023). However, this updated Bayesian method developed in the section below differs from the superiority approach by utilizing the entire confidence interval rather than just the upper limit. In this updated Bayesian method, the overall Bayes' equation remains unchanged, but the interpretation of registry information for calculating each term in Bayes' Theorem is revised. Rather than representing a single value, the posterior, prior, and likelihoods are assumed to be probability distributions, enabling more comprehensive inferences of implant variant performance compared to their representation as singular point estimates. This method's incorporation of confidence intervals in the form of distributions allows for a more subjective interpretation of the posteriors to determine good performance. Confidence intervals are also used in the case of the LROI dataset.

9.1.1 *Choice of Distributions for the Prior, Likelihood and NC*

In Bayes' Theorem, the prior, likelihood, and the reciprocal of the normalizing constant are multiplied to yield the posterior. When the prior and likelihood are treated as probability distributions instead of point estimates, multiplication of the prior and likelihood results in a posterior which is also a distribution. This process is often referred to as "aggregating" probability distributions (Grientschnig & Ignacio, 2014), and it can result in posterior distributions that differ in shape from the prior or likelihood (Clemen & Winkler, 1999; Genest & Zidek, 1986). For some combinations of prior and likelihood distributions, obtaining the posterior may not be possible analytically, and numerical methods may be required (D. Fink, 1997). Determining such posterior probability distributions is a different field of mathematical inquiry beyond the scope of this thesis and the impact of different distributions has not been considered here. Instead, the concept of "conjugate priors" is used to determine posterior distributions without numerical approximation or extensive calculation. Conjugate priors are prior distributions for likelihoods that result in tractable analytical solutions and yield posterior distributions with known shapes (D. Fink, 1997). This means that an analytical solution for the Bayes' equation will be available as a posterior. In the Bayesian method below, the likelihood is a Bernoulli distribution, and a Beta distribution is chosen as a suitable conjugate prior (Schmidli et al., 2014d). This results in a Beta distribution as the posterior.

9.1.2 *The New Bayesian Approach for this Method*

Deriving the New Form of the Bayes' Equation

Suppose that F denotes a characteristic "fixation" for an implant variant and R_t a random variable for its revision risk at a follow-up period t as defined previously. R_t helps determine if the performance of a variant is "good" when compared to regulatory thresholds. Let F_{cem} be a binary random variable denoting the presence of the cemented method of fixation where $F_{cem} = 1$ for an implant variant having this cemented method of fixation and $F_{cem} = 0$ for a variant with any other mode of fixation.

Let the probability of selecting a cemented variant which is "good" (R_t within threshold), denoted by $P(F_{cem} = 1 \mid R_t)$, be v_t and of selecting any other variant be $P(F_{cem} = 0 \mid R_t) = 1 - v_t$. Then, if among n implant variants with fixations $f_{cem,1}, f_{cem,2}, \dots, f_{cem,n}$, the probability of selecting a cemented, good performing one at period t is v_t, it follows that such a probability for the ith variant is given by $p(F_{cem} = f_i \mid R_t)$. This probability then becomes:

$$p(F_{cem} = f_i \mid R_t) = {v_t}^{f_i}(1 - v_t)^{1-f_i}$$

Since selecting a variant is independent of selecting any other, for n variants selected randomly, the probability of selecting n variants with cemented or non-cemented fixations $f_{cem,1}, f_{cem,2}, \dots, f_{cem,n}$ at t is:

$$p\left(f_{cem,1}, f_{cem,2}, \dots, f_{cem,n} \mid R_t\right) = \prod_{i=1}^{n} P(F_{cem} = f_i \mid R_t) = \prod_{i=1}^{n} {v_t}^{f_i}(1 - v_t)^{1-f_i}$$

This is a $Bernoulli(v)$ distribution with a parameter v_t, representing the likelihood of observing n_t cemented implant variants. If there are k_t such variants which are cemented, which means for those with $f_i = 1$, this Bernoulli distribution reduces to:

$$p(f_{cem,1}, f_{cem,2}, \dots, f_{cem,n} \mid R_t) = {v_t}^{k_t}(1 - v_t)^{n_t - k_t}$$

Equation 9 Bernoulli distribution equation for a cemented implant variant given its revision risk

This represents the Bernoulli **likelihood**, indicating the likelihood of a variant being cemented given its revision risk. Information about v_t will be considered as "evidence" to update prior beliefs about R_t into posterior beliefs about the R_t to judge whether the variant's performance is "good" enough by comparing it to regulatory threshold τ_t. Both prior and posterior beliefs about R_t will be reflected in prior and posterior distributions. The thresholds will be considered after the Bayesian implementation to interpret the posterior R_t distributions. Th likelihood is obtained with the help of information from the datasets as shown in the next section.

A suitable prior distribution for representing prior beliefs of R_t is a Beta distribution because it is conjugate to the likelihood's Bernoulli distribution. This will represent prior assumptions about the revision risk at t (R_t) for an implant variant before considering evidence in the form of any characteristic such as fixation. The notation of this prior distribution is $Beta(a_t, b_t)$ where a_t and b_t are shape parameters. Prior information reflecting initial beliefs about R_t can be incorporated into the distribution using these shape parameters. This prior information will be obtained from the two datasets during the implementation of the method in the next section. The PDF for the **prior** this Beta distribution is given by:

$$p(R_t) = \frac{1}{B(a_t, b_t)} {R_t}^{a_t - 1}(1 - R_t)^{b_t - 1}, \ \ for\ R_t \in [0,1]$$

$where\ B(a_t, b_t)$ is the Beta function which normalises this Beta distribution in the range [0,1]. Since the revision risk R_t is assumed to depend on the presence or absence of the fixation "cemented", this PDF can also be written with v_t as:

$$p(R_t) = \frac{1}{B(a_t, b_t)} {v_t}^{a_t - 1}(1 - v_t)^{b_t - 1}, \ \ for\ R_t \in [0,1]$$

Now, the **posterior** is obtained by incorporating both the prior and likelihood into the Bayes' equation, given below:

$$p(R_t \mid f_{cem,1}, f_{cem,2}, \dots, f_{cem,n}) = \frac{1}{B(a_t, b_t)} (f_{cem,1}, f_{cem,2}, \dots, f_{cem,n} \mid R_t) p(R_t)$$

$$= \frac{1}{B(a_t, b_t)} {v_t}^{a_t - 1}(1 - v_t)^{b_t - 1} \cdot \ {v_t}^{k_t}(1 - v_t)^{n_t - k_t}$$

$$= \frac{1}{B(a_t, b_t)} {v_t}^{a_t + k_t - 1}(1 - v_t)^{b_t + n_t - k_t - 1} \ \ Q.E.D.$$

Equation 10 Posterior for the revision risk at Period t for an implant variant given the fixation method

The posterior, as expected, is a Beta distribution with new parameters $a_t + k_t\ and\ b_t + n_t - k_t$.

$$R_t \mid f_{cem,1}, f_{cem,2}, \dots, f_{cem,n} \sim Beta(a_t + k_t, b_t + n_t - k_t)$$

The posterior represents updated beliefs about R_t in the form of a distribution after the incorporation of evidence of a particular type of a characteristic from the datasets. Since the posterior is a distribution, it provides a range of possible values for R_t and indicates the probability associated with each of these values. Similar posteriors can be generated for other types of the characteristics also. In this case, the characteristic considered is Fixation, and characteristic types can be cemented, uncemented, and hybrid.

9.1.3 *Determination of the Prior, Likelihood and Posterior Distributions from the AOANJRR Dataset for the New Form of the Bayes' Equation*

Prior Calculation Procedure

The prior represents an initial belief about an implant's revision risk, which is expressed as a Beta distribution. The steps below highlight how this Beta distribution, defined by two parameters a and b, is obtained with information from the AOANJRR dataset.

1. For each implant in the AOANJRR dataset, the revision risk is expressed in terms of a mean (μ_i) and standard deviation (SD) (σ_i) for each follow-up period. While the mean value of the revision risk is provided in the dataset, the SD value is not present. Thus, the SD needs to be calculated, which is done with the help of the 95% confidence intervals for each implant in the dataset using the formula below:

$$(upper\ 95\%\ confidence) - (lower\ 95\%\ confidence) = 4\sigma_i$$

   Now, there is a value of μ_i and σ_i for each implant in the dataset.

2. The weighted averages of μ_i and σ_i, represented by μ_{wa} and σ_{wa} respectively, is calculated for all implants in the dataset using the number of implants of the column "N Total" of the dataset as the weight for each implant (w_i). For n implants in the dataset, this is given by:

$$\mu_{wa} = \frac{\sum_{i=1}^{n} w_i \mu_i}{\sum_{i=1}^{n} w_i}$$
$$\sigma_{wa} = \frac{\sum_{i=1}^{n} w_i \sigma_i}{\sum_{i=1}^{n} w_i}$$

3. μ_{wa} and σ_{wa} represent a quantified initial belief of the revision risk performance of an implant. ***Note that*** this method of forming of quantifying an initial belief is highly limited, and better methods of obtaining more statistically relevant prior estimates may be present. However, due to limitation in the thesis timeline, this method has been used and further investigation into obtaining more relevant priors may be explored in other future work.

4. A Beta distribution is then obtained by converting μ_{wa} and σ_{wa} into Beta distribution parameters a_t and a_t with the formula below for each t:
   For $\mu_{wa} \in [0,1]$ and ${\sigma_{wa}}^2 < \mu_{wa}(1 - \mu_{wa})$ then:

$$\varepsilon = \frac{\mu_{wa}(1 - \mu_{wa})}{{\sigma_{wa}}^2} - 1$$

$$parameter\ a_t = \mu_{wa}\varepsilon$$

$$parameter\ b_t = (1 - \mu_{wa})\varepsilon$$

The Beta distribution for the prior is completely defined with the two parameters a and b. A prior is constructed for each 1- 3-, 5-, 10-, 15-, and 20-year follow-up periods.

Likelihood Calculation Procedure

The likelihood in the form in Equation 9 need not be computed because the posterior can be obtained directly using the values of k_t and n_t. Recall that the posterior is of the form $Beta(a_t + k_t, b_t + n_t - k_t)$. k_t and n_t are calculated using the equations below:

$$k_t = Count(Implants\ with\ fixation\ F\ AND\ NOT(having\ revision\ risk < threshold\ at\ t))$$

$$n_t = Count(Total\ number\ of\ implants\ considered\ at\ t)$$

This approach might seem counterintuitive for determining k_t. The likelihood represents the number of "successes", which in this context, are the number of implant variants with fixation type F that are considered "not good" in terms of performance, rather than those that are "good." This is because the likelihood function is conditioned on the revision risk R_t, where "good" performance is inversely related to revision risk: a higher revision could indicate poorer performance, while a lower revision risk suggests better performance. Calculating the likelihood in thistatis way gives a higher revision risk estimate if the effect of the characteristic, here fixation F, results in poorer performance.

Normalising Constant Calculation Procedure

The NC is embedded in the posterior, and explicit calculation is not necessary.

Posterior Calculation Procedure

The posterior has been derived to be a distribution $Beta(a_t + k_t, b_t + n_t - k_t)$ or $Beta(a_{posterior}, b_{posterior})$. There is a distinct posterior for each follow-up period and type of fixation.

Expression of the Bayesian Calculation and Results

A single table, along with figures showing the prior and posterior distributions for each t has been used in the next section for the implementation of the Bayesian method to the AOANJRR dataset. The table contains the following columns:

1. The years of follow-up t.
2. The characteristic type of the implant.
3. The prior:
    a. Value of mean, μ_{wa}.
    b. Value of SD, σ_{wa}.
    c. Prior parameter a.
    d. Prior parameter b.
4. The likelihood:

   a. Value of k_t.
   b. Value of n_t.
5. The posterior:
   a. Value of $a_{posterior}$.
   b. Value of $b_{posterior}$.

The figure shows, for each combination of t and Fixation type, the prior and posterior Beta distributions.

Evaluation of the Prior and Posterior: Answering the Question - Is the Implant Good Enough After Incorporating Evidence?

Since the posterior is a distribution, it provides a range of possible values for R_t and indicates the probability associated with any sub-range within [0,1]. For an implant to be "good", its revision risk R_t should be below the threshold τ_t. The probability of the range $[0, \tau_t)$, which is $P(0 < R_t < \tau_t)$ is determined for both the prior and the posterior to allow for discussion of the results of this method. This is the probability of whether an implant variant is "good". A new table is included after the Results and Calculations table showing the mean, SD, and probability of the interval $[0, \tau_t)$ for R_t.

9.1.4 *Determination of the Prior, Likelihood and Posterior Distributions from the LROI Dataset for the New Form of the Bayes' Equation*

The LROI dataset already includes the mean (μ_i) and standard deviation (SD) (σ_i) for each implant variant. Therefore, the prior is computed similarly to the AOANJRR dataset, but starting from step 2 of the procedure as defined in the last section. The procedures for calculating the prior, likelihood, and posterior remain the same. The Bayesian implementation is also expressed in the same manner as in the previous method, with the table and figures showing the prior and posterior. Additionally, the posteriors are only calculated for the 3, 5, and 10-year follow-up periods, as the LROI dataset does not include data for 1, 15 and 20-year follow-up periods.

9.2 Implementation and Results of the Bayesian Method with Confidence Intervals and the AOANJRR Dataset

The new Bayesian methods is implemented using the method outlined in the previous section. A posterior distribution of the revision risk is determined for each t and Fixation type. This posterior represents an updated estimate of the revision risk for an implant variant with a particular characteristic type, taking into account the characteristic and revision risk information from the AOANJRR dataset. In this case the characteristic is Fixation, and characteristic types can be cemented, uncemented, and hybrid as shown in Table 14. Both the prior and posterior Beta distributions for 5 and 10 years of follow-up, shown in Figure 2 and Figure 3, is relevant for the discussion chapter. Figures for 1, 3, 15, and 20 years of follow-up are included in the supplementary material.

Improvement from the previous method

Confidence intervals has been incorporated into the method using a Beta distribution as the prior and a Bernoulli distribution as the likelihood. The prior and posterior are now both Beta distributions.

9.2.1 *Results of this Iteration of the Method*

This iteration of the method generates 18 posterior results for each combination of fixation characteristic and follow-up period. The probability of the range $[0, \tau_t)$ is then deduced for the prior and posterior allowing for interpretation of whether an implant variant is "good". Thus, the developed method yields results that fit well within the thesis context, while also incorporating confidence intervals. Since the posterior is now in the form of a Beta distribution, it allows for a more detailed interpretation of the revision risk of the implant variant by the investigation of probabilities beyond just the range $[0, \tau_t)$.

The posterior distribution shifts to the right compared to the prior for cemented, uncemented, and hybrid characteristics, with this shift becoming more pronounced over longer follow-up periods. This result is discussed in the section *Further Discussion of Key Results of the Implemented Bayesian Method*. For all three characteristics, the probability of the range $[0, \tau_t)$ is 100% at 1 and 3 years of follow-up. This indicates that, according to this method, there is a 100% chance that the implant with the specified characteristic falls within ODEP thresholds. Posterior probabilities for the range $[0, \tau_t)$ are lower than prior probabilities.

		Prior					Likelihood parameters		Posterior	
Year t	**Fixation type**	**Prior mean (%)**	**Prior SD[5] (%)**	**Prior Beta parameter a**	**Prior Beta parameter b**	**Condition $\sigma_{wa}^2 < \mu_{wa}(1 - \mu_{wa})$**	**k_t**	**n_t**	**Posterior Beta parameter a**	**Posterior Beta parameter b**
1	Cemented	0.96	0.09	106.44	11007.91	Yes	1	110	107.44	11116.91
3	Cemented	2.54	0.15	275.45	10565.56	Yes	11	109	286.45	10663.56
5	Cemented	3.34	0.18	343.98	9959.20	Yes	14	105	357.98	10050.20
10	Cemented	4.87	0.22	450.03	8787.52	Yes	16	81	466.03	8852.52
15	Cemented	6.36	0.31	397.35	5849.84	Yes	10	50	407.35	5889.84
20	Cemented	7.93	0.60	162.79	1891.04	Yes	7	23	169.79	1907.04
1	Uncemented	0.96	0.09	106.44	11007.91	Yes	1	110	107.44	11116.91
3	Uncemented	2.54	0.15	275.45	10565.56	Yes	11	109	286.45	10663.56
5	Uncemented	3.34	0.18	343.98	9959.20	Yes	15	105	358.98	10049.20
10	Uncemented	4.87	0.22	450.03	8787.52	Yes	16	81	466.03	8852.52
15	Uncemented	6.36	0.31	397.35	5849.84	Yes	8	50	405.35	5891.84
20	Uncemented	7.93	0.60	162.79	1891.04	Yes	4	23	166.79	1910.04
1	Hybrid	0.96	0.09	106.44	11007.91	Yes	0	110	106.44	11117.91
3	Hybrid	2.54	0.15	275.45	10565.56	Yes	5	109	280.45	10669.56
5	Hybrid	3.34	0.18	343.98	9959.20	Yes	9	105	352.98	10055.20
10	Hybrid	4.87	0.22	450.03	8787.52	Yes	12	81	462.03	8856.52
15	Hybrid	6.36	0.31	397.35	5849.84	Yes	7	50	404.35	5892.84
20	Hybrid	7.93	0.60	162.79	1891.04	Yes	3	23	165.79	1911.04

Table 14 Results and Calculations of the Implemented Bayesian Method Incorporating Confidence Intervals Using the AOANJRR Dataset

[5] SD: Standard Deviation

Year	Threshold Interval $0 < R_t < \tau_t$ (%)	Fixation Type	Prior Probability of Threshold Interval (%)	Posterior Probability of Threshold Interval (%)
1	[0.00,3.00)	Cemented	100.00	100.00
3	[0.00,3.50)	Cemented	100.00	100.00
5	[0.00,4.00)	Cemented	99.98	99.87
10	[0.00,5.00)	Cemented	71.98	50.37
15	[0.00,6.50)	Cemented	67.86	54.59
20	[0.00,8.00)	Cemented	55.81	39.30
1	[0.00,3.00)	Uncemented	100.00	100.00
3	[0.00,3.50)	Uncemented	100.00	100.00
5	[0.00,4.00)	Uncemented	99.98	99.84
10	[0.00,5.00)	Uncemented	71.98	50.37
15	[0.00,6.50)	Uncemented	67.86	58.62
20	[0.00,8.00)	Uncemented	55.81	48.81
1	[0.00,3.00)	Hybrid	100.00	100.00
3	[0.00,3.50)	Hybrid	100.00	100.00
5	[0.00,4.00)	Hybrid	99.98	99.95
10	[0.00,5.00)	Hybrid	71.98	57.92
15	[0.00,6.50)	Hybrid	67.86	60.61
20	[0.00,8.00)	Hybrid	55.81	52.04

Table 15 Prior and Posterior Probabilities of the Implant's Revision Risk Being Below the Threshold Value or the Probability of the Implant being "Good" with the AOANJRR Dataset

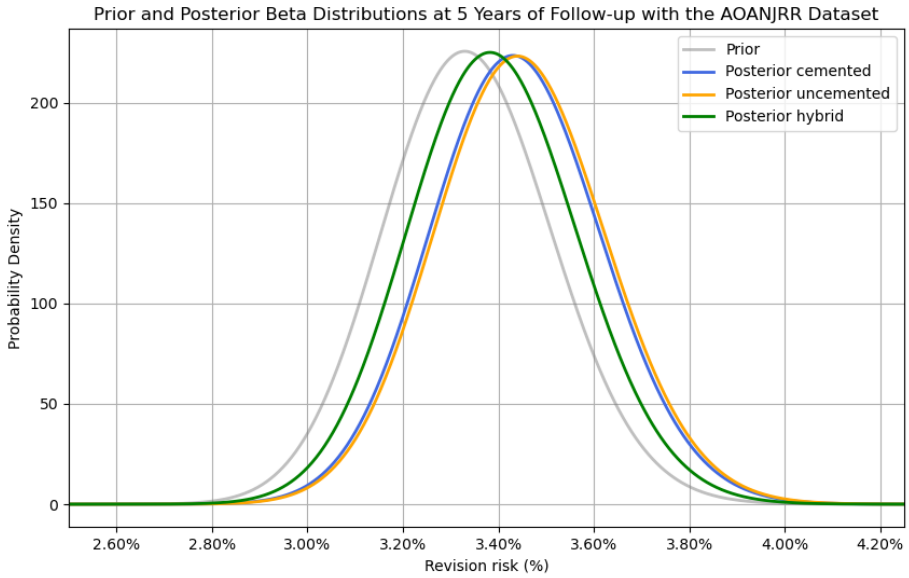

Figure 2 Prior and Posterior Beta Distributions at 5 Years of Follow-up with the AOANJRR Dataset

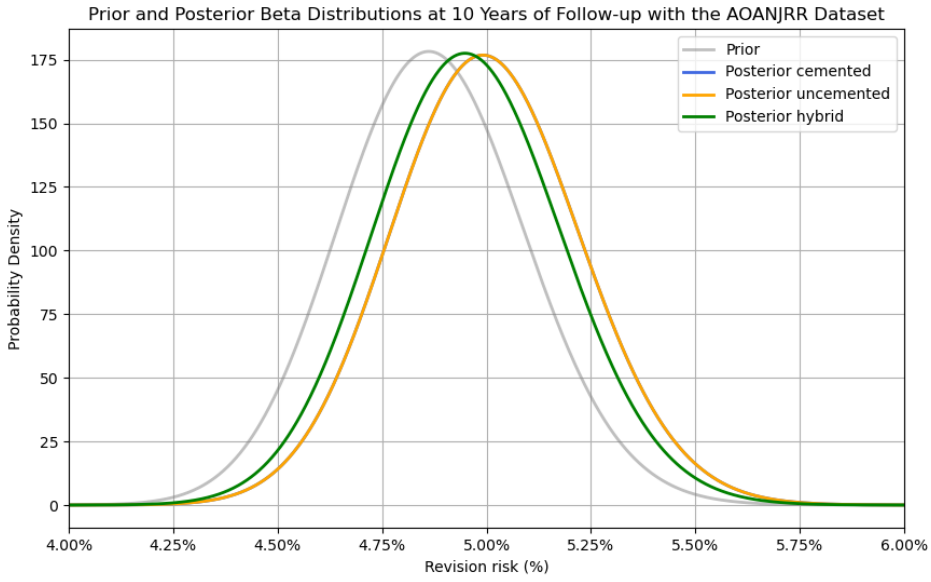

Figure 3 Prior and Posterior Beta Distributions at 10 Years of Follow-up with the AOANJRR Dataset

9.3 Implementation and Results of the Bayesian Method with Confidence Intervals and the LROI Dataset

The same method as that in the previous section has been implemented with the LROI dataset. This posterior represents an updated estimate of the revision risk for an implant variant given a particular characteristic type, given Fixation and revision risk information from the LROI dataset at 3, 5, and 10-years of follow-up. This is shown in Table 16. The prior and posterior distributions for 5 and 10 years of follow-up, shown in Figure 5 and Figure 6, is relevant for the discussion chapter. The figure for the 3-year follow-up period is included in the supplementary material.

9.3.1 *Results of this Iteration of the Method*

The iteration of the method remains the same as the previous but is just implemented with the LROI dataset. It produces results in the same form as that in the previous iteration of the method, and there are 9 combinations of the types of fixation and years of follow-up. For later interpretation, the probability of the interval $[0, \tau_t)$ is calculated.

There is a large deviation of the posterior compared to the prior distribution and the posterior probabilities for the interval $[0, \tau_t)$ for cemented implants is zero, while the prior probability is not. This is discussed in the section *Further Discussion of Key Results of the Implemented Bayesian Method*. Posterior probabilities are also lower than the prior probabilities for all the types of characteristics and years of follow-up.

		Prior					Likelihood parameters		Posterior	
Year t	**Fixation type**	**Prior mean (%)**	**Prior SD[6] (%)**	**Prior Beta parameter a**	**Prior Beta parameter b**	**Condition $\sigma_{wa}{}^2 < \mu_{wa}(1 - \mu_{wa})$**	**k_t**	**n_t**	**Posterior Beta parameter a**	**Posterior Beta parameter b**
3	Cemented	3.34	0.26	159.99	4632.39	Yes	127	362	286.99	4867.39
5	Cemented	4.33	0.31	192.41	4252.90	Yes	109	327	301.41	4470.90
10	Cemented	5.75	0.41	186.22	3050.86	Yes	69	224	255.22	3205.86

Table 16 Results and Calculations of the Implemented Bayesian Method Incorporating Confidence Intervals Using the LROI Dataset, REDACTED

[6] SD: Standard Deviation

Year	Threshold Interval $0 < R_t < \tau_t$ (%)	Fixation type	Prior Probability (%)	Posterior Probability (%)
3	[0.00,3.50)	Cemented	73.84	0.00
5	[0.00,4.00)	Cemented	14.00	0.00
10	[0.00,5.00)	Cemented	2.88	0.00

Figure 4 Prior and Posterior Probabilities of the Implant's Revision Risk Being Below the Threshold Value or the Probability of the Implant being "Good" with the LROI Dataset, REDACTED

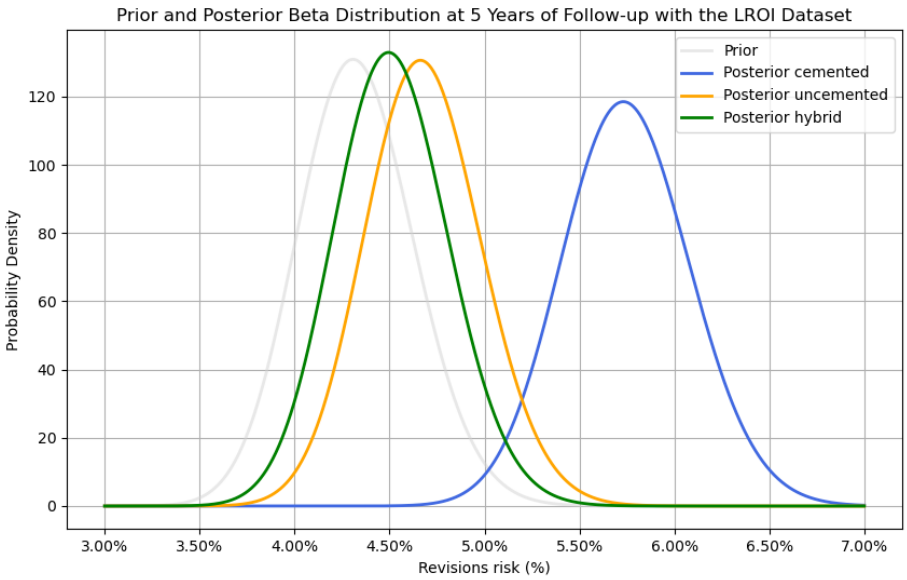

Figure 5 Prior and Posterior Beta Distributions at 5 Years of Follow-up with the LROI Dataset

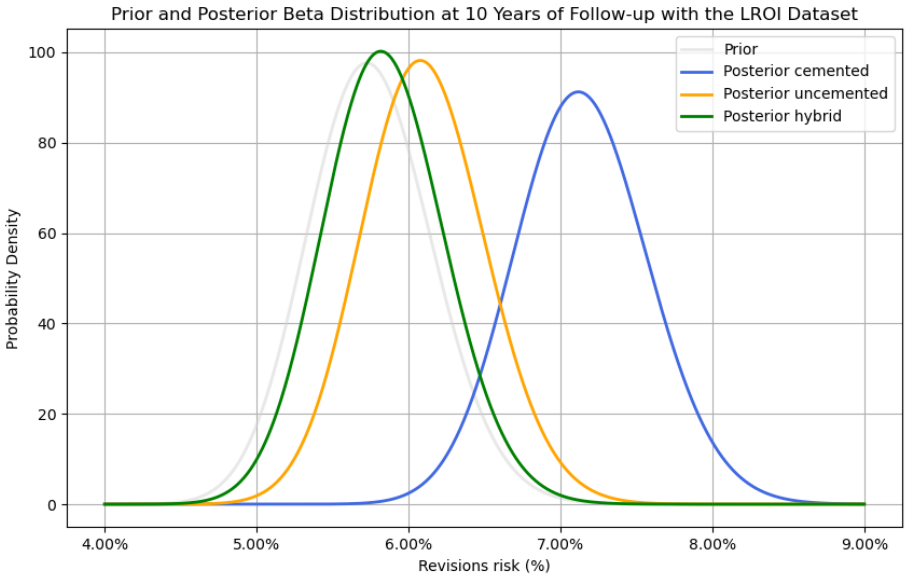

Figure 6 Prior and Posterior Beta Distributions at 10 Years of Follow-up with the LROI Dataset