Predicting Risk in the Management of Infection in Orthopaedics

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To endure uncertainty is difficult, but so are most of the other virtues.
— Bertrand Russell, Philosophy for Laymen, 1946

Since all models are wrong the scientist cannot obtain a "correct" one by excessive elaboration.
— George Box, p.792, Journal of the American Statistical Association, December 1976

Instead of pathologising every human quirk, we should say, *By the grace of this behaviour, this individual has found it possible to continue.*
— Sarah Manguso, 300 Arguments, 2017

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[1] Janelle Monae

Abstract

Bone and joint infections are a significant issue, affecting thousands more people each year and costing over £50 million to treat in the UK alone. Infection returns for many adults, even after intensive treatment with surgery and antibiotics. Ongoing bone and joint infection is painful and dispiriting; one in eight sufferers report a quality of life worse than death. People whose infection is not cured may need life-long antibiotics to suppress it, which can lead to antibiotic resistance and serious side-effects. Ongoing infection may require risky surgery, and itself has a higher mortality than many cancers.

The body's ability to heal and fight infection around the time of orthopaedic surgery is crucial. This is a period where infection may become established on bone and implants, in such a way that only further surgery can reliably eradicate it. Healing may be affected by illness and some behaviours such as smoking. 'Pre-habilitation' before surgery for orthopaedic infection might help healing, and reduce the chances of infection coming back.

Understanding which treatments work for different people affected by orthopaedic infection, and whose infection is most likely to come back, can help to tailor treatments and guide future research. This project describes studies that identify how different people with orthopaedic infection respond to treatment differently. One part describes developing a prognostic tool to predict whose infection is most likely to return. Other sections describe how best to help people with orthopaedic infections achieve the best health before an operation. Throughout the project, the experiences of people with orthopaedic infection are centred, and contribute to guiding recommendations for treatment.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

A&E .... Accident and Emergency

ASA .... American Society for Anaesthesiologists

AUROC .... Area Under Receiver-Operated Characteristic curve

BCT .... Behaviour Change Technique

CMOC .... Context-Mechanism-Outcome Configuration

COM-B .... Capability-Opportunity-Motivation Behaviour model

CRP .... C-reactive protein

DAIR .... Debridement, Antibiotics and Implant Retention

EQ-5D .... Euroqol Five Domain Questionnaire

FRI .... Fracture-Related Infection

GIRFT .... Getting It Right First Time

GP .... General Practitioner (primary care physician)

HbA1C .... Glycated haemoglobin

HTE .... Heterogeneity of Treatment Effects

IMD .... Index of Multiple Deprivation

IPTW .... Inverse Probability of Treatment Weighting

KIPI .... Key InPatient Indicators

MAR .... Missing At Random

MBIC .... Minimum Biofilm-Inhibitory Concentration

MIC .... Minimum Inhibitory Concentration

MICE .... Multiple Imputation by Chained Equations

MNAR .... Missing Not At Random

NRT .... Nicotine Replacement Therapy

PJI .... Prosthetic Joint Infection

PROM .... Patient-Reported Outcome Measure

TDF .... Theoretical Domains Framework

1 | Why this project is necessary

1.1 Aim and Objectives

This thesis describes work carried out as part of National Institutes of Health Doctoral Research Fellowship (NIHR300249) to investigate treatment outcomes for people with orthopaedic infections, and to guide pre-operative optimisation for people with these conditions.

1.2 Thesis Outline

The remainder of this thesis is organised as follows:

Chapter 2 — introduces orthopaedic infections and their treatment.

Chapter 3 — describes a published systematic review of prognostic studies.

Chapter 4 — describes an observational study of multi-disciplinary treatment options for Fracture-Related Infection.

Chapter 5 — presents a prognostic modeling study of treatment outcomes for orthopaedic infections.

Chapter 6 — presents a qualitative study of the barriers and facilitators to pre-operative health optimisation.

Chapter 7 — synthesises recommendations for pre-operative behavioural intervention.

Chapter 8 — provides closing remarks.

1.2.1 Orthopaedic infection in adults is a growing problem with a great personal and financial cost

Orthopaedic (bone and joint) infection is a devastating illness that affects a growing number of people in the UK every year.(Malizos, 2017; Lamagni, 2014; Lenguerrand et al., 2017) Infection is the leading course of morbidity after orthopaedic surgery, and is responsible for around one in seven acute orthopaedic admissions to hospital.(Howell, Parker, Tsitsakaris, & Oddy, 2016) Treatment places a significant financial burden on the NHS, as each admission for revision arthroplasty surgery is estimated to cost £30,110 on average. (Kallala, Vanhegan, Ibrahim, Sarmah, & FS, 2015)

Though the exact incidence is unknown due to differences in diagnostic approach, it is likely that between 1000 and 5000 people in the UK develop prosthetic joint infection every year. (Lamagni, 2014; Lenguerrand et al., 2017; Howell et al., 2016; Patel, Pavlou, Mujica-Mota, & Toms, 2015) This orthopaedic infection is projected to rise over the next 10 years, following rising rates of joint replacement, diabetes mellitus prevalence, and population ageing. (Patel et al., 2015; Zmistowski, Karam, Durinka, Casper, & Parvizi, 2013) Additionally, nearly one in three people with severe limb trauma develop orthopaedic infection. (Malizos, 2017; A. Harris, Althausen, Kellam, Bosse, & Castillo, 2009) More than 5000 people are admitted to hospitals with complications of limb trauma in England every year. (NHS Digital, 2018) On the whole, the incidence of native osteomyelitis and fracture-related infection are likely to be between 10 and 20 per 100,000 adults per year in European countries.(Walter, Rupp, Baertl, Hinterberger, & Alt, 2022)

Orthopaedic infection has a severe impact on a person's life: in one study, 12 percent of people affected by prosthetic joint infection reported a quality of life worse than death; they described severe pain, helplessness, anxiety and depression associated with their infection. (Moore, Blom, Whitehouse, & Gooberman-Hill, 2015) (Cahill, Shadbolt, Scarvell, & PN, 2008) People affected by fracture-related infection had a worse quality of life than those with unhealed fractures or limb amputations. (Lerner, Esterhai, Polomano, Cheatle, & Heppenstall, 1993) The five-year survival of people affected by prosthetic joint infection is lower than that of people diagnosed with breast cancer, prostate cancer, or malignant melanoma. (Zmistowski et al., 2013) Though the surgical treatment of orthopaedic infection is often perceived to be equivalent to primary arthroplasty or fracture fixation, the morbidity and mortality following staged arthroplasty revision may exceed major procedures such as coronary artery bypass grafting and prostatectomy.(Browne, Cancienne, Novicoff, & Werner, 2017)

1.2.2 The pathophysiology of established orthopaedic infection necessitates surgical treatment

Unlike other infections where antimicrobial treatment alone may suffice for cure, established bone or joint infection requires surgical debridement.(Lew & Waldvogel, 2004; Gehrke, Parvizi, & Chen, 2013) In orthopaedic infections, bacteria or fungi form adherent slime –biofilm –on implants or bone. (Gristina, 1987; Lew & Waldvogel, 2004) Bacteria in biofilm are tolerant to antibiotics, sometimes needing more than a hundred times the antibiotic concentration to stop growth.(L. Webb, Holman, de Araujo, Zaccao, & ES, 1994; Zimmerli & Sendi, 2017) Other modes of bacterial adaptation, including intracellular persistence, are likely to contribute to antibiotic tolerance. (Gimza & Cassat, 2021; Tuscherr et al., 2016)

The immune response is ineffective once orthopaedic infection is established.(Lew

& Waldvogel, 2004) Both immune and bacterial damage contribute to bone resorption.(Veis & Cassat, 2021; Asensi et al., 2004; Sanchez et al., 2013) Islands of dead, devascularised bone tissue serve as reservoirs for bacterial persistence.(Veis & Cassat, 2021; Hofstee et al., 2020; Jensen, Johansen, & Jensen, 2017) Thereafter, infection may be temporarily controlled, but cannot be cured, with antibiotics alone. Cure requires surgical debridement to remove biofilm and devascularised tissue. If biofilm has already formed on an implant, washout and antibiotics alone could allow bacterial cells with increased antibiotic tolerance to persist on it.(Urish et al., 2016) Indeed, emerging antibiotic resistance to rifampicin and fluoroquinolone antibiotics can result directly from attempted suppression of staphylococcal orthopaedic infection on a retained infected arthroplasty implant. (Lora-Tamayo et al., 2013)

The curative surgical approach to established orthopaedic infection is complex and requires careful planning. A multi-disciplinary approach including orthopaedic and plastic surgeons, infection physicians, specialist nursing and rehabilitation specialists, improves treatment outcomes.(Gehrke et al., 2013; Bose, Kugan, Stubbs, & McNally, 2015; NHS Commissioning Board, 2013; Takanari et al., 2018) Thus, in current UK practice, it is usual that at least four weeks elapse between specialist clinical assessment and surgical management of established orthopaedic infection.

1.2.3 Healing after surgical treatment is essential to prevent recurrence

Around one in five patients experience a recurrence of orthopaedic infection despite the best available treatment.(Lew & Waldvogel, 2004; Lenguerrand et al., 2017) People whose infection persists may undergo further surgical procedures and take prolonged suppressive antimicrobial treatment. This contributes to morbidity, more than two-fold higher mortality compared with non-infected revision orthopaedic surgery, and antimicrobial resistance. (Zmistowski et al., 2013; Lora-Tamayo et al., 2013; Lensen et al., 2021)

Orthopaedic infection surgery already applies strategies to reduce the risk of recurrence, within the Getting It Right First Time framework: skin preparation, laminar airflow, intra-operative antimicrobial prophylaxis, reduced surgical duration, the maintenance of euglycaemia and euthermia.(Briggs, 2015) These strategies, even when implemented in specialist centres, do not fully eliminate the risk of orthopaedic infection or its recurrence. (Blom et al., 2004)

Around half of patients treated for orthopaedic infections in reported series have at least one comorbidity that might contribute to infection recurrence. (Li et al., 2019; Kunutsor et al., 2018) Modifiable prognostic factors affecting health, such as malnutrition, suboptimal blood glucose control, smoking and alcohol use, can impair healing and immunity. (MacRury, Gemmell, Paterson, & AC, 1989; Ranzer, Chen, & DiPietro, 2011; Barr et al., 2016; Silverstein, 1992; Hawn, Houston, & Campagna, 2011) Behavioural interventions addressing these factors are effective, and have been demonstrated to improve outcomes after surgery. (Boylan, Bosco, & Slover, 2019; Theadom & Cropley, 2006; Norman, Pichard, Lochs, & Pirlich, 2008) Bone healing in particular is adversely affected by smoking, but this, and other outcomes from orthopaedic surgery, may improve with as little as four weeks of pre-operative smoking cessation.(Truntzer, Vopat, Feldstein, & Matityahu, 2014) Nevertheless, pre-habilitation interventions addressing patient behavioural factors that influence recovery are not routinely available within clinical services for orthopaedic infection. (Blom et al., 2004; NHS Commissioning Board, 2013)

1.2.4 Pre-habilitation may improve antimicrobial stewardship in orthopaedic infection

Current recommendations for antimicrobial therapy in orthopaedic infection include long courses of systemic antibiotic treatment in many cases, including the option of lifelong suppressive antimicrobial therapy if surgical treatment is unsuccessful. (Gehrke et al., 2013) Improving the likelihood of successful treatment first time may contribute to reductions in antibiotic use, and reduce selective pressure for antibiotic resistance.

1.2.5 Behaviourally modifiable factors and prognosis after surgery for orthopaedic infection

Current consensus guidelines for orthopaedic infection treatment agree that modifiable factors influenced by patient behaviour, such as nutrition, alcohol and illicit drug use, and smoking, are likely to be associated with worse outcome following both primary arthroplasty surgery and orthopaedic infection surgery.(Gehrke et al., 2013) However, a recent systematic review identified no reliable prognostic scoring tools for infection following primary arthroplasty, let alone any that included behaviourally modifiable factors.(Kunutsor, Whitehouse, Blom, & Beswick, 2017)

Chapter 3 describes a systematic review of prognostic studies aiming to predict treatment outcome in patients with surgically-treated orthopaedic infections, that included modifiable prognostic factors. In summary, no existing clinical prediction models or prognostic epidemiologic studies were identified that were at low risk of bias.

Chapter 4 describes work seeking to elucidate the possible contribution of differences in both surgical and antimicrobial treatment, to outcomes after surgery for orthopaedic infection.

Chapter 5 describes the development and internal validation of a prognostic model for orthopaedic infection recurrence that includes patient health factors chosen for interoperability across healthcare settings.

Chapter 6 shares a qualitative study focusing on the experiences of people with orthopaedic infection, and possible factors affecting treatment outcome, in the pre-operative period.

Chapter 7 describes a realist synthesis providing recommendations for pre-optimisation tailored to the needs of people with orthopaedic infection.

2 | Orthopaedic infections: pathophysiology and clinical features

2.1 Introduction to orthopaedic infection

This section introduces key clinical concepts in the diagnosis and treatment of orthopaedic infection.

2.1.1 Definition

Orthopaedic infection (for the purposes of this work) refers to infections that involve bone tissue, native joints, or orthopaedic implant surfaces. It is understood that isolated musculoskeletal soft tissue infections may be included under this description in other works.

Osteomyelitis is a disorder characterised by inflammation and destruction of bone tissue, due to infection, where the presence of micro-organisms causing the infection is demonstrated or inferred. (Lew & Waldvogel, 2004) There are different subtypes of osteomyelitis, which together make up a spectrum of clinical disorders. These include acute (early and often severe) infections, and chronic (late and often indolent) infections.

Osteomyelitis caused by micro-organisms circulating transiently in the bloodstream is called haematogenous osteomyelitis, and often presents as an acute infection of long bones in children, or vertebrae and intervertebral discs in adults. Persisting haematogenous osteomyelitis can manifest as a chronic infection, sometimes staying asymptomatic until many years after the original infection.

Fracture-related infection (FRI) may follow either an open fracture (where the bone was exposed to the outside world during the injury that caused the fracture) or surgery to repair the fracture. Both these situations allow micro-organisms from the outside world to reach bone tissue. FRI can present as an acute or chronic infection, often accompanies implants used to stabilise a fracture, and may result in the fracture failing to heal (fracture non-union).

Osteomyelitis can result from micro-organisms reaching bone through a persisting defect in the skin and underlying soft tissue. Examples of this kind of infection, termed contiguous focus osteomyelitis, include bone infections in the feet of people with diabetes mellitus (diabetic foot infection), and pressure ulcer associated osteomyelitis. Most commonly this presents as chronic osteomyelitis.

Infection of joint replacements can affect the surrounding bone in which these implants are placed. This is termed prosthetic joint infection (PJI). This can present as both an acute or a chronic infection. Though clinically difficult to distinguish, PJI may be caused either by micro-organisms reaching the implant at the time of surgery or wound healing, or later through the bloodstream.

2.1.2 Pathophysiology

The most common micro-organisms causing osteomyelitis are staphylococci, Gram positive bacteria that live on the skin and mucous membranes. *Staphylococcus aureus* and *Staphylococcus epidermidis*, as well as other coagulase-negative staphylococci, are found in about 20-50 percent of orthopaedic infections. (Lew & Waldvogel, 2004)

Other common pathogens found in osteomyelitis include Gram positive bacteria such as streptococci and enterococci, *Cutibacterium acnes*, *Corynebacterium species*; and Gram negative bacteria such as Enterobacteriaceae and *Pseudomonas aeruginosa*. More than one micro-organism may be involved in an infection, particularly in infections where there has been a communication between the bone and the skin surface, such as contiguous focus osteomyelitis or chronic osteomyelitis where a sinus is present. (Dudareva, Hotchen, et al., 2019)

Chronic infection caused by Staphylococcus aureus has been used as a model system to show bacterial adaptation to survival in bone tissue and on the surface of orthopaedic implants. Other micro-organisms causing osteomyelitis share many of the same pathological adaptations, the most characteristic being the ability to form biofilm. Biofilm is a complex community of one or more microbial species, that adheres to a surface (including the surface of bone cortex or trabeculae, or the surface of an orthopaedic implant), and facilitates the micro-organism's persistence on that surface. (Gristina, 1987) (Zimmerli & Sendi, 2017)

Staphylococcus aureus produces substances that allow it to evade the human immune system. These include Protein A and MHC class II Analogue Protein, both of which alter the behaviour of osteoclasts (bone macrophages) and T lymphocytes. (Gimza & Cassat, 2021) *Staphylococcus aureus* also secretes Coagulase and von Willebrand Factor-Binding Protein, both of which usurp the human clotting cascade to form a shell of clot material around the bacteria. This allows staphylococci, and other micro-organisms that co-occur, to form adherent groups called abscess summary , protected by a shell of fibrin and leukocytes. Abscess communities provoke the immune system further, causing destructive inflammation that can block off the blood supply to islands of bone and lead to patchy bone death.(Hofstee et al., 2020) Large fragments of dead bone are a characteristic of chronic osteomyelitis, and are called sequestra. (Lew & Waldvogel, 2004)

Staphylococcal attachment to bone is facilitated by substances produced by the bacteria, including Collagen Adhesion Protein, and those found within the bone, including bone sialoproteins. Many bacteria secrete extracellular matrix proteins, polysaccharides and nucleic acids including DNA and RNA. These substances are the bacterial contribution to the building blocks of biofilm, though in osteomyelitis, human extracellular matrix substances are also implicated in its persistence. (Jensen et al., 2017) (Gimza & Cassat, 2021) Bacteria living in biofilm may undergo a series of changes to their metabolism, where some bacterial cells become slowly growing and metabolically inactive. This quiescent bacterial phenotype is less susceptible to antimicrobial drugs (antibiotics), often by several orders of magnitude. The concentration of an antibiotic that is needed to stop the growth of staphylococci living in a biofilm is sometimes 100-1000 times what would normally be effective for single-celled rapidly-dividing staphylococci, and hundreds of times higher than what can be achieved in the human body when antibiotics are given as an intravenous injection or a tablet. (L. Webb et al., 1994) Staphylococcal clones called Small Colony Variants (SCVs) sometimes arise in chronic orthopaedic infections. These bacteria are characterised by slowed metabolism, increased tolerance to antibiotics, and infections in which they are found are more resistant to treatment. (Tuscherr et al., 2016)

The human immune response to bacteria that are attached to a surface, is ineffective. It is characterised by a process called frustrated phagocytosis, that manifests in neutrophils and macrophages responding to infection on the surface of bone tissue or implants. (Vaudaux, Zulian, Huggler, & Waldvogel, 1985) The immune response can also contribute to the persistence of osteomyelitis. Cytokines such as IL-6 contribute to a self-reinforcing inflammatory micro-environment in osteomyelitis by extending the lifespan and increasing the activity of neutrophils and macrophages. (Asensi et al., 2004) Bacterial proteins, such as staphylococcal Protein A, can inhibit the differentiation of osteoblasts (bone forming cells), and cytokines that affect phagocyte differentiation also promote osteoclast differentiation and bone resorption. (Sanchez et al., 2013; Widaa, Claro, Foster, O'Brien, &

SW, 2012) These effects can combine with bacterial activity to result in the characteristic bone resorption (osteolysis) observed in osteomyelitis. (Veis & Cassat, 2021)

2.1.3 Clinical presentation

Osteomyelitis may be intensely painful. Bone resorption and death resulting from osteomyelitis can cause bone deformities and resulting functional impairment, such as the inability to put weight through a lower limb.

Acute osteomyelitis is characterised by signs of local inflammation (swelling, warmth and redness around the area of infection). Systemic features of infection, including fever, rigors, loss of appetite, fatigue and malaise, are also common.

In chronic osteomyelitis, infection usually persists without prominent systemic features of infection, other than during flares. Pain may be the only symptom, though fatigue and malaise are also common. Signs of local inflammation are prominent when there is a flare of infection, but may be absent otherwise. A communication from the area of infected bone to the skin surface, called a sinus, is pathognomonic for chronic osteomyelitis, but is not always present. (Lew & Waldvogel, 2004)

There is no clear distinction between when an orthopaedic infection can be called "acute" or "chronic". Definitions of chronic infection sometimes specify the presence of symptoms for at least 6 weeks, though the evidence that different treatment is effective depending on the time from symptom onset is lacking. (Zimmerli & Sendi, 2017) The presence of sequestra or sinuses are indicators of infection where biofilm is established and an inflammatory micro-environment has become self-sustaining, as is typically considered to be the case in chronic osteomyelitis. (Lew & Waldvogel, 2004) However, biofilm is established over a period of hours to days, suggesting that these changes may be present in what would otherwise be considered acute infection. (Tomizawa et al., 2021) (Jensen et al., 2017)

Unlike other infections, chronic osteomyelitis usually fails to respond to systemic (tablet or injection) antibiotics. Antibiotics without surgery cannot eradicate bacteria on or in dead bone, abscesses, implants and bacterial biofilm. (Zimmerli & Sendi, 2017) (Lew & Waldvogel, 2004) Once biofilm and sequestra form, and sinuses provide an ongoing channel for bacteria to re-enter the bone, or the persistence of bacteria is enabled by the presence of an implant (such as in PJI), definitive cure requires a combination of surgical debridement and antimicrobial therapy.

2.1.4 Diagnostic criteria

No clinical features reliably distinguish between orthopaedic infection and other osteoarticular pathologies, such as inflammatory arthritis, aseptic prosthetic joint loosening and sterile fracture non-union. (McNally et al., 2021)

There are no blood biomarkers in routine diagnostic use that can identify osteomyelitis, or that are sensitive enough to rule it out. Inflammatory markers including C reactive protein (CRP) and peripheral white blood cell counts may be elevated in both acute and chronic osteomyelitis, but are very commonly in the normal range, particularly in chronic osteomyelitis and after the administration of antibiotics. (Michail et al., 2013)

Radiology imaging including plain radiography, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) can all contribute data towards making a diagnosis of osteomyelitis. In chronic infection, sequestra, abscesses, sinuses and new areas of growing bone around an area of chronic osteomyelitis, known as involucra, can be often visualised on plain radiographs. (Lew &

Waldvogel, 2004) However, in people with acute infection, those who have had recent surgery or who have had previously treated bone infection, some changes and abnormalities may persist that are non-specific. In infections where implants are present, an area of bone resorption around the implant (also called implant loosening) can indicate infection, though it can also indicate other disease processes such as metallosis. (Lohmann, Rampal, Lohrengel, & Singh, 2017) Imaging modalities that target the presence of local inflammation, including nuclear imaging techniques, may show non-specific changes in the first three months after surgery, and are not sensitive enough to reliably rule out the presence of quiescent chronic osteomyelitis when the clinical suspicion is otherwise high. (Govaert, IJpma, & McNally, 2017)

Since all body surfaces, including wounds and ulcers, are normally colonised by bacteria, surface swabs for microscopy and culture are not able to confirm, exclude or guide treatment in contiguous focus osteomyelitis, or where a sinus is present. Sinus or wound bacterial culture does not predict the results of deep tissue specimen culture. (Mackowiak, Jones, & Smith, 1978) Microbiological culture from surgical debridement or biopsy, where several deep bone specimens are collected in an aseptic and mutually independent manner, can confirm the presence of infection and guide treatment. One or two specimens are much less reliable, because of the possibility of specimen contamination, and the fact that the most frequent pathogens in osteomyelitis are also bacteria that are present on the skin and are the most frequent contaminants during sample harvesting and laboratory processing. (B. L. Atkins et al., 1998; Dudareva, Barrett, et al., 2021)

Even so, around a quarter of cases of osteomyelitis are culture-negative, which means that no bacteria are identified on adequate deep surgical tissue sampling with optimal laboratory culture techniques, despite there being clear signs of osteomyelitis. (Tan et al., 2018; Dudareva, Hotchen, et al., 2019) This means the absence of micro-organisms identified at the time of biopsy or debridement surgery cannot rule out an infection. Sometimes this is due to the presence of bacteria that are difficult or impossible to culture using routine laboratory methods (*Brucella* species, *Coxiella burnettii*, mycobacteria, staphylococcal small colony variants). In other cases this results from pre-operative antibiotic exposure making live bacteria more difficult to recover. Lastly, osteomyelitis often follows a patchy microscopic distribution, so not all bone samples might contain bacteria. (Lew & Waldvogel, 2004)

Diagnostic criteria for osteoarticular infections such as PJI and FRI include confirmatory intra-operative tests that have higher specificity for infection, and can be used to rule out infection or diagnose other pathology. Pre-operative diagnosis, and thus pre-operative selection of study participants that definitely *do* have orthopaedic infections, is not currently feasible.

The EBJIS definition of PJI, for example, includes several confirmatory criteria for infection. The following factors confirm that infection is present, for someone in whom it is suspected synovial fluid leukocyte count and neutrophil percentage, synovial fluid alpha defensin, intra-operative microbiological culture from deep tissue specimens or sonication of implants, and histopathological detection of neutrophils in bone specimens. (McNally et al., 2021) Nevertheless, people who do not meet the criteria for confirmed infection may still have PJI, and it is not expected that all PJI will meet confirmatory criteria. Confirmatory criteria in other diagnostic definitions, including the MSIS 2018 definition and the IDSA 2013 definition, also include only intra-operative results and the presence of a sinus as major criteria for diagnosis. (Parvizi et al., 2018) (Osmon et al., 2013) A validation study of diagnostic criteria for FRI found that though confirmatory criteria had excellent specificity for dianosing FRI, many clinically diagnosed FRI were only identified through a combination of suggestive criteria. (Onsea et al.,

2022) This means that there is no extant gold standard for ruling out orthopaedic infections, or for distinguishing them from other similar pathological processes including inflammatory and degenerative conditions.

2.1.5 Principles of surgical treatment

Surgical debridement is an essential part of chronic osteomyelitis treatment, and should include abscess drainage and removal of dead and devascularised bone fragments, foreign bodies and loose implants. This may be planned electively for people who do not have structural skeletal instability, acute soft tissue compromise, or systemic symptoms of infection. Implant loosening, fracture non-union and bone deformity are common in orthopaedic infections, and generally require surgery.

Multi-disciplinary surgical planning including arthroplasty specialists, limb reconstruction surgeons and plastic surgical specialists helps achieve the best chance of cure. (Bose et al., 2015) (Takanari et al., 2018) One-stage surgery where the surgical wound is closed immediately prevents bacteria from re-entering bone and forming biofilm, but also improves healing, functional outcomes and patient satisfaction. (Galitzine, Wilson, Edington, Burumdayal, & McNally, 2017)

2.1.6 Principles of antimicrobial therapy

Antibiotics may be curative in acute haematogenous osteomyelitis, but treatment of chronic or complicated osteomyelitis usually requires a combination of antibiotics and surgery. Suppressive antibiotic therapy without surgery is usually ineffective in preventing symptom flares, sinus discharge, or implant loosening. (Lensen et al., 2021)

Oral antibiotics may be as effective as intravenous antibiotics for acute osteomyelitis and surgically debrided chronic osteomyelitis or implant-associated infection. (Li et al., 2019) Biofilm active antibiotics such as rifampicin are recommended when a well-fixed implant is retained. Rifampicin-combination regimes have been associated with improved outcomes in staphylococcal osteoarticular infections. However drug interactions and inadvertent rifampicin monotherapy (which risks selection of rifampicin-resistant staphylococcal clones) must be avoided. (Zimmerli, Widmer, Blatter, Frei, & Ochsner, 1998)

2.1.7 Economic cost of orthopaedic infection

Orthopaedic infections occur in a growing number of people in the UK and other countries. (Lamagni, 2014; Lenguerrand et al., 2017; Malizos, 2017; Kremers et al., 2015) Infection is the leading cause of morbidity after orthopaedic surgery, and is responsible for one in seven acute orthopaedic admissions to hospital.(Howell et al., 2016; A. Harris et al., 2009) Revision arthroplasty surgery in particular places a significant financial burden on the NHS, with each admission for revision surgery estimated to cost an average of over £30,000. (Kallala et al., 2015) The projected cost of treatment in the UK alone is expected to exceed £50 million per year in the next decade. (Lenguerrand et al., 2017)

According to National Joint Registry data, the rate of revision surgery for infected arthroplasty is continuing to rise in the UK, affecting several thousand people annually. (Lenguerrand et al., 2017) As more arthroplasties are performed to treat osteoarthritis and inflamatory arthritides, and people survive longer with joint implants, the risk of infection is played out over longer implant lifetimes. Up to one in three people affected by severe orthopaedic trauma develop FRI. (Kremers et al., 2015) The annual incidence of FRI and other osteomyelitis in Western Europe is estimated to be around 20 per 100,000 people. (Walter et al., 2022) Diabetic foot infection is the leading cause of admission for people with diabetes. Amputation for diabetic foot disease including osteomyelitis was estimated to cost the NHS in excess of Â£960 million per year. (Kerr et al., 2019)

2.2 Prognosis of orthopaedic infection

The prognosis of surgically-treated chronic orthopaedic infection, which is the major focus of this project, is comparable. Chronic long bone osteomyelitis, either FRI or of haematogenous or other aetiology, has a good prognosis, with around 10 percent recurring after 1-2 years, and better treatment outcomes with excellent multi-disciplinary care in specialist centres.(McNally et al., 2016; Ferguson et al., 2014; Taggart, Kerry, Norman, & Stockley, 2002)

PJI may be treated with several surgical approaches, including implant retention, single-stage revision or staged revision surgery. The selection of the treatment approach depends on whether the implant is well fixed - if there is osteomyelitis with radiological or clinical evidence of implant loosening, implant retention approaches are not recommended. The prognosis of people receiving surgical revision arthroplasty (where an implant is removed and exchanged) for infection is similar between single stage and two-stage revision, but varies depending on the population treated.(Kunutsor et al., 2018) Cohort studies often report between 70% and 90% success at two years.(Bejon et al., 2011; Stockley, Mockford, Hoad-Reddick, & Norman, 2008)

Contiguous focus osteomyelitis including diabetic foot infection and pressure ulcer related osteomyelitis have relatively similar prognosis, with surgical treatment, to other forms of osteomyelitis. (Lipsky et al., n.d.; Lew & Waldvogel, 2004; Larson, Hudak, Waring, Orr, & Simonelic, 2012)

2.2.1 Clinical criteria for treatment failure

Consensus criteria for treatment success have been developed for PJI. (Diaz-Ledezma, Higuera, & J, 2013) These include: the eradication of infection, characterised by wound healing without pain, the absence of infection with the same micro-organism strain as at initial treatment, no further surgical intervention after reimplantation of a prosthetic joint, and no infection-related mortality. However, these have not been universally applied in reported studies. Additionally, suppressive or episodic antimicrobial therapy are not included in this definition, and may characterise failure in the absence of other features.

2.2.2 Patient Reported Outcome Measures (PROMS)

Both generic and disease-specific Patient Reported Outcome Measures (PROMs) can be used to assess quality of life after orthopaedic surgery. Disease-specific scales include measures designed to assess function after specific arthroplasty surgery (hip and knee) and FRI affecting the lower limb. As these do not apply outside of specific anatomical constraints, it is difficult to use them to compare outcomes in people selected for cohort inclusion by the presence of infection, which can affect any bone.

Generic PROMs such as EQ-5D and SF-36 have been used to track changes in patient-reported quality of life following surgery for orthopaedic infections including PJI. (Walter et al., 2021) (Cahill et al., 2008) Baseline factors including the extent of bone involvement and clinician-assessed health status in the BACH classification of osteomyelitis are associated with generic PROMs at baseline and following surgery. (A. J. Hotchen, Dudareva, Corrigan, Ferguson, & McNally, 2020)

2.3 Peri-operative health and surgical outcomes in orthopaedics

Studies focusing on both primary post-operative orthopaedic infection, and recurrence of existing orthopaedic infection, have shown strong associations with baseline health. Existing illness can impair recovery after orthopaedic surgery and reduces the chances of successful orthopaedic infection treatment.

High BMI, diabetes mellitus, rheumatoid arthritis, chronic obstructive pulmonary disease, anaemia, and opioid use were associated with PJI after primary arthroplasty in a meta-analysis of 40 studies. (Ren et al., 2021) Chronic obstructive pulmonary disease was associated with 20% higher odds of primary infection, though self-reported smoking was not; measures of elevated BMI were associated with five-fold higher odds of primary PJI.

As well as anaesthetic complications including respiratory infection and peri-operative mortality, people who smoke at the time of surgery experience a higher risk of surgical site infection compared to people who have successfully quit smoking, and people who have never smoked, according to data from the Veteran's Affairs Health Network. (Hawn et al., 2011) People who smoked on the day of surgery were found to have a two-fold higher risk of surgical site infection in a case-control study, that observed a similar magnitude of the association between smoking and surgical site infection, in health records from the Mayo Clinic. (Nolan et al., 2017) A meta-analysis upheld the reduced incidence of post-operative complications in people who were able to stop smoking, compared with ongoing smokers. (Theadom & Cropley, 2006) Smoking cessation interventions were found to reduce surgical site infections by more than half in a meta-analysis of four randomised controlled trials involving participants undergoing a range of surgical procedures. (Sorensen, 2012) Smoking cessation interventions focusing on people awaiting primary arthroplasty surgery, where post-operative infection occurs in only between one in fifty and one in two hundred people, were found to be cost-effective in a decision analytic economic modelling study using reported outcome expectancies. (Boylan et al., 2019) Smoking cessation as little as 4 weeks before surgery appears to reduce surgical complications in surgery including arthroplasty. (Lindstrom et al., 2008)

2.3.1 Principles of Getting It Right First Time (GIRFT)

Getting It Right First Time started as a pilot project to improve the quality and cost-effectiveness of orthopaedic services by reducing unexplained variation in care, supporting evidence-based practice and reducing unnecessary expenditure such as the loaning of operating theatre equipment. This project continued as a peer-visiting and evidence gathering intervention, with wider reaching impacts including supporting high-volume surgical centres, the matching of training programmes to growing demand for arthroplasty and reducing funding shortfalls by ringfencing funding to enable quality care. (Briggs, 2015)

Evidence-based principles for surgical treatment in orthopaedics, particularly aiming to reduce post-operative orthopaedic infections, include perioperative euthermia and normoglycaemia, operative antimicrobial prophylaxis appropriate to the procedure being performed, and early rehabilitation interventions. CDC guidance for the prevention of surgical site infection recommend the following interventions:

- Bathing the day before surgery, using antiseptic, antimicrobial wash or normal soap
- Antimicrobial prophylaxis where therapeutic concentrations of the antimi-

crobial reach the surgical site during the procedure

- Skin preparation with an alcohol-based cleaning agent
- Intraoperative glycaemic control aiming for <200mg/dl
- Normothermia throughout surgery
- Increased inspired FiO2 intra-operatively and after extubation.

(Berrios-Torres et al., 2017)

Observational studies show conflicting results from better adherence to peri-operative best practice principles, possibly because the complexity of treatment or the baseline health of people being treated has also changed contemporaneously.(Blom et al., 2004)

2.3.2 Biological mechanisms for effects of peri-operative health on treatment outcomes

It is biologically plausible that smoking, nutrition, alcohol use and blood glucose have a consistent and dose-dependent effect on treatment outcomes after orthopaedic surgery, including surgery for infection.

Smoking has a complex effect on the immediate response to injury or surgery, including effects on the clotting cascade, granulocyte chemotaxis and behaviour, resulting in decreased migration of neutrophils into the surgical site. (Sorensen, 2012) Wound healing is impaired directly by the systemic effects of smoking through a combination of processes, including oxygen delivery and vasoconstriction, as well as systemic inflammatory responses. (Silverstein, 1992)

Alcohol has an acute and chronic effect on granulocyte RNA expression in primates, as well as changing the patterns of tissue lymphocyte subsets. (Asquith et al., 2014) (Barr et al., 2016) Mouse studies suggest that a single dose of ethanol at the time of an injury may reduce fibroblast collagen production and resulting wound breaking strength. (Ranzer et al., 2011)

Host factors including "nutritional immunity" affect bacterial access to glucose and other metabolic substrates. (Veis & Cassat, 2021) Hyperglycaemia has a direct effect on neutrophil function, impairing degranulation and phagocytosis. (MacRury et al., 1989) Malnutrition, conversely, has an observed association with surgical site infection owing to the modulation of host tissue remodelling by macronutrient and micronutrient availability. (Norman et al., 2008)

2.3.3 Observed effects of peri-operative health on treatment outcomes

Peri-operative comorbidity can predict treatment outcomes in people receiving arthroplasty surgery where an joint replacement implant is retained rather than exchanged. (Tornero et al., 2015), (Wouthuyzen-Bakker et al., 2019a) Additionally, associations between baseline health and outcome after primary arthroplasty have also been found in many retrospective studies. (Bozic, Lau, Kurtz, Ong, & Berry, 2012; Ren et al., 2021)

Quantifying these associations for people with existing orthopaedic infection has been hampered by small patient numbers and a lack of comparability between both inclusion criteria (diagnostic criteria for orthopaedic infection) in cohort studies, and outcome measures for treatment success.

The next chapter describes an analysis of existing literature focusing on the possible association between peri-operative health and prognosis in adults treated for orthopaedic infections. This work explores further the possible relationships with, and prediction value of peri-operative health factors for, treatment outcome after orthopaedic infection surgery.

3 | Systematic review of existing prognostic studies in orthopaedic infection

3.1 Aims and objectives

Risk prediction is part of all clinical decision making. A risk prediction model, an equation built on predictors and outcome data from patients, can contribute to evidence-based clinical care, and reduce bias and unwarranted variation in clinicians' decisions. Risk prediction models aim to estimate the probability of a patient experiencing a particular health outcome in the future, such as response to a treatment or mortality, within a certain period.(Grant, Collins, & Nashef, 2018) Risk prediction models may be used to decide the setting in which a patient is looked after,(NICE, 2016b) whether or not a diagnostic test should be used (Stiell et al., 1992) or a particular treatment should be offered,(NICE, 2016a) and to communicate risk around clinical decisions in a clear and open way.(Wishart et al., 1992) Risk prediction models may also be used as benchmarks to review treatment outcomes in different settings, adjusting for illness severity. In research, they can target the testing of new treatments towards patients most likely to benefit from them.

In the treatment of orthopaedic infection, a risk prediction model might be useful to inform discussions between clinicians and patients, if it were possible to accurately predict the success of treatment according to existing health and demographic parameters. The CRIME-80 points-based risk calculator and KLICC nomogram have been proposed to predict the risk of recurrent PJI after DAIR, wherein an infected prosthetic joint is retained during surgery, to guide clinical decision making.(Wouthuyzen-Bakker et al., 2019b; Duffy et al., 2018)

Existing classification systems for orthopaedic infections include modifiable behaviours such as smoking in the stratification of 'host status': the relevant elements of health that predict prognosis. The McPherson classification of PJI includes behaviours and comorbidities to stratify 'host status', however the rationale for their selection is not elucidated.(McPherson et al., 2002) The validation for this classification system described no association between host status and treatment outcome in 50 consecutive patients.

The BACH stratification tool for long bone osteomyelitis has recently been developed and validated.(A. J. Hotchen et al., 2020) The BACH classification system categorises the distribution of infection within a bone, the antibiotic options dictated by the microbes causing the infection, whether tissue transfer is required for wound closure at the time of surgery, and 'host status'. Host status is classified as favourable (H1) or unfavourable (H2). Some comorbidities were suggested to help clinicians differentiate between H1 and H2, but in practical use there was significant heterogeneity in how the host status classification was interpreted.(A. J. Hotchen, Dudareva, Ferguson, Sendi, & McNally, 2019)

The Cierny-Mader classification of long bone osteomyelitis divides adverse host status into local and systemic compromising conditions.(Mader, Shirtliff, & Calhoun, 1997) The Cierny-Mader classification of osteomyelitis specifies 'tobacco abuse, i.e. more than 2 packs per day' as the cut-off for conferring local compromise, but does not describe how this cut-off was derived. Phrases such as 'major vessel compromise' were not defined at all.

Classification systems for orthopaedic infection, such as the BACH system, would be compatible with a risk prediction model that included demographic factors, comorbidities and behaviours that predicted outcome after treatment for orthopaedic infection. This could be used to accurately stratify 'host status' in such a classification system.

Outcomes and experiences important for patients considering and undergoing orthopaedic surgery include pain, mobility and independence, fear (including that of acute septic deterioration for patients with infection), sleep, work, social function, and the possible burdens of treatment.(Moore et al., 2015; Trickett, Mudge, Price, & Pallister, 2012; Baumhauer, McIntosh, & Rechtine, 2013) Some of these domains are included in generic patient-reported outcome measures (PROMS) such as the EQ-5D score.(van Reenen et al., 2019) Prognostic models that predict quality of life after treatment may be at least as relevant for pre-operative decision making with patients as those that predict prognosis according to clinical features.

Consensus criteria for treatment success in orthopaedic infection are available for PJI but not for other orthopaedic infections.(Diaz-Ledezma et al., 2013) Primary diagnostic criteria for infection are sometimes used to classify treatment outcome.(Metsemakers et al., 2018; Lipsky et al., n.d.) Unfortunately, these clinical criteria may not be sufficiently sensitive to detect all reinfections or cases of infection recurrence, and for prosthetic joint infection, include a recursive definition that is open to confounding by decisions around investigation and treatment ('No infection recurrence caused by the same organism strain; no incident (new) infection with a different organism').(Diaz-Ledezma et al., 2013) Composite outcome measures with high inter-observer reliability, and appropriate PROMS, may provide most value for prediction modelling in orthopaedic infection.

The development, reporting and validation of risk prediction models has been extensively reviewed, and guidance is available for publication and for assessing the quality of published risk prediction model development and validation.(Collins, Reitsma, Altman, & Moons, 2015; Wolff et al., 2019; Moons et al., 2019, 2014) Particular points of importance in the development of prediction models include:

- How participants are selected, and whether this represents the population of interest;
- Sufficient numbers of participants with the outcome of interest to allow accurate modelling for all the prognostic variables of interest;
- How potential prognostic variables were chosen, measured and how many were considered from the start;
- Whether potential prognostic variables would be known at the time a clinical decision needs to be made;
- Retention of study participants to follow-up and primary outcome measurement;
- How and when outcomes are ascertained;
- Whether the measurement of prognostic variables and outcomes was independent;
- The assumptions and appropriateness of the modelling techniques used, including appropriate handling of missing data, non-linear associations, and retention of continuous variables without categorization, whether model discrimination and calibration were assessed, and whether model performance is adjusted for any potential overfitting.

(Moons et al., 2019)

A recent systematic review confirmed that there were no models able to accurately predict who was most at risk of infection following primary arthroplasty. (Kunutsor et al., 2017) No similar study has focused on prediction modelling for treatment failure in existing orthopaedic infections.

3.1.1 Aims

The aims of this systematic review of prediction studies in surgically-treated orthopaedic infection were:

1. To review and appraise clinical prediction models for surgical treatment of orthopaedic infection that included behaviourally modifiable factors. Clinical prediction models sought included substance use (at least smoking and alcohol intake), glycaemic control in the context of diabetes mellitus, malnutrition, and obesity.

2. To review and appraise other prognostic studies for surgical treatment of orthopaedic infection that did not fit the definition of clinical prognostic modelling, in order to identify the direction of effect of the association between behaviourally modifiable prognostic factors and successful treatment.

This systematic review has been published. (Dudareva, Hotchen, et al., 2021)

3.2 Methods

A systematic review (PROSPERO CRD42020177814) was carried out to identify and evaluate published studies reporting prognostic modelling of orthopaedic infection recurrence after surgical treatment (where this included removal of infected orthopaedic implants and bone debridement).

3.2.1 Search strategy

EMBASE and MEDLINE databases were searched. Secondary searching used reference lists from studies identified during the review process. Full search strings are presented in supplementary materials with the published study. (Dudareva, Barrett, et al., 2021)

The following studies were excluded:

- Case-control studies that did not adjust for population outcome risk;
- Those that focused predominantly on patients treated without surgery or without infected implant removal;
- Those that focused on orthopaedic infection affecting participants <18 years of age;
- Those that did not include follow-up of at least 6 months following surgical treatment.

3.2.2 Study population

Included studies specified that participants were adults with orthopaedic infection of any type.

3.2.3 Diagnostic criteria

Participants with any clinical diagnosis of orthopaedic infection were included, whether or not any specific diagnostic criteria were applied. Any diagnostic criteria that were used for participant selection, or the proportion of participants that met specific diagnostic criteria, was recorded during data extraction.

3.2.4 Treatment

This project specified that surgical treatment of orthopaedic infection necessitated debridement and infected implant removal or exchange where an infected implant was present. Studies focusing on surgical management where orthopaedic implants were retained at the site of index orthopaedic infection (such as in DAIR) were excluded, as the patient population and nature of the infections treated in this way were expected to differ systematically, and the recurrence rate was anticipated to be higher.

3.2.5 Predictors

Clinical prediction models sought included behaviourally modifiable factors such as narcotic substance use (at least smoking and alcohol intake), glycaemic control in the context of diabetes mellitus, malnutrition, and obesity. Other predictors included or considered in modelling were recorded. The direction and magnitude of the association between common predictors and outcome were assessed.

3.2.6 Outcome

The main outcome was recurrence of orthopaedic infection following treatment, or new orthopaedic infection at the same anatomic site as the index infection, defined using any criteria. This is referred to as ’treatment failure’. Composite outcomes that included diagnosis of, or treatment for, infection recurrence were also included if these were the primary outcome in the study. Patient reported outcome measures (PROMS) were considered as a secondary treatment outcome.

3.2.7 Model development and validation

Studies were identified as risk prediction modelling studies if they reported a multivariable (two or more predictors) risk prediction model for treatment failure. It was not always clear from reported aims and methods whether the study was intended to expose epidemiological associations or to construct a clinical prediction model for treatment failure. To group studies into clinical prediction modelling studies and other prognostic studies, several factors were extracted from the study report: the aims of the study, statistical modelling methods, model interpretation, intended use, and validation procedures.

3.2.8 Data extraction and analysis

Data extracted from each published study included:

- Study design;
- Participant selection and loss to inclusion or follow-up;
- Predictor selection and measurement;
- Incidence of the primary outcome;
- How the primary outcome was defined and ascertained;
- Handling of missing predictor and outcome data;
- Choice of statistical model;
- Handling of competing risks for the primary outcome, such as mortality and limb amputation.

For clinical prediction modelling, model shrinkage for overoptimism, model calibration and discrimination, and procedures for internal validation (such as bootstrap validation) and external validation were recorded.

For clinical prediction studies, applicability and risk of bias were assessed using the PROBAST tool.(Moons et al., 2019; Wolff et al., 2019) For other prediction studies, domains from the QUIPS tool and CHARMS checklist were used to ascertain study relevance and stratify risk of bias from low to high across methodological domains, in accordance with existing reporting guidelines for prognostic studies. (Hayden, van der Windt, Cartwright, Cote, & Bombardier, 2013; Moons et al., 2014) Appropriateness of sample size was assessed according to the number of listed predictors specified in the methods section of the report, or if this was not available, the predictors listed in univariable analysis. The minimum appropriate sample size was estimated using the pmsampsize package for R, assuming an estimated R^2 of 0.16 and parameters from the study report. (Martin, Riley, Collins, & Sperrin, 2021) Assuming an estimated average orthopaedic infection recurrence rate of 20 percent at least 12 months following treatment, the maximum attainable Cox-Snell R^2 is 0.63.

Data were extracted from studies by two researchers in parallel (Maria Dudareva and Andrew Hotchen), who independently assessed the risk of bias of included studies using pre-specified criteria described above. Disagreements were resolved by consensus with supervision from a third researcher if required.

Due to the anticipated heterogeneity of studies following a preliminary search in November 2018, guidance for Synthesis Without Meta-analysis (SWIM) was followed to specify summary measures for the prognostic factors of interest.(Campbell et al., 2020)

The direction of the association with outcome was determined for each prognostic variable. This was defined as positive (point estimate of odds ratio of treatment failure >1 for participants with the prognostic factor), negative (point estimate of odds ratio of treatment failure <1 for participants with the prognostic factor), or null (estimated odds ratio equal to 1). Adjusted values were preferentially recorded from multivariable modelling, if this included the prognostic factor of interest. Unadjusted odds ratios not reported in included studies were estimated from tables of baseline characteristics or calculated from published datasets if available.

Analyses were performed using R version 3.6.3.(R Core Team, 2020)

3.3 Results

Study selection is shown in 3.1. In total 35 studies met eligibility criteria and were included in the review, involving 92,693 participants recruited between 1987 and 2018. These are listed in detail in tables 1 and 2. All studies were retrospective analyses from secondary and tertiary care centres. The geographical distribution of reported studies included 18 from the USA, three from Taiwan, two each from the UK, Germany, France and China, and one each from Canada, Brazil, Spain, Italy, South Korea and Denmark.

Included studies are described in Table 1 in the published study. (Dudareva, Hotchen, et al., 2021) No studies performed multivariable modelling using generic or treatment-specific PROMS as outcomes, and only one study investigated the association between a prognostic factor and PROMS (Houdek et al., 2014). Twenty-five studies included a multivariable analysis of treatment outcomes, while 9 studies reported univariable analyses only. No studies published a model equation, though this was possible to estimate from data presented by Kheir et al. (2018).(Kheir et al., 2018)

Statistical synthesis was not undertaken as all studies were assessed to be at high overall risk of bias using the QUIPS tool, predominantly due to lack of reporting around how risk factors were measured, blinding between risk factor measurement and outcome measurement.(Moons et al., 2019) Studies did not include the same prognostic factors of interest in adjusted analyses. Additionally, sample size was assessed for each study, and model overfitting resulting from the inclusion of too many prognostic variables contributed to the assessment of risk of bias.(Hayden et al., 2013; Moons et al., 2014, 2019)

Study	Kheir et al. 2018	Sabry et al. 2014
Diagnostic definition	Standard	Non-standard
Participant flow	16.5% excluded (missing predictors or outcomes)	10.5% excluded (missing outcomes, no reimplantation)
Predictors	Smoking (ever) Injecting drug use BMI Sinus present Prior operations No blinding reported 10 predictors based on Akaike information criterion	Diabetes mellitus Immunocompromise Heart disease Symptom duration Prior operations No blinding reported Predictor selection not described
Outcome	At least 12 months follow-up Standard outcome definition	Minimum 59 days follow-up Ad hoc outcome definition
Analysis	C statistic: 0.69 (0.65 to 0.73) Calibration reported Validation not reported	C statistic: 0.77 Calibration not reported External validation not performed

3.3.1 Clinical prediction modelling studies

Two studies fit the definition of risk prediction modelling studies, and stated an aim of developing a prognostic model.(Kheir et al., 2018; Sabry, Buller, Ahmed, Klika, & Barsoum, 2014) Neither study performed an internal validation using bootstrap or cross-validation, nor external validation, nor was an external validation of these risk prediction models identified during this systematic review. Both studies were assessed against the PROBAST tool to have an overall high risk of bias, as described in the table.(Wolff et al., 2019)

Kheir et al. (2018) presented a logistic regression model for treatment failure as a risk calculator based on points scored for baseline prognostic factors following surgery for PJI.(Kheir et al., 2018) They included body mass index (BMI) and ever smoking in the prognostic calculator, as well as a number of other non-modifiable factors. The largest estimated odds ratios of treatment failure for dichotomous variables were conferred by treatment with irrigation and debridement rather than implant revision (OR 2.48), and a history of myocardial infarction (OR 1.57). For every unit increase in BMI, the odds of treatment failure were estimated to increase 1.02-fold. For participants who had ever smoked, the odds of treatment failure were estimated to increase 1.2-fold.

Sabry et al. (2014) created a nomogram, based on a logistic regression model, for predicting treatment failure following two stage revision arthroplasty for knee PJI.(Sabry et al., 2014) The prognostic variables included BMI, but adjusted odds ratios for the variables of interest were not reported.

3.3.2 Prognostic studies

A summary of the direction of effect reported for potentially modifiable prognostic factors, and related variables, is shown in 3.2. One study reported unadjusted and adjusted odds ratios (OR) for treatment failure in study participants with a history of injecting drug use.(Jhan et al., 2017) No studies identified the effect of nutritional status on the risk of treatment failure for bone and joint infection. Pre-operative albumin level, a surrogate marker used to assess nutritional status, was however included as a prognostic factor in three studies, of which two studies reported a direction of effect. (Cook et al., 2007; Barshes, Mindru, Ashong, Rodriguez-Barradas, & Trautner, 2016) Two studies reported variables relating to glycaemic control (peri-operative blood glucose variability and HbA1C).(Barshes et al., 2016; Wang et al., 2020)

A greater proportion of larger studies, with more than 100 participants with the primary outcome, reported a higher odds of treatment failure (positive direction of effect) for smoking, a diagnosis of diabetes mellitus, and BMI when compared to smaller studies. The ratio of studies reporting a positive direction of effect was greatest for glycaemic control and HbA1C (100%, 2/2) and albumin (100%, 2/2), BMI-related variables (86%, 19/22), followed by alcohol intake (75%, 3/4), and smoking (57%, 8/14). One study reported a positive direction of effect for injecting drug use (100%, 1/1).This is summarised in Figure 2.

Many prognostic studies reported the results of a hypothesis test of the direction and magnitude of the association between modifiable prognostic factors and treatment failure following surgery. The ratio of studies reporting a significant ($p<0.05$) positive association was greatest for albumin (67%, 2/3), variables relating to BMI (42%, 11/26), followed by alcohol intake variables (25%, 2/8), diabetes diagnosis (20%, 6/30), smoking (17%, 4/24), glycaemic control (0/3) and injecting drug use (0/4).

Associations between smoking and prognosis were mixed, as shown in 3.3. These associations were not synthesised into an estimate of association due to the high risk of bias of many of the studies identified.

3.3.2.1 Sources of bias

The identification and selection of participants were reported in 21 of 35 studies. Study setting and recruitment dates were reported in all studies.

Study sample size was often insufficient relative to the number of prognostic factors investigated. Of 25 studies that reported multivariable statistical analyses, 20 did not have sufficient participants with the outcome of interest to model the number of prognostic factors, given assumptions about R^2.(Martin et al., 2021) In 30 of 35 studies that included univariable prognostic modelling, fewer than ten outcome events were included per prognostic variable of interest. In 14 studies, the number of prognostic variables described was equal to, or more than, the total number of participants experiencing the treatment outcome of interest. This contributed to prognostic model overfitting, and most studies were considered at high risk of bias for this reason.

Participant exclusion following enrolment was often reported, but may not have been justified. For example, a participant who died of severe infection that may have been related to treatment failure was excluded from the analysis.(Cha et al., 2015) Study follow-up duration was well-described, but loss to follow-up was up to 17 percent and may have been higher for participants who had not experienced treatment failure.(Kheir et al., 2018)

No studies described the measurement of prognostic factors in sufficient detail to allow replication. The source, definition, independence, and particularly timing, of the prognostic factor was not specified. This could have been remedied if study protocols had been published. Additionally, few studies described the handling of missing values; only one study reported using multiple imputation.(Sabry et al., 2014)

3.4 Discussion

This systematic review aimed to identify what host factors, particularly those that concerned potentially modifiable aspects of behaviour or health, may be most useful for the prediction of orthopaedic infection after surgery. However, in light of the methodological quality of existing published studies, there remains considerable uncertainty regarding the associations between host factors and prognosis.

No studies were found that included modifiable prognostic factors in models of infection recurrence after surgery, that were also at low risk of bias.

The identification and selection of patients, study settings and recruitment periods were generally well reported. Sources of bias that were identified in many of the studies included participant exclusion for sometimes spurious reasons, considerable loss to follow-up, and differential follow-up duration for included participants.

It was difficult to understand how prognostic factors were measured or recorded in most of the studies examined in this review. This made it more difficult to compare their usefulness, as it was not always clear what was meant by 'smoking' or 'alcohol', for example.

'Smoking' may refer to a diagnostic code in the secondary care record, a note on an anaesthetic chart,(Russell, Tsang, R., & Sutherland, 2020) or direct ascertainment from a patient including carbon monoxide measurement as part of a consultation about risk factor modification. It may refer to smoking at any time in the past, a particular minimum pack-year history,(Cochran, Ong, Lau, Mont, & Malkani, 2016) pre-operative smoking,(Cook et al., 2007) or ongoing smoking after surgery. The timing and dose is important: quitting 4 weeks before surgery appears to be associated with improved healing and a lower risk of primary osteomyelitis.(Truntzer et al., 2014) Without a good description of how exactly a prognostic factor was defined, its use in in a clinical prediction model may result in inaccurate prognoses.

Studies generally did not specify a time period during which the relevant prognostic factor was measured, including whether it was before or after surgery. With retrospective data collection from participant notes, it may be that prognostic factors were measured more contemporaneously with the outcome than with the surgical treatment. Only one study reported that predictors were measured at least 12 months before the outcome. (Son et al., 2017)

The handling of missing predictor values was frequently not reported, and only one study used multiple imputation rather than complete case analysis to make sure participants with missing predictors or outcomes were included in the prognostic model. (Sabry et al., 2014)

The treatment pathway for patients with orthopaedic infection may be complex and difficult to standardise. This is illustrated by Anderson et al 2018,(Anderson et al., 2018) who focused on predicting successful outcome in patients with total knee arthroplasty infection that also required extensor mechanism reconstruction, and by Barton et al 2019,(Barton et al., 2020) describing attrition in participants intending to receive two-stage revision hip or knee arthroplasty for infection. In the first study, 6 participants did not start the intended treatment, and those who did had between 1 and 14 surgical procedures. In the second study, only 68 percent of patients completed the intended treatment pathway, and the reasons for spacer retention instead of second stage revision arthroplasty were unclear. The modes of treatment failure were functionally different, and hence described as separate outcomes in the study report. These study reports focused, rightly, on the complexity within the participant data. This complexity can make it particularly challenging to select the appropriate a priori treatment outcome for risk prediction modelling, as outcomes and interim management steps are subject to competing risks.

Measuring a treatment failure also posed some problems. Many studies did not count deaths, amputations or long term suppression of infection with antibiotics to be treatment failures. In fact, antibiotic suppression is explicitly not included in the one standard definition of treatment failure following revision arthroplasty for infection. (Diaz-Ledezma et al., 2013) Ignoring deaths and amputations could make a sizeable difference to outcome predictions, as during the follow-up period there were sometimes more deaths than infection recurrences. (Jhan et al., 2017; Houdek et al., 2014)

Finally, external validation of prognostic models benefits from the publication of model equations, to enable an assessment of their calibration and discrimination in new patients. None of the studies included in this review published the model equation derived for the prediction of any outcome measure.

Limitations of the review process include limits on the language of study reports due to the databases included (though studies published in German and French were reviewed for inclusion), limitations of the search strategy, and amalgamation of orthopaedic infections affecting differing patient populations and carrying differing prognoses. Nevertheless, the anticipated biological mechanisms and dose-response gradient underlying associations with the prognostic factors of interest across all orthopaedic infections are expected to be comparable.

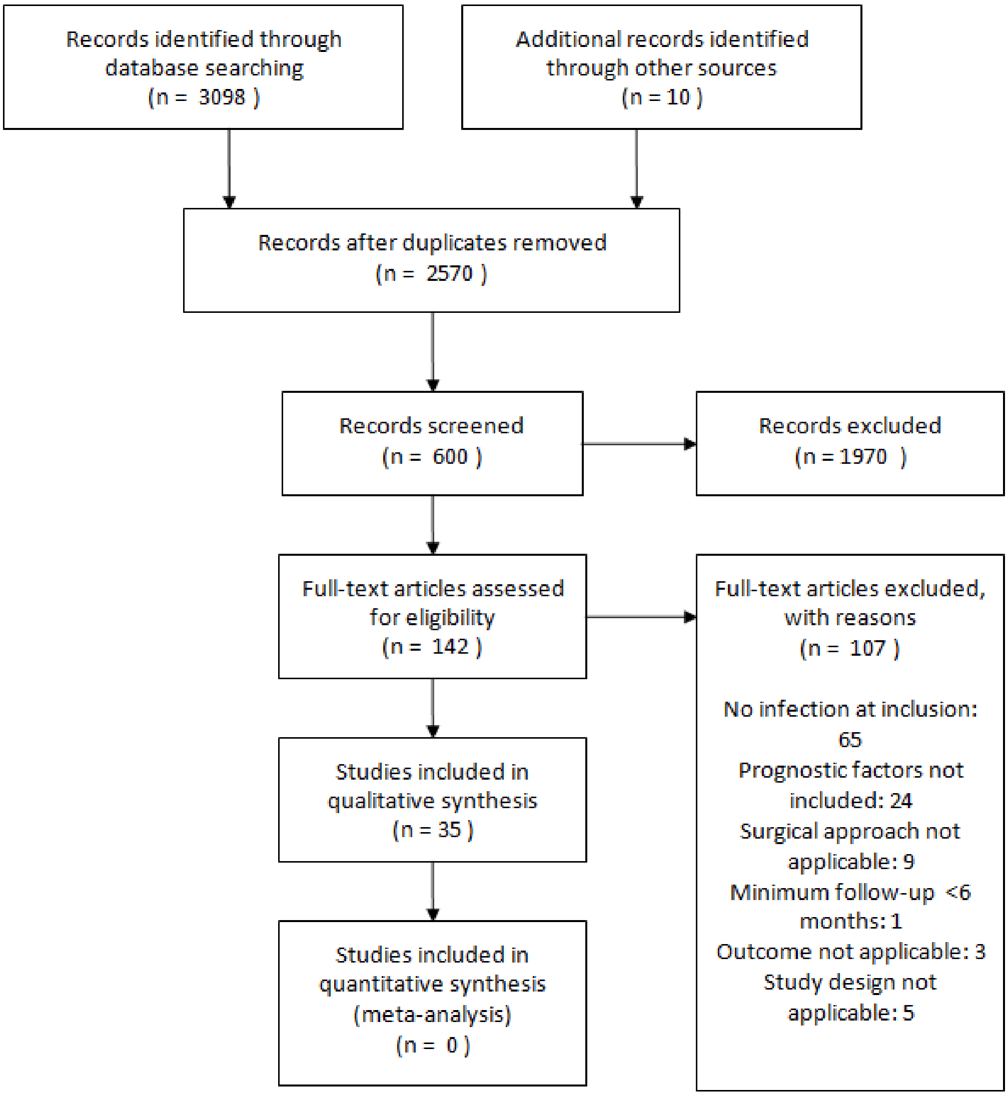

Figure 3.1: Inclusion flowchart for systematic review, reproduced with permission from Dudareva et al. 2021

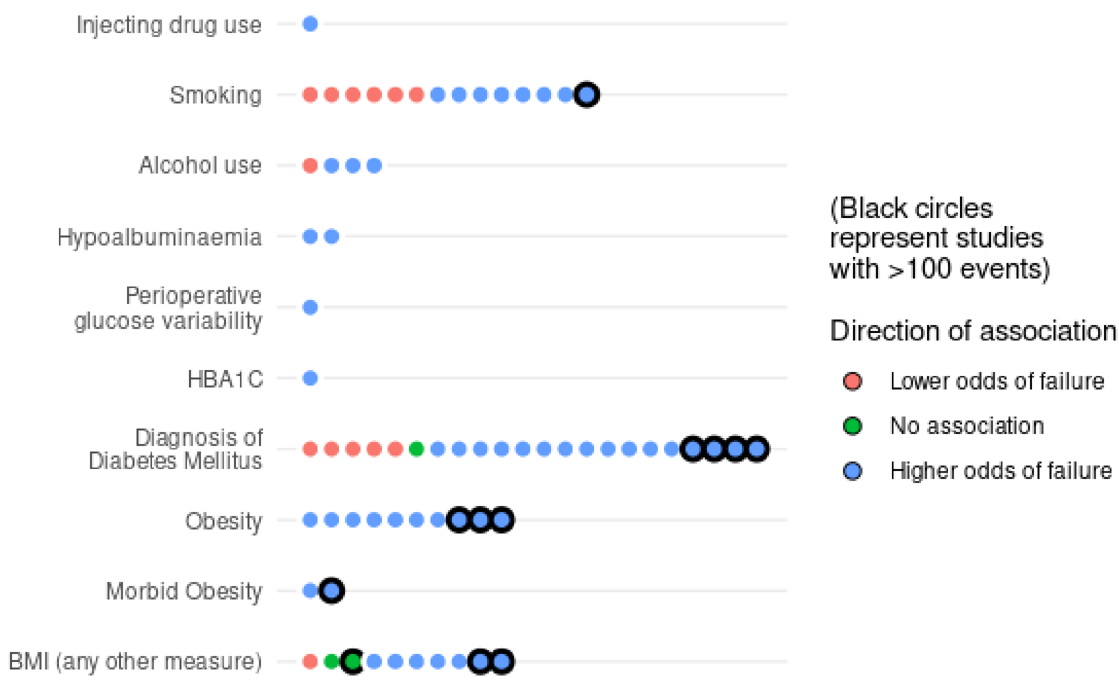

Figure 3.2: Direction of association with prognosis for variables of interest in systematic review, adapted with permission from Dudareva et al. 2021

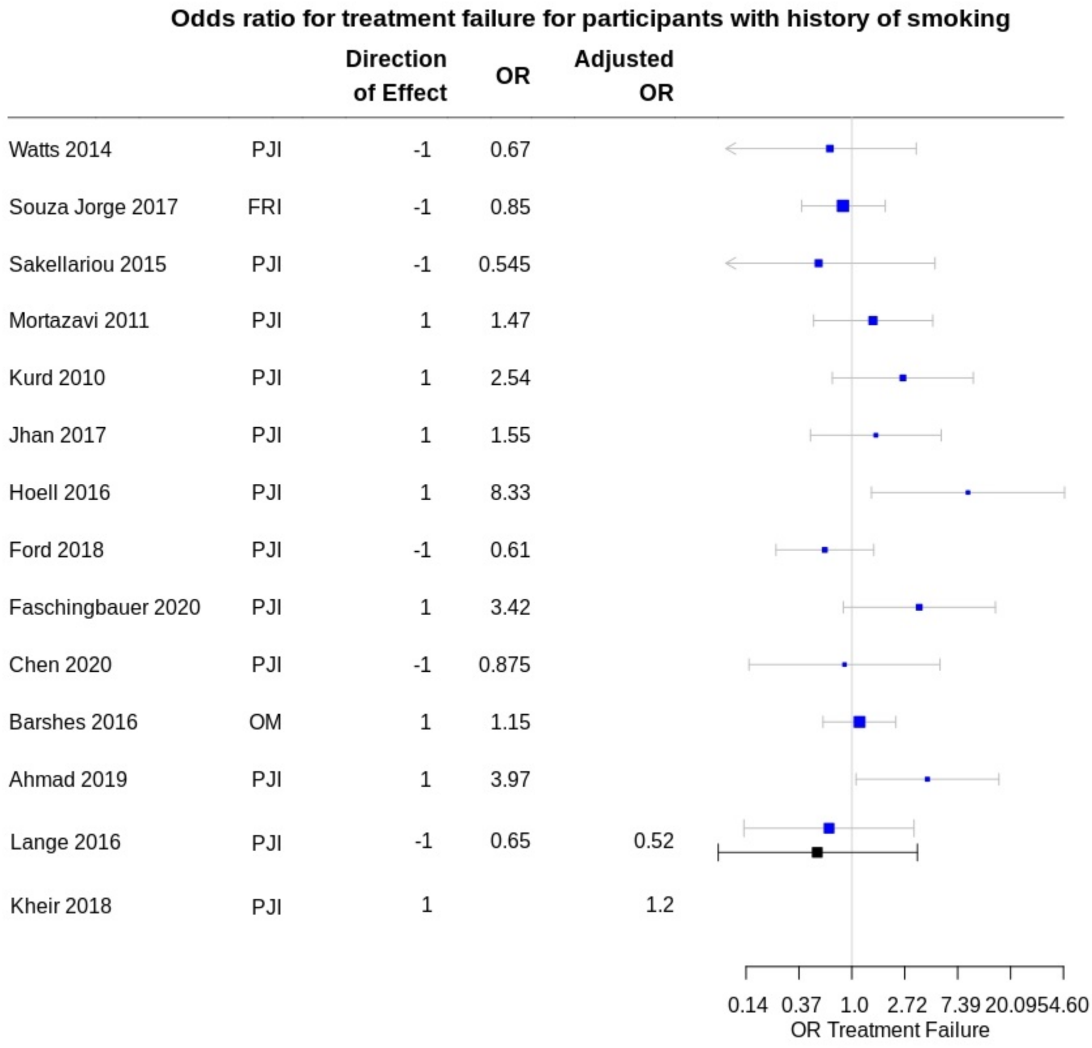

Figure 3.3: Association between smoking and treatment failure, adapted with permission from Dudareva et al. 2021

4 | Exploring the effects of diagnostic definition and treatment differences: Fracture related infection (FRI)

Prognosis depends crucially on the person for whom it is sought, and the condition to which it relates. Small differences in the definition of an illness, in the way in which it is treated, or in the way that treatment success and failure are defined, may have effects on the validity of a prognostic model.

Laboratory findings in surgical specimens form the basis of confirmatory criteria for FRI.(Metsemakers et al., 2018) Histopathological assessment of neutrophils in affected bone tissue is highly sensitive and specific for the diagnosis of FRI.(Morgenstern, Athanasou, et al., 2018) However, this diagnostic test is often not available, so may be systematically missing in data from some treating centres. Furthermore, the number of microbiology specimens submitted during surgery, and whether they represent deep infected bone tissue, affects the diagnostic accuracy of microbiology as a confirmatory criterion for infection.(B. L. Atkins et al., 1998; Dudareva, Barrett, et al., 2021) Surgeons send different numbers of microbiology specimens depending on how likely they feel an infection is to be present.(Dudareva, Barrett, et al., 2021)

Separately to this, accepted treatments in routine clinical use change over time. Prior to the turn of the century, it was unusual to offer Debridement, Antibiotics and Implant Retention (DAIR), particularly for people with fracture-related infections (FRI). This is now standard practice.(McNally et al., 2022) Nevertheless, what constitutes standard practice in one centre may be shunned in another, owing to differences in training, procurement, and regional incentives and guidance governing surgery and antimicrobial prescribing.

The way in which individuals respond to treatments varies depending on aspects of their infection. Heterogeneity of Treatment Effects (HTE) is a term used to describe the multiplicative effect of an additional treatment, usually for people with more severe disease or additional adverse prognostic features. In short, treatments that improve outcome usually do so more for people with a worse prognosis otherwise.(Kent, Steyerberg, & Klaveren, 2018) This is relevant because secondary data for prognostic modelling often come from randomised controlled clinical trials, where some participants are given additional treatments. The effect of these treatments often varies across baseline disease severity.Heterogeneity of Treatment Effects can be said to be present in these cases, contributing additional variation in the prognosis particularly of participants with more severe disease.

In daily clinical practice, treatments might be affected by the perceived severity of a disease. Differences in treatment may lead to an underestimate of the effectiveness of those treatments overall, if it is assumed that everyone in a cohort study has been treated the same way.(Pajouheshnia, Damen, Groenwold, Moons, & Peelen, 2017) Sometimes it may not be possible to offer certain treatments in certain contexts. In FRI, it would often not be feasible to leave an unhealed fracture without internal or external fixation. In this case, reconstructive surgery is often limited to strategies where metalwork can be retained or replaced. If severe untreated peripheral vascular disease is present, it may not be reasonable to offer wound closure with free tissue transfer, for example, because of the low likelihood of graft success. Alternatively, people who receive DAIR may represent the extremes of disease severity: those with well-fixed implants for whom infection is felt to be least likely to recur, so bone loss from debridement surgery is not justified; and those who are too ill to tolerate a major operation where an implant is exchanged.(Wouthuyzen-Bakker et al., 2019b)

4.1 Aims and objectives

The aim of this work, which I carried out alongside other analyses contributing to an international study collaboration (EAT FRIs), was to consider how systematic differences in treatment for orthopaedic infection could affect what associations were observed between prognostic factors and outcome.

The primary aim of the observational study as a whole, work from which is described in this section, was to assess the causal effect of different post-operative systemic antimicrobial treatment strategies on outcome (infection recurrence) for people affected by FRI. Secondary aims included a descriptive analysis of surgical treatment for the cohort, including the use of local antimicrobial therapy. (Corrigan et al., 2023; Sliepen et al., 2022; McNally et al., 2022; Corrigan et al., 2022)

My aims were

- To assess the variation in treatments offered for FRI in different specialist centres
- To understand if anti-biofilm systemic antibiotics or local antibiotic therapy might show HTE in adults with FRI
- To assess the association between treatment modalities and prognosis in adults with FRI
- To understand the causal effect of treatment variation on prognosis for adults with FRI.

4.2 Study population

The participants included in this study did not overlap with those included in the prognostic modelling study in Chapter 5. Adults affected by FRI were identified retrospectively from prospectively collected surgical records in three specialist centres providing multidisciplinary treatment for orthopaedic infection in Europe. Surgical treatment for included cases was performed from January 2015 to December 2019 inclusive. This work was undertaken as part of a multi-centre audit of routinely available clinical treatment in each centre. Institutional review and ethical approval was granted or waived at each participating centre (UMCU waiver 20-004/C).

4.2.1 Inclusion criteria

Adults affected by FRI were eligible for inclusion if they had appropriate surgery for FRI, judged by their treating surgeon. Additionally, they needed to have had at least three surgical deep tissue specimens taken during their operation for diagnostic assessment, and a minimum of one year follow-up with a documented clinical treatment outcome. FRI was defined according to the Consensus definition.(Metsemakers et al., 2018) Clinical criteria for confirmed FRI included a sinus tract or fistula (synonyms), pus around a fixation implant, or wound breakdown all the way to the implant. Surgical confirmatory criteria included the isolation of phenotypically indistinguishable micro-organisms from two or more deep tissue specimens; positive histology examination with >neutrophils per 400x field; or microscopically visible micro-organisms on Gram staining. 433 people affected by FRI were included.

4.2.2 Baseline characteristics

Available data included:

- Demographics gender and age at surgery
- Baseline health parameters C Reactive Protein (CRP) and creatinine, diabetes mellitus, current smoking status, the use of immunosuppressive medications
- Clinical characteristics of the infection confirmatory diagnostic criteria, the affected bone, whether the fracture had healed and whether implants (metalwork) was present prior to the operation
- Microbiological investigations
- Characteristics of the systemic antimicrobial strategy, including whether this included an anti-biofilm antibiotic, and whether it was concordant with consensus guidance for treatment of FRI (Metsemakers et al., 2020)
- Characteristics of the operation, including whether metalwork was retained or replaced, whether local antibiotic therapy (an implanted antibiotic carrier) was used, and the soft tissue closure
- Duration of follow-up
- Outcomes including reinfection or infection recurrence, amputation and mortality.

Missing baseline variable values were imputed using Multiple Imputation with Chained Equations (MICE) using all predictor and outcome variables. Missingness was not more than 3% for any baseline variable other than pre-operative CRP (26.7% missing). Missing outcome data at 12 months and 24 months were not imputed, because loss to follow-up was not assumed to have occurred at random. Participants were included in outcome analyses at 12 and 24 months if they had experienced treatment failure at any time during those periods, or had completed at least that period of follow-up without treatment failure.

4.3 Differences in antimicrobial treatment

One of the overall aims of the study was to ascertain whether differences in antimicrobial treatment, and differences in surgical approach, had an impact on individual participants' likelihood of successful treatment for infection.

For antimicrobial therapy, two aspects of primary interest were whether the systemic antimicrobial treatment regimen included an antibiofilm antibiotic, and whether the antimicrobials were selected and dosed according to international consensus guidelines for orthopaedic infection. (Depypere et al., 2020)

Antibiofilm antibiotics generally include antimicrobials with favourable pharmacokinetic properties, those with low minimal biofilm inhibitory concentrations (MBIC) relative to their minimum inhibitory concentrations (MIC), and those where there is a suggestion from existing research that treatment outcomes are improved in biofilm infections. Antimicrobial combinations with rifampicin or a fluoroquinolone (or both) are considered to have anti-biofilm activity when administered systemically.(Martinez-Pastor et al., 2009; Aboltins et al., 2011; Widmer, Gaechter, Ochsner, & Zimmerli, 1992) Incidentally, fluoroquinolone antibiotics and rifamycins also have excellent penetration into eukaryotic cells, favouring elimination of intracellular bacteria. (Smith, Baltch, Franke, Michelsen, & Bopp, 2000; Krut, Sommer, & Kro nke, 2004) It is not clear which of these effects explains the differences in treatment outcome.

Four infectious disease specialists, with no access to outcome data for participants in the cohort study, assessed each participant's post-operative systemic antimicrobial treatment recommendation against consensus guidance.(Depypere et al., 2020) The same clinicians also recorded whether a fluoroquinolone- or rifampicin-containing regimen was used. In polymicrobial infection, the systemic antimicrobial treatment strategy was considered non-compliant with consensus guidance if any identified pathogen was not targeted with antimicrobials recommended in consensus treatment guidelines, at an appropriate dose. All participants in the cohort study were prescribed systemic antibiotic treatment for at least 6 weeks after surgery.

4.4 Differences in surgical treatment

Secondary analyses focused on differences in the surgical approach to the treatment of FRI. Specifically, different fracture fixation strategies for participants who needed ongoing fixation, which included retained metalwork (DAIR), replaced internal or external fixation metalwork, were compared. Implantation of antibiotics in the surgical field (local antimicrobial therapy) was also compared against surgery where no antibiotic carriers were implanted. These different surgical approaches were routinely offered to some participants in the cohort and as such were part of normal clinical care for the purposes of the audit.

Not all participants were able to have every surgical approach, depending on the anatomical location of their fracture and whether it was healed or not. Excision included all surgical strategies where debridement was performed and internal fixation metalwork, including screws, plates and intramedullary nails, was removed if present, but no new surgical fracture fixation was used. This strategy was not appropriate for unhealed unstable fractures.

4.5 Analysis

Three statistical analysis strategies for the association between elements of treatment and clinical treatment failure were specified a priori:

- Adjusted and unadjusted logistic regression for treatment failure at 12 months
- Adjusted and unadjusted logistic regression for treatment failure at 24 months
- Survival analysis using Cox proportional hazards modelling

Clinical treatment failure was ascertained blinded by a clinician who was unaware of the baseline characteristics and treatment given to each participant. Survival analysis included amputation and mortality as competing risks, unless they were related to infection recurrence, in which case they were counted as treatment failures. Records were censored when:

- findings consistent with treatment failure were first identified;
- at the date of last recorded follow-up;
- at the date of death;
- if amputation of the affected limb occurred during follow-up, at the date of amputation.

Structural causal analysis (based on contributing clinicians' understanding of causes contributing to both treatment and outcome) using inverse probability treatment weighting (IPTW) was undertaken separately to attempt to quantify the magnitude of a causal effect from differences in medical and surgical treatment. A Directional Acyclic Graph showing hypothesised causal effects is shown. 4.1

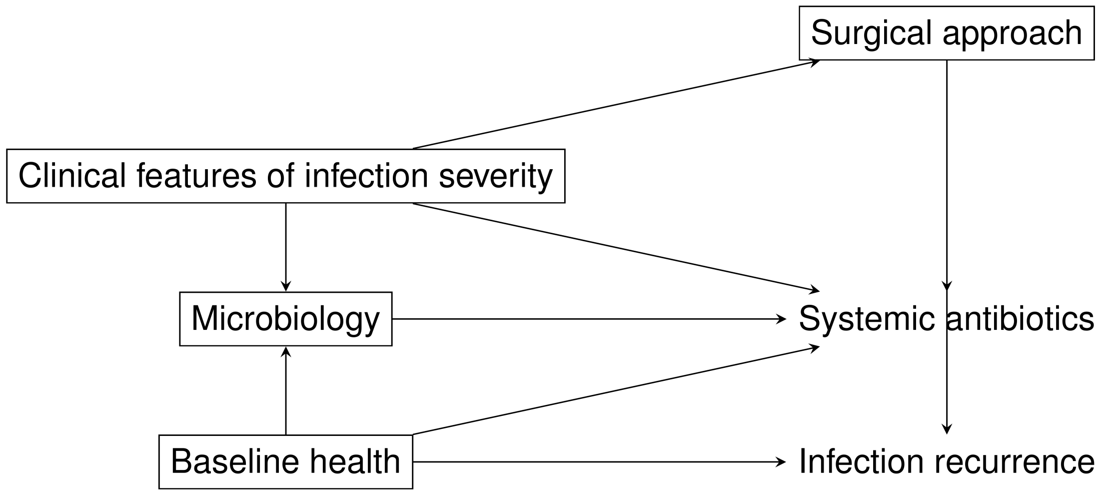

Figure 4.1: Anticipated causal contributors to treatment outcome for people having surgery for FRI. Contributors were selected *a priori* based on discussion and interdisciplinary consensus between study clinicians.

4.6 Results

4.6.1 Baseline characteristics

This retrospective analysis included 433 people treated for FRI in three specialist centres. The mean age of participants was 50 years. Just under three quarters were male, which is expected given the epidemiology of osteomyelitis and FRI. Baseline characteristics are summarised in 4.2.

The distribution of affected bones was similar across all three referring centres, with tibial FRI making up approximately half of all cases. The majority of participants (326 people) had a fracture fixation implant present prior to their operation, which was left in situ during the operation, as part of a Debridement, Antibiotics and Implant Retention (DAIR) treatment protocol, in 42% of people. Over half of participants received local antimicrobial therapy at the time of their operation. Not all participants had primary wound closure at the time of their index operation, and some were treated with negative pressure wound therapy in place of surgical wound closure.

Around half of infections were monomicrobial, 36% were polymicrobial, and 14% were culture-negative. *Staphylococcus aureus* was the most commonly identified micro-organism from deep tissue specimens taken at the time of surgery. 4.3

In total, 59 participants experienced a clinical recurrence of their infection during follow-up. Eight participants died, in all cases from factors unrelated to FRI or its recurrence. Nine participants underwent amputation of the affected limb, of whom 5 had recurrence of their infection.

One unexpected, large difference between treating centres was the chronicity of the infection. Participants treated in one of the centres had a median of more than 140 weeks of symptoms after their fracture, compared with less than 10 weeks in the other two centres. The number of prior treatment attempts was not quantified in this dataset. This difference may reflect variation in local referral pathways: the centre with the greatest median symptom duration provided tertiary referral care. Participants in the three centres did not necessarily have infection of comparable severity.

4.6.2 Differential allocation of treatment between treating centres

The proportions of participants with selected health conditions available at the time of baseline assessment, the micro-organisms contributing to infection (including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, two clinically relevant pathogens capable of forming biofilm in most cases), and the concordance of the systemic antimicrobial treatment approach with international consensus guidelines, did not vary greatly by treating centre.

Though all three centres that contributed participants to this multi-centre audit were secondary or tertiary referral centres with both surgical and clinical infection specialist input for orthopaedic infection, the surgical treatments offered to the participants were not uniformly distributed. These differences may be partially explained by differences in case mix, as already described.

Surgical treatments are summarised in 4.4

The centre with the greatest proportion of participants with late fracture-related infections, treated more than 12 months after the initial injury, also noted the greatest proportion of excision-only surgery, where infected bone was excised, and no fracture fixation implants were retained or implanted. The use of local antimicrobial therapy was also far more common in this centre than either of the others. Implant retention (DAIR) is a strategy often used in acute FRI, where fractures have not yet had a chance to partially or fully heal, and where implant removal and refixation risks making the original injury unstable. Implant retention often leaves no anatomical space for implanting local antibiotic carriers or antibiotic-impregnated bone fillers. This means that people with acute FRI may have been less likely to receive local antimicrobial therapy, not because it was not indicated, but because the mechanical aspects of the operation made it less likely to be feasible.

4.6.3 Systemic antimicrobial treatment and outcomes

Corrigan *et al.* found no differences in treatment outcome for people treated with systemic antimicrobial regimens that complied with recent consensus guidelines, compared to antimicrobial treatment that did not comply with guidance (mainly due to lower antibiotic dosing).(Corrigan et al., 2023; Depypere et al., 2020) Infection recurrence during the follow-up period was identified in 14.2% of participants treated with consensus-compliant antibiotics, compared with 12.1% for participants treated with a non-compliant antibiotic regimen.

For the 291 participants whose infection involved staphylococci (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and other coagulase-negative staphylococci), treatment failure affected 19.6% of those who received a rifampicin-containing antibiotic regimen, compared to 17.6% of those who did not (p=0.85, Chi squared test). No patients who did not receive ciprofloxacin for Gram-negative bacterial infection experienced a treatment recurrence, compared to 10.7% of those who did (p=0.49, Fisher exact test).(Corrigan et al., 2023)

Overall, antibiofilm antimicrobial regimens were not associated with improved treatment outcome in survival analysis 4.5.

I hypothesised that there may be a differential effect observed for antibiofilm antimicrobial regimens depending on the severity of the underlying infection. One option for stratifying FRI severity are the BACH and JS-BACH classification systems, particularly the B (Bone defect) element of these classification systems, which correlates well with patient-reported quality of life measures as well as clinical treatment outcome at 12 months.(A. J. Hotchen et al., 2019, 2020; A. Hotchen et al., 2021) Unhealed fractures are classified as B3 in the BACH classification, and B2 or B3 in the JS-BACH classification system. Though in this cohort study antimicrobial treatment was not randomised, there was no *a priori* reason to suspect that antimicrobial prescribing might have directly reflected the surgical severity of FRI, specifically the nature of the bone defect.

Data from this cohort did not include classification according to BACH or JS-BACH, but did include whether or not participants had an unhealed fracture. In this cohort, 190 participants had healed fractures prior to surgery, while 243 had unhealed fractures. 9.4% of those whose fractures had healed experienced treatment failure during follow-up, compared with 17% of those whose fractures had not healed (p=0.04, Chi squared test), which agreed with the findings of Hotchen *et al.*(A. J. Hotchen et al., 2019)

Of the participants who had unhealed fractures before surgery, 18/91 experienced treatment failure when not given an antibiofilm treatment regimen, compared to 23/152 of those given an antibiofilm treatment regimen. This was in contrast to the observed association for people whose fractures had healed: 10/120 who did not receive an antibiofilm treatment regimen experienced treatment failure, compared to 8/70 who did receive antibiofilm antibiotics. This is summarised in 4.6

Though participants numbers were small and the study design did not involve randomisation to different systemic antibiotic regimens, these findings suggest that differences in systemic antimicrobial therapy may affect outcome differentially depending on anatomical factors of the underlying infected bone. Caveats may thus apply to the use of clinical trial data with differential systemic antimicrobial treatment allocation, such as the OVIVA and SOLARIO studies, to secondary analysis for individual risk prediction. (Li et al., 2019; Dudareva, Kumin, et al., 2019) Heterogeneous treatment effects for participants with different baseline characteristics may increase the variability of treatment outcomes, particularly for those with more severe infections. (Kent et al., 2018)

4.6.4 Local antimicrobial therapy and treatment outcome in FRI

It is difficult to separate out any possible causal effect of local antibiotic therapy on treatment outcome, from the effect of the type of operation. DAIR usually does not leave space in the bone cortex that can be filled with a local antibiotic carrier.

If an implant is retained, the medullary cavity of an infected bone is usually not accessed, so intramedullary absorbable local antimicrobial therapy is also usually not used.

In this cohort, there were systematic differences in how often, and what, local antimicrobial therapy was used in each treating centre (4.7). Due to differences in the populations treated, which are hinted at but not fully explored by baseline characteristics (such as the time from injury, the baseline inflammatory markers), it is difficult to separate the effect of local antibiotics in particular from differences in host factors. These effects would be difficult to eliminate outside a randomised study.

25 of 251 participants who had local antibiotic therapy as part of their operation experienced a recurrence of infection, compared to 34 of 182 participants who had no local antibiotics; the hazard ratio for recurrence was 0.48 (95% confidence interval 0.29 to 0.81 in unadjusted analysis). The direction of effect was once again consistent across different sensitivity analyses, and apparent in crude survival analysis 4.8

The use of local antimicrobial therapy is described in 4.9, for participants whose fractures had and had not healed. However, this analysis needs to be interpreted with caution, as local antimicrobial therapy is constrained by aspects of the surgical approach to FRI, and was not randomised in this population.

4.6.5 Surgical treatment strategy and infection recurrence

Before the index operation, 56% of participants had an unhealed fracture, and 291 of 433 (67%) had internal fixation metalwork present.

Debridement and retention of stable fracture fixation metalwork is an accepted strategy in the management of FRI, particularly when a fracture has not yet healed.

Retaining fracture fixation metalwork during index surgery for FRI was associated with a greater proportion of participants experiencing treatment failure by 12 months, and in survival analysis. Retaining metalwork was not an unusual choice, with 140 of 433 participants treated in this way. Those receiving DAIR had a 21% chance of experiencing an infection recurrence overall.(McNally et al., 2022)

The difference in observed outcome between participants treated with DAIR and other surgical modalities, including implant replacement and external fracture fixation, was consistent throughout sensitivity analysis at different time points and statistical comparisons. DAIR was associated with a hazard ratio of 2.32 for treatment failure (95% CI from 1.39 to 3.87), 4.10

Analysis using IPTW supported the association between DAIR and treatment failure, taking factors into account that can influence both the choice of surgery and the outcome. These factors included gender, age, diabetes mellitus, smoking, immunosuppression, the presence of a sinus or frank purulence at the fracture, whether the fracture had healed, and whether the injury was more than 6 weeks ago. When participant data was inversely weighted for the probability of DAIR to create a pseudo-population where the chance of having DAIR treatment was more even between participants, DAIR was associated with an odds ratio for treatment failure at 12 months, of 2.16 (95% confidence intervals 0.96 to 4.86).

This difference in outcome supports the rationale for modelling prognosis separately for people treated with DAIR. This is because there is likely be a systematic difference in the effectiveness of DAIR compared to other surgical strategies, as well as differences in the population who receive it. DAIR is sometimes necessary in cases where a well-fixed implant supports an anatomically challenging unhealed fracture, and it is often a less invasive and better tolerated option. It is worth noting that in this cohort, 79% of participants treated with DAIR for FRI did not experience recurrence of their infection.(McNally et al., 2022)

4.7 Discussion

The aim of this chapter was to investigate the magnitude of the impact on outcome from different treatment options in current clinical use, and the possibility of Heterogeneous Treatment Effects (where the magnitude of the benefit from a treatment depends on the severity of the disease), in a separate group of people receiving surgical treatment for orthopaedic infection.(Kent et al., 2018) In this case, the available data were from a retrospective multi-centre cohort of surgical and antimicrobial treatment for FRI in adults, with the aim being to evaluate treatment modalities in current routine clinical use.

Using pre-operative fracture healing as a proxy measure of surgical infection severity, there was some suggestion of HTE from the choice of systemic antimicrobial strategy in this cohort.(A. J. Hotchen et al., 2019) However, as antimicrobial treatments were not randomised, and participant numbers in the specific subgroups were small, it is not possible to refute this possibility definitively with the data available.

Several sensitivity analyses were pre-specified for each other study aim. For example, it was suspected that people treated for FRI would be more likely to attend their treating centre for follow-up if they had persistent symptoms due to infection recurrence, and more likely to be lost to follow-up if their infection had resolved, so logistic regression analyses at different follow-up periods were compared. These analyses suggested that implant retention was associated with a worse treatment outcome, and local antimicrobial therapy was associated with a better treatment outcome, for adults with FRI treated in specialist centres.

Local antibiotic therapy is already considered to confer an advantage in preventing infection recurrence for people with FRI.(Li et al., 2019; Dudareva, Kumin, et al., 2019) The differences observed for participants who did and did not receive implanted antibiotic carriers in this study is similar to the differences observed in existing research. A meta-analysis of local antimicrobial therapy for the prevention of FRI showed a RR of 0.3 (95% CI from 0.22 to 0.40) for subsequent FRI in people who had antibiotics implanted at the time of their fracture fixation, compared to those who just had systemic prophylactic antibiotics at the time of their operation.(Morgenstern, Vallejo, et al., 2018) Analysis within this study cohort did not suggest a difference in the magnitude or direction of the possible association between treatment outcome and local antimicrobial therapy, though due to the profoundly uneven application of this treatment between centres and between participants, this analysis did not quantify a causal effect. Differential use of local antibiotic therapy may introduce Heterogeneous Treatment Effects in prognostic modelling, where this treatment is not offered to all patients.

Inverse Probability of Treatment Weighting was used to compare the effect of surgical and medical treatments on outcome. In order use this technique to analyse an observational study as if it were a conditionally randomised experiment that would allow inferences about the causal effect of different treatments, three assumptions must be met. (Hernan & Robins, 2020)

Firstly, the treatments being compared need to be clearly defined and clinically relevant. In this study, the definition of consensus antimicrobial treatment was clearly pre-specified, but does not necessarily correspond to a clear set of causal pathways. In that respect, the observational data at best represents a conditionally randomised pragmatic study of a strategy, subject to the specific definition of that strategy.

Secondly, the conditional probability of receiving any of the treatments being compared must depend only on the measured factors that are included in the structural causal model. This was not possible to confirm. Unmeasured contributors to both treatment decisions and outcome may have included: the history of prior failed treatment attempts including pre-operative antibiotic exposure; other unmeasured health factors including heart disease, hepatic failure and mental illness that could have influenced antimicrobial choice due to tolerability and drug interactions; and social factors including self care skills, distance from the treating centre, family and carer support, all of which may influence whether antibiotics that need regular blood test monitoring were prescribed or not or whether external fracture fixation was offered.

Thirdly, the treatments being compared all need to be possible, in principle, for every participant in the cohort. This may not have been the case for antibiofilm regimes and consensus antibiotics, which only apply to particular micro-organisms. Due to the specific indications and definitions of these treatment strategies, they applied to most, but not all, of the included cases.

Lastly, the degree to which study populations from the three treating centres differed from each other was surprising, particularly with reference to the chronicity of infection and the use of different surgical treatment strategies. Despite these differences, the rates of infection recurrence were remarkably similar. Treatment failure could not be fully explained by differences in medical or surgical treatment, or by the anatomical location or chronicity of the infection. This finding supports the analysis now presented in Chapter 5, aiming to develop a prognostic model for surgically treated orthopaedic infection, taking the baseline health of those affected into account.

Characteristic	**G**, N = 64 [1]	**O**, N = 235 [1]	**U**, N = 134 [1]
Gender			
Female	16 (25%)	52 (22%)	47 (35%)
Male	48 (75%)	183 (78%)	87 (65%)
Age at operation (years)	50 (35, 61)	50 (38, 62)	53 (34, 63)
Affected bone			
Clavicle	2 (3.1%)	2 (0.9%)	2 (1.5%)
Femur	10 (16%)	60 (26%)	24 (18%)
Fibula	0 (0%)	12 (5.1%)	1 (0.7%)
Foot	4 (6.2%)	4 (1.7%)	11 (8.2%)
Forearm	3 (4.7%)	15 (6.4%)	8 (6.0%)
Humerus	3 (4.7%)	13 (5.5%)	4 (3.0%)
Other	0 (0%)	2 (0.9%)	1 (0.7%)
Pelvis	9 (14%)	0 (0%)	17 (13%)
Tibia	33 (52%)	127 (54%)	66 (49%)

[1] n (%); Median (IQR)

Figure 4.2: Baseline characteristics for people with FRI included in the EATFRIs multi-centre audit.

Characteristic	G, N = 64[1]	O, N = 235[1]	U, N = 134[1]
BMI	25.9 (23.3, 30.2)	27.7 (23.5, 31.5)	26.4 (23.0, 29.4)
Unknown	0	12	2
Current smoking	32 (50%)	48 (20%)	32 (24%)
Diabetes mellitus	5 (7.8%)	28 (12%)	14 (10%)
Staphylococcus aureus	38 (59%)	84 (36%)	76 (57%)
Pseudomonas aeruginosa	4 (6.2%)	23 (9.8%)	4 (3.0%)
Consensus guidance for systemic antimicrobials	21 (33%)	48 (20%)	38 (28%)
Antibiofilm antimicrobial regimen	41 (64%)	93 (40%)	88 (66%)

[1] Median (IQR); n (%)

Figure 4.3: Baseline characteristics for people with FRI included in the EATFRIs multi-centre audit: comorbidities and medical findings.

Characteristic	**G**, N = 64[1]	**O**, N = 235[1]	**U**, N = 134[1]
Fracture healed	5 (7.8%)	160 (68%)	25 (19%)
Internal fixation present	48 (75%)	17 (7.2%)	97 (72%)
Time between injury and surgery (weeks)	8 (4, 25)	143 (43, 832)	5 (2, 38)
Unknown	0	3	1
Operation			
Removal	13 (20%)	158 (67%)	30 (22%)
External Fixation	6 (9.4%)	60 (26%)	2 (1.5%)
Internal Fixation	8 (12%)	10 (4.3%)	6 (4.5%)
DAIR	37 (58%)	7 (3.0%)	96 (72%)
Local antimicrobials implanted	8 (12%)	217 (92%)	27 (20%)

[1] n (%); Median (IQR)

Figure 4.4: Anticipated causal pathways affecting treatment outcome for people having surgery for FRI. Variables were selected *a priori* based on discussion and interdisciplinary consensus between study clinicians.

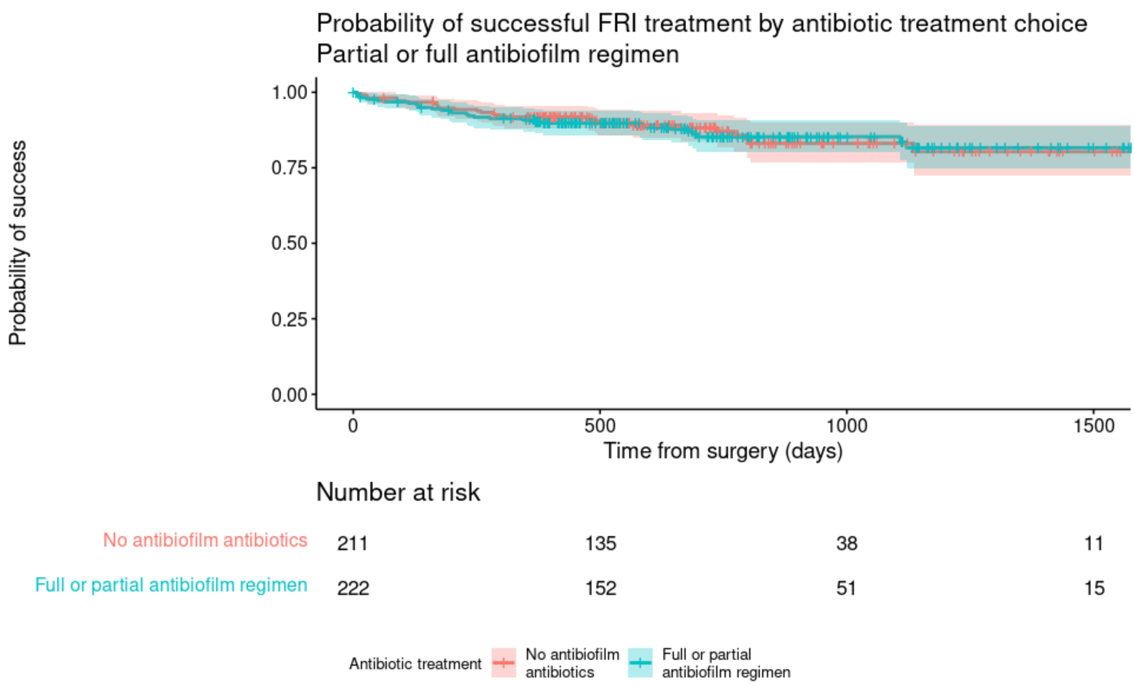

Figure 4.5: Kaplan-Meier survival curve for participants treated with and without antibiofilm antibiotics, where susceptible micro-organisms with the potential to form biofilm were present.

Figure 4.6: Treatment outcome for participants with healed and unhealed fractures in the EATFRIs multi-centre audit. Magnitude of absolute and relative associations between prognosis and use of antibiofilm antibiotics.

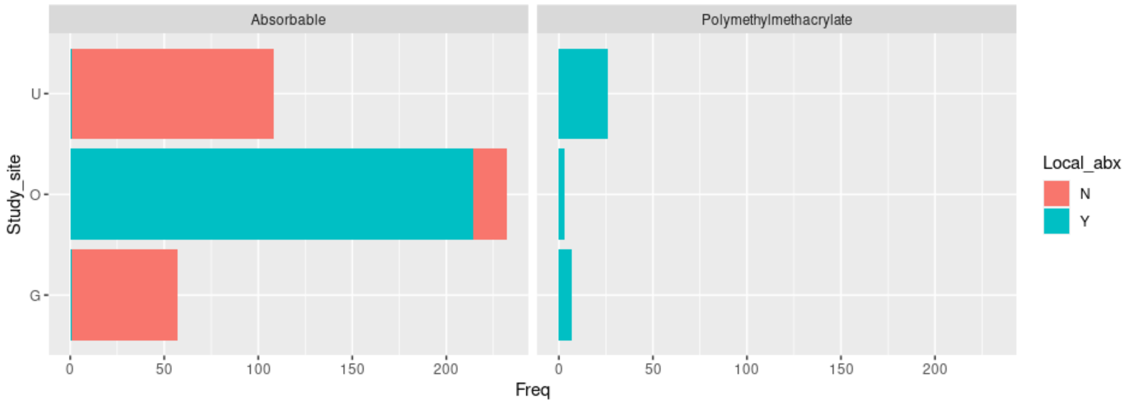

Figure 4.7: Distribution of absorbable and non-absorbable (PMMA, or polymethylmethacrylate) local antimicrobial carrier use for participants in different study sites.

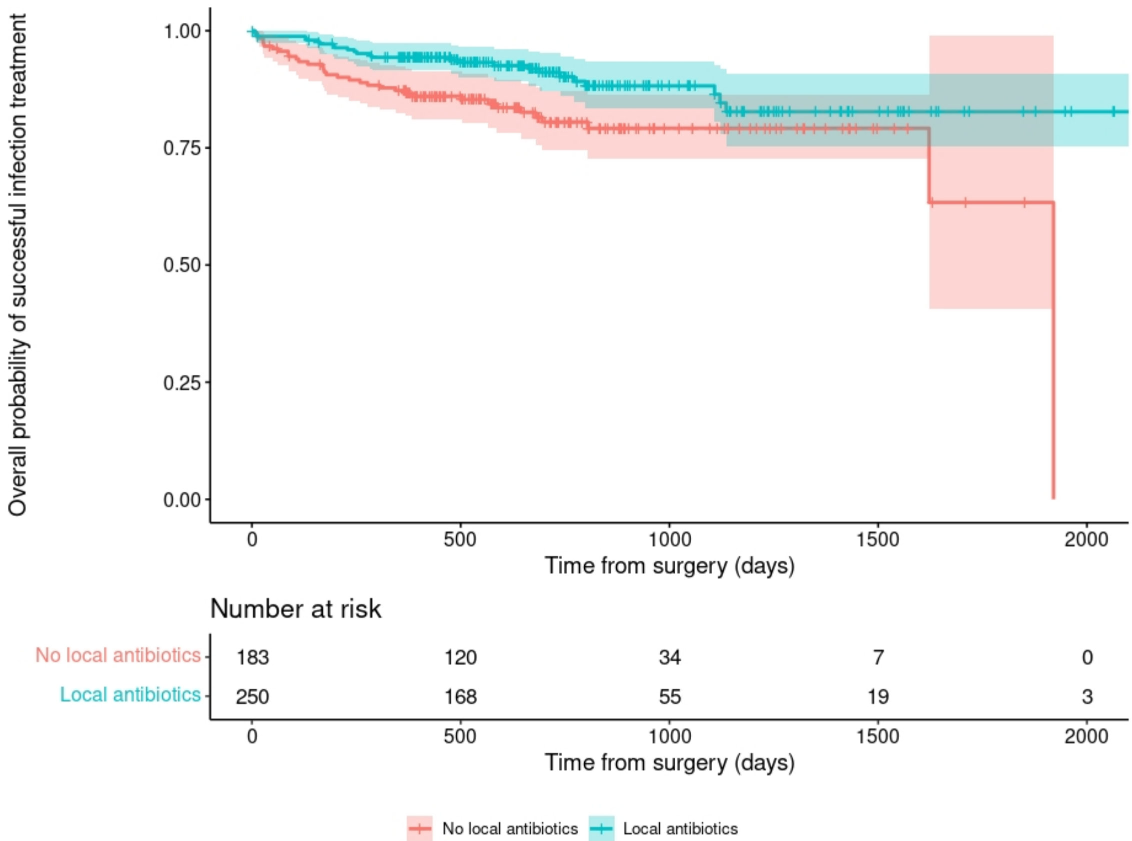

Figure 4.8: Kaplan-Meier survival curve for participants treated with and without local antimicrobial therapy.

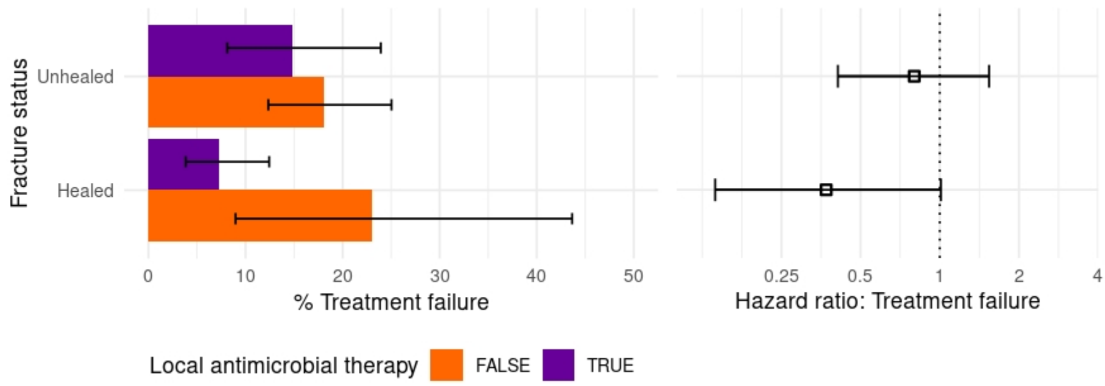

Figure 4.9: Treatment outcome for participants with healed and unhealed fractures in the EATFRIs multi-centre audit. Magnitude of absolute and relative associations between prognosis and use of local antimicrobial therapy.

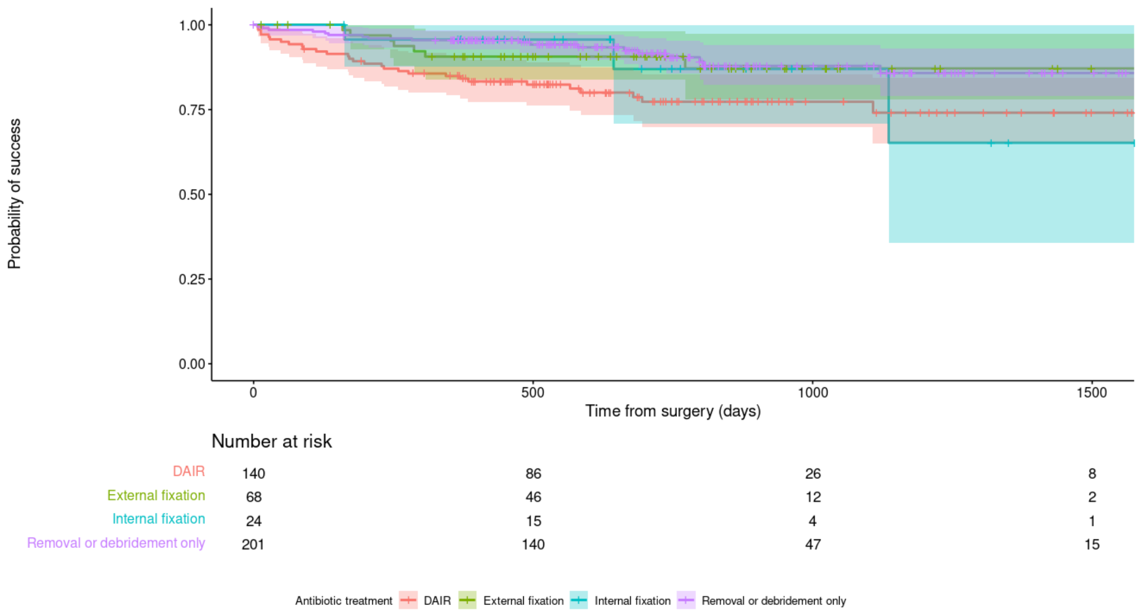

Figure 4.10: Kaplan-Meier survival curve for participants treated with for FRI with different surgical approaches: DAIR (red), internal fracture fixation (turquoise), external fracture fixation (green), debridement or metalwork removal only (violet).

5 | Prognostic modelling: Developing a risk prediction model for the recurrence of orthopaedic infection after surgical treatment

This chapter describes the development of a prognostic model for surgically treated orthopaedic infection without implant retention, using both primary and secondary prospectively-collected data with pre-specified outcome definitions.

5.1 Aims and objectives

The aims of this study focused primarily on prediction, rather than causal inference. The aims at the outset of the study were as follows

- To quantify the predictive value of modifiable behavioural factors, including smoking, alcohol intake, hyperglycaemia and malnutrition, for infection recurrence in adults receiving surgical treatment for orthopaedic infection.
- To construct and validate a risk prediction model for the recurrence of orthopaedic infection after surgical treatment.
- To assess the association of potentially modifiable risk factors, as described above, with patient-reported outcome measures following surgical treatment for orthopaedic infection.

5.2 Ethical approval

Ethics committee approval and HRA approval were sought prospectively. No changes in treatment resulted from inclusion into the prospective cohort study, which provided primary data for prediction modelling. The OVIVA and SOLARIO randomised controlled trials of systemic antimicrobial treatment for osteomyelitis and PJI, and the Lange *et al.* cohort study of PJI, had prospective ethical approval including for secondary data analysis.(Li et al., 2019; Dudareva, Kumin, et al., 2019; Lange, Troelsen, & Soeballe, 2016) Ethical approval for the PRIMIO prospective cohort study of osteomyelitis and PJI, conducted as part of this doctoral research fellowship, was provided by the London Bloomsbury Research Ethics Committee, reference 20/LO/0140.

5.3 Study participants

Potential participants in the PRIMIO prospective cohort were approached during their admission to the Nuffield Orthopaedic Centre, Oxford, for treatment of orthopaedic infection. Adult patients with orthopaedic infection were identified by the clinical team. Only patients likely to meet the inclusion criteria were invited to take part.

Participants in the SOLARIO trial were also enrolled through several NHS hospitals in the UK, that provided specialist care for people with orthopaedic infection, and through European specialist centres in Portugal, Austria and Spain. There was some overlap between UK recruiting centres for SOLARIO and for OVIVA. (Li et al., 2019; Dudareva, Kumin, et al., 2019)

5.3.1 Inclusion criteria

Three studies that contributed data to this prognostic modelling study had overlapping inclusion criteria. These included:

1. Provision of informed consent,

2. Being aged 18 years or over,
3. Presenting with an orthopaedic infection, defined by one or more of the following criteria:
   (a) localised pain, OR
   (b) localised erythema, OR
   (c) temperature $\geq$ 38.0 degrees C, OR
   (d) a discharging sinus or wound;
4. Undergoing surgical treatment for a clinical diagnosis of orthopaedic infection.

One of the studies, SOLARIO, specified that participants needed to have had a local antimicrobial carrier implanted at the time of their operation, in order to take part. The SOLARIO study was actively recruiting participants at the same time as the PRIMIO prospective cohort study, so this aspect of participant selection was partially mitigated by offering participation in the prospective cohort study to people who were not able to join SOLARIO in the majority recruiting centre (Nuffield Orthopaedic Centre, Oxford). Therefore the prospective cohort study mainly included participants requiring tertiary care, who did not have local antimicrobial therapy as part of their treatment, or where pathogens were identified that were resistant to local antimicrobial therapy, or where the person was interested in taking part in research but did not want to join an interventional trial.

Patients who were not comfortable discussing the study in spoken English were approached through a telephone interpreting service and/or a bilingual member of staff fluent and proficient in medical terminology relating to their condition. Study materials were be adapted and translated to assist inclusion of any potential participants interested in both the SOLARIO and PRIMIO studies. Participants were thus approached in Hindi, Urdu, Punjabi, Nepali and Russian, in addition to English.

5.3.2 Exclusion criteria

Participants were excluded from PRIMIO and SOLARIO if they did not have surgery aiming to cure the infection. This was defined as surgery where the wound was not closed, or where infected metalwork was retained (including DAIR).

DAIR and infected implant retention, as discussed earlier, carries a higher risk of infection recurrence than other surgical approaches for orthopaedic infection.(McNally et al., 2022; Lora-Tamayo et al., 2013) Including participants with DAIR would preclude comparison across the cohort due to heterogeneity and confounding by treatment indication. DAIR is, in most cases, emergency rather than elective surgery.(Gehrke et al., 2013)

For participants already recruited in the OVIVA study, only those who received surgical treatment with implant removal or replacement, rather than retention, were included in prognostic modelling.(Li et al., 2019)

5.3.3 Diagnostic definitions

The diagnosis of orthopaedic infection was based on clinical concern sufficient to warrant surgery for infection, as people who were not offered surgical treatment for infection were not eligible to participate in any of the studies contributing data to this analysis. This mode of inclusion is supported by work confirming that confirmatory definitions of orthopaedic infection exclude many cases.(Onsea et al., 2022; Metsemakers et al., 2018; McNally et al., 2021)

Microbiological confirmation of orthopaedic infection prior to surgery has poor sensitivity. Up to 40 percent of infections have negative microbiological cultures despite optimum diagnostic sampling, so this was not required at the time of enrolment.(Lew & Waldvogel, 2004) Microbiological and histological confirmation of infection was sought and recorded, but in practice was not always available for secondary data analysis or as part of routine clinical care in the centres where participants were recruited, in the case of histology. These results were sought and recorded when available.

5.4 Baseline variable recording

Pre-operative blood tests results from within three months before surgery, including haemoglobin, albumin, and glycated haemoglobin (HbA1C) in patients with diabetes mellitus, were sought from the participant's clinical record.

Participants were asked to complete an EQ-5D-5L questionnaire within 7 days of their operation for orthopaedic infection.(van Reenen et al., 2019) Prognostic factors of interest were sought directly from the participant, or were gathered from the participant's clinical record. The number of previous operations at the same anatomic site were sought directly from participants at the time of study enrolment. Baseline information regarding weight loss in the past 3-6 months and recent limitations on dietary intake enabled the calculation of a Malnutrition Universal Screening Test (MUST) score.(BAPEN, 2016) The clinical diagnosis of orthopaedic infection and baseline microbiology, prior surgical history, presence or absence of implanted metalwork before and after surgery, histopathology findings, and health status measured through the American Society for Anaesthesiologists (ASA) score and Charlson Comorbidity Index, were sought from the participant's clinical record.(ASA, 2019; Charlson, Pompei, Ales, & MacKenzie, 1987) MUST score and ASA score are recorded before surgery by the clinical care team as part of routine care.

5.5 Treatment of orthopaedic infections

All participants in this secondary data analysis received surgical care according to best practice in their specialist treating centre at the time of recruitment. No experimental surgical interventions were included as part of the study design of any of the contributing studies. Care took place in secondary and tertiary orthopaedic centres with an active orthopaedic infection research department to enable perioperative study approach and informed consent to be sought for as broad a range of potential participants as possible.

5.5.1 Surgical treatment

Surgical therapy received by participants included in prognostic modelling comprised debridement of osteomyelitis, removal of implants or metalwork, internal or external refixation, single stage arthroplasty revision, two stage arthroplasty revision, excision arthroplasty; and for a small number of participants, open arthrotomy for native joint septic arthritis.

5.5.2 Peri-operative care

Perioperative care included pre-operative surgical and anaesthetic assessment, and standard strategies to reduce the risk of adverse events in orthopaedic surgery. These included but were not limited to, screening for hospital-associated pathogens including MRSA and CPE where appropriate, peri-operative glycaemic monitoring and control, chlorhexidine surgical site prophylaxis, intra-operative antimibrobial treatment initiation, active warming during surgery, and post-operative prophylaxis against venous thromboembolism using mechanical means and low molecular weight heparins as appropriate.

5.5.3 Local antimicrobial therapy

One of the studies contributing data to the prognostic model, SOLARIO, specified that participants needed to have had routine clinical treatment with a CE approved local antimicrobial carrier to take part.(Dudareva, Kumin, et al., 2019) In other studies contributing to the prognostic model, local antimicrobial therapy was not mandatory for inclusion, but its use was recorded.

5.5.4 Systemic antimicrobial therapy

For participants in the SOLARIO study, half were randomised to receive a reduced duration of systemic antimicrobial treatment compared to standard consensus care. All participants contributing data to the prognostic modelling study received several days of intravenous antimicrobial therapy at the time of and after their surgery. Most also received intravenous or oral antimicrobial therapy for a minimum of four weeks, except those randomised to short systemic antimicrobial therapy in SOLARIO, who received up to one week of systemic therapy. (Dudareva, Kumin, et al., 2019; Li et al., 2019) Half of the participants in the OVIVA study received post-operative intravenous antimicrobial therapy. Since the conduct and analysis of OVIVA, oral antimicrobial therapy has become the standard of care, and the majority of participants recruited to subsequent studies were treated with oral antimicrobials.

Pre-operative antimicrobial therapy was allowed, but not recorded, in all studies. Pre-operative recommendations for the treatment of chronic orthopaedic infection specify that at least 2 weeks without systemic antimicrobial therapy prior to definitive surgery facilitates microbiological diagnosis and targeted antibiotic treatment.(McNally et al., 2021; Metsemakers et al., 2018)

5.6 Outcome measures

In three studies contributing data to the prognostic modelling study, treatment failure was evaluated by an independent endpoint committee of specialist clinicians with experience of treating orthopaedic infections. The committee did not receive information relating to baseline treatment or health when making their decision about whether treatment failure had occurred.

A consistent outcome definition was used in three of the contributing studies, that was independent of the type of orthopaedic infection, and included the criterion of clinician concern when no other criteria were met.

The primary endpoint was treatment failure within 12 months of surgery. Treatment failure was evaluated by the committee for all participants in PRIMIO and SOLARIO who met pre-defined criteria for possible infection recurrence (a Potential Primary Endpoint), including where the treating clinician was concerned that infection recurrence may have occurred.

5.6.1 Potential Primary Endpoints - criteria for endpoint evaluation

A potential primary outcome was defined as any of the following:

1. Readmission to hospital for investigation or treatment of illness that may be associated with the site of incident infection;
2. Unplanned re-operation at the anatomical site of infection;
3. Wound dehiscence, discharge or appearance of new sinus at the site of incident infection;
4. Prescription of additional systemic antibiotics for orthopaedic infection at

the incident anatomic site following completion of systemic antibiotic treatment for index orthopaedic infection;

5. Mortality during the trial follow-up period;

6. Concern from the local study clinicians that there has been a recurrence of infection, where none of the above criteria have been met.

5.6.2 Criteria for evaluating primary outcome and treatment failure

The primary endpoint was treatment failure within 12 months of surgery, as determined by an endpoint committee using redacted information from the patient record. The criteria described below were applied to all participants that had any potential primary outcome criteria recorded at any time during 12 months follow up.

The criteria for defining the primary endpoint have been applied in two randomised controlled trials, allowing combined data analysis.(Li et al., 2019; Dudareva, Kumin, et al., 2019)

Definite treatment failure was defined as:

1. the isolation of a pathogen in one or more deep orthopaedic surgical samples,
2. histology diagnostic of orthopaedic infection,
3. purulence and sinus formation in continuity with bone or orthopaedic implant,
4. elevated synovial white cell count or positive leukocyte esterase testing in prosthetic joint infection,

5. death resulting from orthopaedic infection at the same anatomic site as the participant's initial surgery.

Death from any cause during the follow-up period will be recorded, in addition to mortality thought to result from orthopaedic infection or its recurrence.

5.6.3 Secondary Outcomes: Possible and probable treatment failure at 12 months

These outcome measures will classify participants without unequivocal clinical evidence of orthopaedic infection, and those who are not willing or able to undergo further surgery for their condition. The same definitions were applied in the SOLARIO and OVIVA studies.

The following criteria will be considered by the blinded endpoint committee to determine 'probable' or 'possible' infection.

Infection will be categorized as 'probable' where microbiological sampling had not been undertaken, AND none of the other criteria for definite infection had been fulfilled AND any one of the following were met:

- The development of a discharging wound at the site of the bone/prosthetic joint/orthopaedic device at clinical review, OR
- Erythema, warmth and localized pain at the site of previously treated infection on clinical review, OR
- Radiological or operative findings of periosteal changes suggesting osteomyelitis or prosthetic joint infection, OR
- Rapid loosening of a joint prosthesis/orthopaedic device (i.e. leading to localized pain in less than 3 months since implantation), in the absence of

a mechanical explanation for rapid loosening, on radiological, clinical or operative examination, OR

- The presence of deep pus close to but not adjacent to bone/prosthetic joint/orthopaedic device at reoperation, OR
- The presence of peri-prosthetic necrotic bone on operative histology, OR
- Amputation at the site of initial orthopaedic infection.

5.7 Planned statistical analysis

5.7.1 Data management

Data for two recent studies (the SOLARIO randomised controlled trial and the PRIMIO prospective cohort study) was collected through an online Data Management System, with a programmable data entry and storage capacity (REDCap).(P. Harris et al., 2009) All research staff seeking participant consent and recording data using the databases for SOLARIO and PRIMIO received training in advance of using the databases. Access to data was monitored. All data fields were explained in a CRF manual, and many baseline fields were given additional explanatory text within the input interface itself to optimise accuracy. Numeric fields included both character filtering and expected ranges. Date fields had validation to ensure the correct year was selected, and rules to prevent negative time periods being recorded.

5.7.2 Predictor handling

The following predictors were measured:

- Charlson comorbidity score parameters, including diabetes mellitus and peripheral vascular disease

- ASA score
- Immunosuppressive conditions or medications
- HbA1C in the three months before surgery
- Peri-operative blood glucose
- Smoking at the time of surgery and in the three months before surgery
- BMI
- Presence of a sinus at the site of infection
- Alcohol intake in the three months before surgery
- Affected bone and/or joint

5.7.3 Sample size

All patients included in the analysis received treatment for existing orthopaedic infection, which is estimated to recur in approximately 10-20% of patients within 12 months.(Li et al., 2019; McNally et al., 2016; Ferguson et al., 2014) Definite treatment failure was the primary outcome of interest. An estimate of 13% definite treatment failure at 12 months is based on the Oral Versus IntraVenous Antibiotics (OVIVA) randomised controlled trial for post-operative treatment of orthopaedic infection.(Li et al., 2019) This trial recruited similar patients in many of the same orthopaedic centres in the UK as the prospective cohort study and SOLARIO study, between 2010-2015; the trial intervention treatment has since been accepted internationally as standard practice. In this study, the definite treatment failure rate, ascertained against the same criteria as in the SOLARIO study and proposed prospective cohort study, was 13% at 12 months; loss to follow-up was 4%.

The *a priori* sample size calculation was performed as follows. Assuming a definite treatment failure rate, at 12 months, of 13%, a loss to follow-up rate of 5%, a maximum of 10 variables to be modelled (including study centre, pre-operative health summarised through ASA score, operation type and antibiotic treatment category) and an event-per-variable minimum of 20, (understanding that events-per-variable criteria do not provide sufficient specification for all aspects of model performance) 1620 participants, in total across all datasets, would be required. This would allow analysis of the main predictors adjusted for five other variables.(van Smeden et al., 2018; Steyerberg & Vergouwe, 2014; R. Riley et al., 2020; Martin et al., 2021)

Data were available for 727 patients from the OVIVA study (patients are excluded if no surgery was performed, or debridement and implant retention (DAIR) was performed). In addition, data for 500 participants was expected to be available from the SOLARIO clinical trial if recruitment and follow-up had been completed. Recruitment was unexpectedly and severely delayed by both postponed elective surgical lists and research staff diversion to COVID-19 clinical management and research. The target participant number for the prospective cohort study was 393 participants, though this was also affected by changes to clinical and research provision during the COVID-19 pandemic. The study protocol stated *a priori* that in the event that recruitment did not continue as expected, two non-modifiable predictive variables would be prioritised for inclusion (ASA score, operation type.) If the target participant number was not achieved, shrinkage techniques would also be considered as a contingency analysis to limit variables selected for modelling in secondary analyses.(Steyerberg & Vergouwe, 2014)

Predictor	Units, source, measurement	Timing
Malnutrition Universal Screening Test score	Unitless rank score, range 0 - 6. Recorded from biometric measurements and interviews at study enrolment.	Weight loss in 6 months before surgical procedure
Glycosylated haemoglobin Concentration (HbA1c)	Routine laboratory measurement as part of pre-operative care for people with diabetes or suspected diabetes	Up to three months before surgery
Maximal peri-operative plasma glucose	Routine point of care monitoring for people with diabetes mellitus and those requiring post-operative high-dependency care	Up to 7 days before and after surgery
Patient reported smoking (dose)	Maximal number of cigarettes per day or tobacco equivalent in three months before surgery. Excludes vaping.	Up to three months before surgery
Patient reported alcohol intake	Usual alcohol intake per week, converted to number of UK standard units per week (1 unit = 10ml ethanol)	Up to three months before surgery

5.7.4 Predictor selection

Five prognostic factors were selected *a priori* for modelling. Additional prognostic factors that were specified for inclusion if the sample size was sufficient, that were not amenable to modification in the pre-operative period, included ASA score, type of surgery, study centre, post-operative systemic antimicrobial duration, number of prior operations at the same anatomical site, BMI, immunosuppressive medications and Charlson index.(Charlson et al., 1987; ASA, 2019) These predictors were selected based on existing prognostic studies detailed in Chapter 3.

The prognostic factors chosen *a priori* for investigation are described below.

During the project, it became clear that some predictors could not be included. Study site, for example, was not relevant to the development of a clinical prediction model. Charlson comorbidity index and ASA were strongly correlated. Charlson index could not be completely calculated from the comorbidities recorded in secondary data, and some comorbidities in the Charlson index might no longer have the same prognostic value due to worldwide changes in management since the time of Charlson model development (HIV/AIDS and gastroduodenal ulcers, for example).

Prognostic factors subject to behavioural variation were not all amenable to inclusion. For example, following data collection for SOLARIO and PRIMIO, it became apparent that the incidence of malnutrition identified through a MUST score of 2 or more, was only 3%. Malnutrition screening was not available in two secondary datasets, leading to unacceptable data sparsity. Furthermore, MUST scores from earlier datasets may no longer reflect changing population norms in the UK due to post-pandemic economic stress.

Through discussions with the supervisory team and advice from other researchers, it became clear that predictors that may be expected to have a causal effect on treatment outcome were not always the predictors with the best prognostic discrimination, the easiest to measure and record, and the most useful in clinical practice. In light of this, I decided to reduce reliance on the specified modifiable predictive factors for the purposes of prognostic modelling, but instead investigate the possible causal effect on treatment failure attributable to these factors separately.

5.7.5 Missing data

Missing values, including systematically missing predictors in any dataset used for analysis, were planned for Multiple Imputation by Chained Equations (MICE) using a random study effects model. (van Buuren & Groothuis-Oudshoorn, 2011;

Held, Kessels, & Aymerich, 2016; Jolani, Debray, & Koffijberg, 2015) MICE is applicable when data are missing completely at random (MCAR) or missing at random (MAR). The distribution of missingness for all predictor and adjustment variables was assessed. Multiple imputation allows greater accuracy in prognostic modelling than complete case analysis, including for systematically missing predictors as long as they are MAR.(Jolani et al., 2015)

5.7.6 Pre-specified analysis methods

Logistic regression was planned to estimate the risk of treatment failure. It was anticipated that some predictor variables will have a positively skewed distribution; logistic regression is suitable for modelling in this situation, providing model residuals are normally distributed.(Harrell, 2015) Due to the possible risk of differential follow-up (where patients without infection recurrence are more likely to be lost to follow-up than patients with infection recurrence) Cox proportional hazards modelling may be less suitable. (Harrell, 2015)

Model calibration and discrimination were planned to be assessed visually, with estimates for intercept and slope, and using the C statistic (AUROC). External validation was planned, using existing datasets including the population of interest, a prospective study design and baseline assessment for any potentially modifiable risk factor.

Modifications to the a priori analysis plan included the use of restricted cubic splines in the modelling of the prognostic association with participant age at surgery. Due to the difficulty in interpreting restricted cubic spline coefficients in a point score clinical prediction model, and the finding that including restricted cubic splines did not improve model calibration or discrimination, these were not included in the final analysis.

5.7.7 Assessment of distributional assumptions

Possible non-linear associations between the predictors under investigation and the primary outcome were assessed by categorization of the predictors into quartile groups. Previous studies suggested that nutritional status and smoking may have an interacting effect on the risk of primary orthopaedic infection; interactions between MUST score, BMI and smoking were assessed in a planned secondary analysis.

In the event that model residuals were not approximately normally distributed, or that odds ratios for outcome were not distributed approximately linearly, predictor variable transformation and binary categorization was planned as part of planned secondary analysis.

5.8 Additional statistical analysis - Patient-reported outcome measures

The proportion of patients with improved EQ-5D-5L health score was modelled against predictors of interest using logistic regression.(van Reenen et al., 2019) The EQ-5D-5L health questionnaire provides evaluations in five domains of daily experience, on a specific day, for an individual. These five domains (mobility, self-care, daily activities, pain and mood) are graded on a five-point scale. If the highest score is rated in all domains, the individual is scored as fully healthy. The interpretation of other score combinations is more complex. One accepted interpretation relies on weighting each combination according to nationally-specific state scores. These scores are updated regularly and based on time trade-offs and discrete choice experiments by representative people. They give each score combination a value, as a fraction of full health. (Dolan, 1997; Devlin, Shah, Feng, Mulhern, & van Hout, 2017) Separately from the five domain scores, the EQ-5D questionnaire gives participants a chance to summarise their health in one overall number from zero to one hundred using a visual analogue scale (EQ-5D-VAS).

Though the EQ-5D-5L scale is not specific to limb disorders or infections, it is able to capture the experience of having orthopaedic infection, because orthopaedic infection frequently affects mobility and independence, is often painful, and is frequently accompanied by low mood.(Moore et al., 2015; Cahill et al., 2008)

5.8.1 Heterogeneity of treatment effects (HTE)

Systematic differences were noted in the treatment participants received, both between and within the datasets contributing to this project. Specifically, the surgical approach to orthopaedic infections varied: single stage or two-stage arthroplasty revision for PJI; internal or external fixation for fracture-related infection with non-union; whether tissue transfer is used to enable wound closure. There were also unsystematic differences in the local antimicrobial therapy that participants received (the dose, antibiotic type and carrier), and differences in systemic antimicrobial therapy (drug, dose, method of administration, and duration).

In OVIVA, half of participants were randomised to receive oral rather than intravenous systemic antimicrobial therapy after the first one to two weeks of treatment. Since publication of this study, the norm in international practice has been to give oral systemic antimicrobial therapy following surgery for orthopaedic infection, as this strategy was found to be non-inferior for prevention of infection recurrence at 12 months.(Li et al., 2019)

In the SOLARIO study, one of the inclusion criteria for participation is local antimicrobial therapy at the time of surgery.(Dudareva, Kumin, et al., 2019) In metaanalyses for both prevention and treatment of orthopaedic infection, the presence of local antimicrobial therapy has been found to be associated with a lower risk of infection and infection recurrence. (McNally et al., 2022; Morgenstern, Vallejo, et al., 2018) Both intravenous systemic antimicrobial therapy and local antimicrobial therapy might also be expected to have a greater effect in preventing infection recurrence for people who are non-concordant with oral antimicrobial therapy.

Throughout model construction it was not possible to fully account for heterogeneous treatment effects due to absent data (such as the amtibiotics, their doses and durations, administered after surgery, and the presence or absence of local antimicrobial therapy) across all cohorts. The severity of surgical disease, including the size and nature of bone defects, and soft tissue scarring, was also absent.

5.8.2 Social and demographic factors

Data relating to demographic parameters such as employment, functional status, socioeconomic status, education and ethnicity were systematically missing for most or all participants. Index of Multiple Deprivation (IMD) was recorded based on postcode of residence for participants from England in the PRIMIO prospective cohort study only.(DfCLG, 2015) Ethnicity, as recorded on the participant's health record, was also recorded only in the PRIMIO prospective cohort study.

However, as not all participants in other datasets were from England, and because participants in PRIMIO were expected to be systematically different from those in the other cohorts (more severe disease could lead them to decline participation in a non-inferiority trial; resistant micro-organisms causing the orthopaedic infection might restrict interventional trial participation), IMD data for this group would not be representative.

Participants	OVIVA	SOLARIO	PRIMIO	Lange et al. 2016
Screened	2077	664	138	461
Eligible	1449	Not determined	138	130
Total study population	1054	252	104	130
Included	727	252	104	130

5.9 Results

5.9.1 Participant inclusion and flow

Participant screening and inclusion is described briefly in the table below. Only a fraction of participants in the OVIVA study were selected, due to the inclusion of other participants who had been treated non-operatively or through DAIR.(Li et al., 2019) More information relating to participant inclusion and exclusion is available from study publications. (Dudareva, Kumin, et al., 2019; Lange et al., 2016)

5.9.2 Participant baseline, outcome and and demographic data

In total, 1213 participants contributed data to model building, of whom 195 experienced definite, possible or probable treatment failure by 12 months after their operation. All participants had no retained infected metalwork at the site of orthopaedic infection, from before their surgery. Due to the inclusion of an additional cohort study with a more inclusive definition of treatment failure, definite, probable and possible endpoints were included in primary analysis for consistency.(Lange et al., 2016) Of the 1083 participants for whom evaluation for definite, probable and possible endpoints was carried out, 139 experienced definite treatment failure, 25 probable treatment failure, and 5 possible treatment failure. The proportion of possible, probable and definite treatment failure at 12 months is shown in Table:

Study	Total N	12 months N	Definite outcome	Probable outcome	Possible outcome	Any outcome
OVIVA	727	702	89	8	1	98
SOLARIO	252	229	23	12	4	39
PRIMIO	104	96	24	5	0	29
Lange et al. 2016	130	115	-	-	-	10

Not all baseline characteristics were recorded in all of the contributing cohorts. The distribution of missingness in each predictor variable is shown in 5.1

A summary of demographic characteristics for included participants is presented in 5.2. Lange et al. 2016 included only people having surgery for PJI of the hip, while the three other studies included participants with a broad range of orthopaedic infections.

The medical comorbidities identified among cohort participants and recorded at baseline are presented in 5.3.

A summary of the surgical management of participants is included 5.4.

Systemic antimicrobial treatment was not recorded uniformly across the cohorts, so it was difficult to compare between participants. As discussed in Chapter 4, antimicrobial prescribing would be expected to vary across study sites, resulting from differences in local antimicrobial guidance and availability, and individual clinicians' practice. In the OVIVA study, the route of administration for post-operative systemic antimicrobial treatment was the subject of the study intervention.(Li et al., 2019) In the SOLARIO study, the duration of post-operative systemic antimicrobial therapy was reduced by three or more weeks for participants in the intervention arm. (Dudareva, Kumin, et al., 2019) The systemic antimicrobial treatments offered to all participants in the PRIMIO and Lange 2016. cohorts reflected standard clinical practice at the time of enrolment. Prior work presented in Chapter 4 showed that the choice of antimicrobial treatment may have complex associations with outcome.

5.9.3 Prognostic variables

The prognostic factors chosen *a priori* for investigation included MUST score, perioperative peak measured blood glucose, pre-operative HbA1C, pre-operative smoking and pre-operative alcohol intake.

5.9.3.1 Peri-operative nutrition and glycaemic control

MUST score was recorded for the majority of participants in SOLARIO and PRIMIO, however it was systematically missing in OVIVA and Lange et al 2016. BMI was available for three cohorts but systematically missing for participants in OVIVA.

Among participants who had a MUST score recorded at the time of surgery, only 3% had a screening score suggesting risk of malnutrition. This was less frequent than anticipated, and due to the sparsity of participants affected and the systematic missingness in two cohorts that may not have been directly comparable, was felt to be less useful for prognostic modelling than other predictors that were non-dichotomous and where the information density would be higher. BMI and albumin are both frequently available at the time of clinic review, but are limited in their value as markers of malnutrition. Albumin is affected by many pathological processes including systemic inflammation, disorders of renal glomerular filtration, and malignancies; and has a half life of around 20 days which limits its sensitivity for acute reductions in oral intake.(Levitt & Levitt, 2016) BMI is included as part of the MUST score, but is neither sensitive nor specific for detecting macronutrient and micronutrient deficiencies.(Budzynski & Szukay, 2022) BMI was included in modelling due to its ease of measurement and its association with clinical outcome in studies reviewed in Chapter 3.

Glucose and HbA1C were found to be not missing at random. Peri-operative blood glucose was not recorded unless a patient had known diabetes mellitus, required care in a high dependency unit with venous blood gas testing, or had an episode of acute deterioration in the perioperative period. Imputation of blood glucose and HbA1C using MICE was attempted by including the binary variable diabetes mellitus, which was recorded across the four cohorts.(van Buuren & Groothuis-Oudshoorn, 2011) With this strategy, however, 74% of the resulting interpolated values were in the range for clinical diabetes mellitus, whereas only 18% of participants had a known diagnosis of diabetes mellitus. As multiple interpolation gave systematically biased values, both peri-operative glucose and HbA1C were abandoned as prognostic variables for modelling. This could be overcome using testing at enrolment in future studies.

5.9.3.2 Pre-operative substance use

Current smoking at the time of surgery was recorded for all but two participants across all four cohorts, and 17% of participants reported smoking around the time of their operation. The maximum participant-reported daily tobacco intake was available for participants in the SOLARIO and PRIMIO cohorts. Confirmatory cotinine testing and CO testing was not available for any participants in studies contributing to modelling.

Smoking dose was not recorded in all study sites contributing data to the four cohorts. Variations in local prevalence of smoking, and in how heavily participants from different study sites might smoke, meant that it was likely that maximal preoperative tobacco intake was not Missing At Random. These values were not

Study Centre	Smoking (%)	Not smoking (%)	Proportion of participants with recorded smoking dose (%)
Cambridge	2 (7.1%)	26	0
Birmingham	4 (12.5%)	28	0
Denmark	33 (25.3%)	97	0
Swindon	3 (13.0%)	20	6 (26.1%)
Guys & Thomas'	1 (4.3%)	22	0
Porto	4 (25%)	12	4 (25%)
Oxford	98 (15.6%)	532	200 (31.7%)
Liverpool	13 (22%)	46	3 (5.1%)
Royal Free	3 (9.7%)	28	0
RNOH	15 (13.5%)	96	3 (2.7%)
Other	30 (23.4%)	98	19 (14.8%)

imputed for modelling for this reason. The clustering of smoking ascertainment by study site is shown in the table by study centre (I^2=50.8%, moderate heterogeneity).

Alcohol use at the time of surgery was recorded for three of the cohorts but was systematically missing for OVIVA. For Lange et al. 2016, pre-operative excess alcohol use was recorded; for all other participants, data were marked as missing. In SOLARIO and PRIMIO, average participant-reported alcohol intake in the three months before surgery, was recorded. However, the flexible requirements for data entry, maximally lenient to try to improve completeness, meant that interpreting recorded alcohol intake from recorded data was not straightforward.

The impact of interpretation on recorded pre-operative alcohol intake for these two studies was examined using concordance of the interpreted data value by two trained clinicians with experience assessing alcohol intake as part of clinical history taking (Maria Dudareva and Alisha Sattar). The average alcohol intake was interpreted in number of UK units per week. One unit was defined as 10ml 100% ethanol, or 8g 100% ethanol. The following steps were applied by both clinicians:

1. Where a brand, type and volume of a drink are given, the product information itself is used to calculate units
2. If that is unavailable, the type of beverage and size is estimated from UK Department of Health 2008 published guidance (Department of Health, 2008)
3. If the number of units is given, that is taken at face value
4. If a range is given, the mid-point of the range is used to calculate the number of units consumed.

Assumptions that were agreed during data interpretation were:

- Lager, unspecified contains 5% alcohol by volume
- One bottle of wine contains 10 UK units
- Glasses of wine contain 14% alcohol by volume
- A home measure glass of wine is equivalent to a standard 175ml glass, and contains 2.5 UK units
- A home measure of spirits is equivalent to a 50ml spirit double, and contains 2 UK units unless specified
- Alcohol drinking less than weekly is quantified as 0 UK units per week
- Alcohol drinking on "most days" is interpreted to mean alcohol drinking 7 days per week
- Strong cider is assumed to contain 8% alcohol by volume.

Alcohol intake was double coded for 251 participants in SOLARIO and PRIMIO. A Bland-Altman plot is presented (5.5, showing the difference in interpreted values for alcohol units reported per week, against the mean estimated value by both rating clinicians.

This comparison suggests that two trained clinicians using instructions for interpreting recorded alcohol intake made errors in interpretation that increased in size with the magnitude of the reported intake. This confirms the difficulty other researchers have reported with accurately quantifying alcohol intake for hospital inpatients, based on information obtained during the clinical encounter. The lack of reliable quantification for alcohol intake data meant this variable was not included in prognostic modelling.

Data on illicit substance use was not collected or reported for any of the contributing cohorts. People who reported injecting drugs in the peri-operative period were excluded from participating in OVIVA, though not from SOLARIO and PRIMIO.

5.9.3.3 Choice of prognostic variables

The variables included in logistic regression modelling, based on published prognostic models reviewed in Chapter 3, were:

- Age at surgery (years)
- Gender at surgery (as identified on healthcare record)
- Number of previous operations (categorised as 0,1,2,3,4,5+)
- ASA score (categorised as 1,2,3+) (ASA, 2019)
- BMI (continuous)
- Diagnosis of diabetes mellitus
- Immunosuppressive medications in the three months before surgery
- Current smoking at the time of surgery

5.9.4 Distributional assumptions for predictors

Age at surgery was approximately Normally distributed. The median age of participants across all cohorts was 60 years and the mean was 58 years. The age distribution is shown in 5.6.

BMI was available for 477 participants. BMI values were approximately Normally distributed, with mean of 28.2 kg/m^2 and median 27.6 kg/m^2, and a range from 15.0 to 53.5. Implausible values were corrected to missing prior to further analysis. 5.7

The number of previous operations at the same anatomic site as the index orthopaedic infection was available for 457 participants. This variable was not Normally distributed, with a mode of one previous operation. 52 participants had no prior operations at the time of their index surgery. The maximal number of operations recalled prior to index surgery was 43, including incision and drainage procedures, sustained by one participant in the PRIMIO cohort treated for recurrent prosthetic joint infection. The distribution of number of previous operations experienced by participants at the same anatomic site as their index surgery is shown in 5.8:

As very few participants had six or more operations prior to their index surgery, for the purposes of multiple imputation and model construction, five or more past operations were combined in one category, and this variable was treated as a categorical variable. The association between number of previous operations and treatment failure is shown below, and follows an approximately linear pattern 5.9:

ASA score, another categorised variable (as few participants had a score of 4 or more), had the following raw association with outcome:

The analysis plan specified that there may be an interaction between BMI and smoking in relation to treatment outcome after surgery for established orthopaedic infection. The following plot shows the proportion of participants across all cohorts where BMI was available (excluding OVIVA) who experienced treatment failure, according to whether they reported currently smoking at the time of their operation. 5.11

The absolute number of participants in the greatest BMI category (>40) was small, comprising only 17 participants who reported not smoking (of whom 4 experienced treatment failure) and 2 participants who reported smoking (of whom one experienced treatment failure). In aggregate, the association between BMI and treatment failure may be affected by smoking, though the small number of participants make it challenging to conclusively demonstrate or rule out an interaction between these predictor variables.

5.9.5 Model elaboration and performance

An initial logistic regression model included all variables as specified above. Ten rounds of imputation using the MICE package for R were performed for missing predictor variables and outcomes. Multiple imputation included other baseline variables: operation, study site, other comorbidities (including end organ complications from diabetes mellitus and peripheral vascular disease) as well as the prognostic variables of interest. A full logistic regression model that included a three knot restricted cubic spline for treatment failure in relation to participant age was compared with a simple additive logistic regression, and found to have minimally improved fit compared to a full model including age as a linear predictor.(Harrell, 2015) The model with restricted cubic splines was not amenable to straightforward evaluation and pooling of estimates, and was not pursued further.

The model equation for the full logistic regression model with linear and categor-

Predictor variable	**Coefficient (beta)**	**Standard error**
(Intercept)	-4.37	0.78
Age (per year)	0.0036	0.0069
Male gender	0.15	0.19
Each prior operation	0.30	0.08
ASA 2 (relative to 1)	1.14	0.40
ASA 3 (relative to 1)	0.74	0.44
BMI (per unit)	0.020	0.020
Diabetes mellitus	0.47	0.25
Immunosuppression	1.03	0.39
Current smoking	0.066	0.24

Table 5.1: Coefficients for full logistic regression model.

ical predictors follows.

$$\begin{aligned} &\mathrm{P}(\text{Treatment failure} = 1 \mid \text{Host characteristics}) \\ &\quad = \frac{\exp(\beta_0 + \beta_1\text{Gender} + \beta_2\text{Age} + \cdots + \beta_8\text{Current smoking})}{1 + \exp(\beta_0 + \beta_1\text{Gender} + \beta_2\text{Age} + \cdots + \beta_8\text{Current smoking})} \end{aligned} \tag{5.1}$$

Figure 5.12 summarises the performance of a pooled logistic regression model (coefficients and uncertainty estimated from ten independently-derived logistic regression models based on 10 rounds of imputation with Predictive Mean Matching, pooled using Rubin's rules) (Harrell, 2015) against a full dataset obtained through one round of multiple imputation. (van Buuren & Groothuis-Oudshoorn, 2011) The plot compares predicted risk of treatment failure for study participants, relative to their observed risk of treatment failure. A perfectly calibrated model would have intercept 0 and slope 1, and be able to separate participants into groups, such that the estimated risk of failure for people in each group would be equivalent to the observed rate of treatment failure in the group. c

The slope and intercept of the model suggested reasonable calibration, according

Predictor variable	Coefficient	Standard error
(Intercept)	-3.76	0.42
Age (per year)	0.0040	0.0058
Male gender	0.14	0.17
Each prior operation	0.28	0.049
ASA 2 (relative to 1)	1.27	0.26
ASA 3 (relative to 1)	1.06	0.29

Table 5.2: Coefficients for parsimonious logistic regression model.

to internal comparison among 10 imputed datasets. Discrimination (estimated by the C statistic, or AUROC) ranged between 0.64 and 0.66, which suggested limited predictive performance for treatment failure. 5.12

A parsimonious model was built for comparison, including only age, gender (as listed on the healthcare record), categorised ASA score and categorised number of prior operations, had similar performance to the full model. These variables were chosen because they could be ascertained pre-operatively during history taking alone, with no requirement for radiology, invasive testing or specialty-specific assessment, for most people seeking surgical treatment for orthopaedic infection. These factors were expected to affect the outcome from any orthopaedic infection treated with surgery. The coefficients for the parsimonious logistic regression model are given below:

The distribution of residuals was not Normal, but was not evidently dependent on age, the only variable that could be transformed to account for a possible non-linear relationship: 5.13,5.14, 5.15.

The calibration and discrimination parameters of this parsimonious model are summarised in the plots below. Calibration was marginally less accurate than for the full model, with reduced certainty for the model slope, and a calibration curve suggesting overfitting (overestimated probability of treatment failure at high and low probabilities of treatment failure). The discrimination of the parsimonious four-variable model was comparable to the full model, with C statistics for the pooled model, in 10 imputed datasets, ranging from 6.3 to 6.4, once again indicating limited predictive performance for treatment failure at 12 months. 5.16

Using this model, 236 of 1213 participants had predicted treatment failure risk of 20% or more at 12 months after surgical treatment (19.5% of all participants). This was a potentially convenient and memorable message for clinical practice, wherein roughly one in five patients represented by study participants in the prognostic modelling population, had a risk of recurrence of one in five or more at 12 months.

5.9.6 Model optimism and internal validation

Bootstrap internal validation was used to estimate the optimism, or overfitting to the data, of the parsimonious predictive model that included age, gender, ASA score and number of previous operations. Boostrap resampling (sampling with replacement yielding samples containing a mean of 63% of all study participants) was used to derive the parsimonious model anew 200 times, to obtain an average estimate of model discrimination when derived from 200 hypothetical populations equivalent to that from which the original participants were drawn. Mean optimism-corrected model C statistic discrimination for these models was 0.61, which was low, but not greatly reduced from the initial estimate of discrimination for the parsimonious model.

The calibration of the optimism-corrected pooled parsimonious model is shown in 5.17. In all, prognostic model calibration was not greatly reduced after adjustment for optimism.

Bootstrap validation did not include multiple imputation for missing variables in each resampled population, and as such, was likely to have underestimated the degree of optimism, or overfitting, for this prediction model. (Wood AM, 2015; Wahl, Boulesteix, Zierer, Thorand, & de Wiel, 2016) Wood et al. also noted that including outcomes when performing multiple imputation for missing data during the development of prognostic models is important, as it allows the relationship between predictors and outcome to be maintained. However, they found that this led to overoptimism when assessing model performance through bootstrap internal validation. They evaluated two strategies for internal validation for models constructed with data imputed using MICE with Predicted Mean Matching (as in this project). The 'pooled performance' strategy tests each imputation-specific model within the imputed data set, then pools the performance measures. The 'pooled predictors' strategy pools model coefficients derived in different imputed datasets, then tests the performance of the pooled prediction model. The 'pooled predictors' strategy yielded non-optimal calibration slopes, so though the 'pooled performance' strategy gave over-optimistic estimates of performance, it was recommended.

At the start of the modelling project, it was apparent that study populations across the four cohorts included were dissimilar. Demographic parameters, infections that affected participants, and specifics of both surgical treatment and peri-operative care differed between each cohort. To assess the impact of study population on model performance, leave-one-cohort-out cross-validation was performed. Model performance was assessed against outcome data for one of the four study cohorts at a time. Each time, the model was derived in the same way as the original model, but with multiply-imputed data for the remaining three cohorts only. Calibration and discrimination parameters were assessed visually and numerically. Summary calibration curves for each omitted cohort are presented, 5.18, 5.19, 5.20.

Mean model calibration estimates for the logistic regression slope when omitting Lange *et al.* 2016, PRIMIO, and SOLARIO were 0.82, 2.06, and 0.34 respectively. Ideal calibration has a slope of 1. This supported the hypothesis that model calibration was very specific to the population under study. Though model discrimination was still better than chance, the parsimonious prediction model would be unlikely to give well-calibrated risk estimates for treatment failure at 12 months, for people considering treatment for orthopaedic infection in a different clinical setting from the European specialist centres that contributed data to this project. Leave-one-out assessment was not possible for the OVIVA cohort, as BMI was systematically missing for all study participants.

Decision analytic curves were constructed to estimate the incremental prognostic benefit for the full and parsimonious prognostic models, showing similar performance for the two models. This comparison supported further work with the parsimonious model, as incremental benefit was similar between models when assessed visually. 5.21

Unfortunately, external validation was not possible for this prognostic model, due to new research findings during the project period. For accurate estimates of performance, hundreds of participants who had experienced treatment failure would need to be included in a validation dataset, to precisely estimate external calibration and discrimination and net benefit.(R. D. Riley et al., 2021) No datasets were available that met this specification, despite enquiries to the authors of studies in orthopaedic infection that used the Medicare 5% cohort,(Bozic et al., 2012) and to members of the European Bone and Joint Infection Society.

5.9.7 Quality of life

It would be expected that a model that was able to discriminate between treatment failure and treatment success may also predict the improvement in quality of life that people may experience from their treatment. Increment in EQ-5D score over 12 months between baseline and post-operative questionnaires was calculated for 611 participants for whom survey responses at baseline and 12 months after surgery were available, using state scoring for England.(Devlin et al., 2017; Dolan, 1997) The relationship between deciles of predicted risk of treatment failure from the parsimonious prognostic model, and increment in EQ-5D health score over 12 months after surgery, is presented in 5.22.

This suggests there is little association between predicted risk of treatment failure at 12 months with the parsimonious model, and the change in quality of life as quantified from five domains using the validated EQ-5D survey and scored according to state evaluations for England.(van Reenen et al., 2019; Devlin et al., 2017; Dolan, 1997)

5.9.8 Model reporting and user preferences

The original aim of this modelling study was to validate host criteria (demographic, behavioural or existing diagnoses) that would best predict treatment outcome for people with orthopaedic infection, as part of an existing classification system (BACH and JS-BACH).(A. J. Hotchen et al., 2019; A. Hotchen et al., 2021) The host status prognostic classification system could also be used to stratify people according to the risk of treatment failure in orthopaedic infection, to tailor study recruitment, and to allow reporting of heterogeneous treatment effects (HTE) in interventional studies in orthopaedic infection.

The parsimonious prognostic model was used to construct a point score, following published recommendations.(Bonnett, Snell, Collins, & Riley, 2019) The maximal available score was 14 and the minimal score was 0. After reviewing the distribution of risk, a simplified high/low risk cut-off could be specified from the

Predictor variable	**Points**
Male gender	+1
Age 60 or more	+3
ASA 2+	+5
Each prior operation	+1

Table 5.3: Points scoring system derived from parsimonious logistic regression model

points score: 10 or more points indicated a 20% or greater risk of treatment failure, while fewer than 10 points indicated a lower than 20% risk of treatment failure.

High risk (20% or more chance of treatment failure at 12 months) could be achieved through a combination of factors. For example, a female person aged 36 with controlled comorbidities, having an operation on an infected total hip replacement following initial corrective operations for developmental dysplasia (totalling five prior procedures), would score 10 points. Alternatively, a male person aged 65 who had controlled comorbidities, but who had had a previous primary partial knee replacement that was now infected, would also score 10 points.

The point score is summarised in the adjacent table.

A representative plot of the estimated calibration and discrimination of the point score are shown: 5.23, 5.24

In the absence of other information, the discrimination of this point score is very limited. It was scarcely better than chance at predicting prognosis at 12 months following surgery for orthopaedic infection.

Several versions of the parsimonious prognostic model (including age, gender, ASA score and categorised number of previous operations) were presented at the European Bone and Joint Infection Society conference in Graz, Austria in September 2022. The audience for this presentation, comprising clinical and research specialists in orthopaedic infection, were asked in what format they would prefer to use a prognostic model. The survey contained options in a randomised order and was available at a short URL that attendees were encouraged to share, linked by a QR code presented during the lecture. The results are shown below, 5.25

The majority of 38 anonymous conference attendees replied that they would prefer to use a risk score or a simple high/low risk classification when assessing prognosis. However, it was clear from one response that not all respondents took the question seriously ('Bridget' likely refers to Dr. Bridget Atkins, Consultant in Clinical Infection and international research leader in the field of orthopaedic infection). A significant proportion of respondents reported preferring their own judgement over prognostic models. This is relevant when understanding one of the reasons this prediction model may have had poor discriminative performance.

5.10 Discussion: Model interpretation

Throughout this process, I attempted to follow best practice in elaborating a prognostic model from combined prospective clinical data, with the aim of predicting treatment failure for surgically treated orthopaedic infection. I focused on the prognostic value of self-reported host factors, which are available at the initial clinic visit when surgery is discussed with a person with orthopaedic infection. I aimed to include participants with a variety of orthopaedic infections, as the effect of host factors on prognosis would be expected to be uniform regardless of whether the infection being treated was osteomyelitis, FRI, or PJI, and which bone was affected. The treatments these participants received were necessarily different. Treatment was tailored to the specific anatomy of the infected bone or joint, to surgical training, and to the materials available at each treating centre.

The population included in all four studies were people who had a clinical diagnosis of orthopaedic infection that was secure enough for an operation to be carried out to treat it. Confirmatory diagnostic criteria were not available for all participants in each cohort, and would not (other than the presence of a sinus to the bone or implant) be possible to confirm during an initial clinic visit.

Including participants from many study centres, with diverse baseline predictors and receiving a variety of treatments, increased the heterogeneity of the data contributing to model building, but would be expected to reduce the degree of overfitting affecting any model derived from this data. The external validity of a model produced using diverse (but accurate) clinical data might be greater, as it might better reflect the true heterogeneity of clinical practice. This is particularly relevant as it was not currently possible to externally validate any prognostic model derived from this data, given constraints on sample size for external validation.(R. D. Riley et al., 2021)

5.10.1 Clinicians' prognostic reasoning and treatment decisions

One potential reason for the poor discrimination of this prognostic model could be that people who are offered surgery for orthopaedic infection are already selected based on informal risk prediction. Clinicians predict risk when deciding to offer an operation. It would not be ethical to offer surgery to someone whose treatment was obviously destined to fail. Clinicians may build up such risk prediction heuristics through personal and vicarious experience, and through the synthesis of other research findings that do not purport to represent validated prognostic models.

Only people who had surgery were included in model building in this study. However, only people whose treatment was felt likely to succeed would be offered surgery in the first place. Therefore, people at greatest risk of treatment failure were likely not represented in the study population, as they were not treated. This is a manifestation of survivorship bias, where inferences about a wider population are made from a small number of selected participants or events where a better-than-average outcome occurred.(Mangel & Samaniego, 1984)

I hypothesised that smoking, for example, may be felt by many clinicians to increase the risk of treatment failure. Therefore, as a proportion of those referred for treatment of orthopaedic infection, people who currently smoked might be less likely to proceed to surgery than people who did not currently smoke at the time of their clinic assessment. Smoking was singled out as a variable likely to get recorded, rather than the only factor influencing clinicians' assessments of their patients' surgical risk.

5.11 Smoking and the risk of orthopaedic infection recurrence: further investigation

This additional investigation aimed to consider explanations for the poor prognostic performance of the full logistic regression model. The full model included prognostic variables that may also be expected to also have a causal impact on treatment failure, including immunosuppression, proxy variables for perioperative hyperglycaemia, and smoking. The model's discrimination between those people with orthopaedic infections who had surgical treatment and experienced treatment failure by 12 months, and those who did not, was not much better than a parsimonious prediction model that did not include those variables.

The type of orthopaedic infection, aspects of the anatomy involved, and differences in treatment, are likely to account for some of the unexplained variation in prognosis experienced by people included in the prognostic modelling study. However, an additional reason for the lack of improvement in model discrimination could be that people with combinations of factors that might have a causal influence on outcome, such as people who smoke and are older, may have been systematically eliminated from the study population by not undergoing surgical treatment. A visual model of a possible explanatory interaction is presented in the following Directional Acyclic Graph: 5.26

The distribution of smoking in the general UK population also varies with age, gender and health status. Older people living in the UK are less likely to smoke, and women are less likely to smoke than men, in each age group.(Office for National Statistics, 2020)

5.11.1 Smoking and treatment pathways for people with orthopaedic infection

To test the validity of the causal pathways described in 5.26, and to investigate the hypothesis that people at greater risk of treatment failure may not have been represented in the prognostic study population because they did not have reconstructive surgery, I analysed the proportion of people referred for orthopaedic surgery who went on to have their operation, according to whether they currently smoked at the time of their specialist clinic assessment. This analysis used existing audit data from the BACH referral cohort from the Nuffield Orthopaedic Centre specialist orthopaedic infection clinic, Oxford. This audit was approved by the hospital governance board (OUH 2021 6739).(A. J. Hotchen et al., 2020)

Briefly, data relating to baseline characteristics and treatment pathways were collected prospectively for participants attending the specialist tertiary referral clinic, by two audit clinicians (Andrew Hotchen and Faiza Rage Omar). Only people who had a clinical diagnosis of orthopaedic infection at the time of clinic assessment were included. Duplicate records were removed.

In total, the treatment pathways of 186 people with a clinical diagnosis of orthopaedic infection confirmed at the time of their clinic visit, were recorded. Of those people, 137 were not recorded as currently smoking at the time of their clinic assessment, while 49 people were recorded as smoking. 75 of 137 recorded non-smokers proceeded to have an operation for orthopaedic infection (55%) compared to 24 of 49 smokers (49%) ($p=0.48$, Chi^2 test).

Though a greater proportion of non-smokers in this clinical referral cohort went on to have an operation, the absolute difference between post-referral treatment pathways for clinic smokers and non-smokers was small and may have been due to chance variation. This small difference may be compounded by additional pre-referral differences, for example in referral pathways from primary or secondary care.

An investigation of social deprivation and referral for specialist care suggested that people who smoke may have been less likely to have been referred for tertiary care for orthopaedic infection. This suspicion came from an analysis of the distribution of residential Index of Multiple Deprivation (IMD) for people who had surgery for orthopaedic infections at the Nuffield Orthopaedic Centre, a tertiary referral centre. This information was collected for participants in the PRIMIO prospective cohort, based on participants' postcode of residence listed on the clinical record at the time of enrolment.

Smoking is a behaviour that is not evenly distributed across social opportunity or deprivation. In the Health Survey for England, 2021, an inverse linear relationship was observed between residential IMD and smoking prevalence. People living in postcodes listed among the 20% most deprived areas in England were around three times as likely to smoke as those living in the 20% least deprived areas. (Office for National Statistics, 2022)

In contrast, people enrolled in the PRIMIO cohort were more likely to live in the least deprived areas in England. Participants in the PRIMIO cohort gave informed consent for baseline information gathering and follow-up, and all received surgical treatment for orthopaedic infection in one tertiary referral centre. The IMD pattern observed may have been partly been due to differences in study consent rates between people living in different social circumstances, but may also have related to differences in referral to tertiary care in the first place, and to differential treatment decisions made after referral.

5.11.2 Peri-operative smoking and the risk of treatment failure: causal inference

Separately from the question of whether smoking was able to predict prognosis after surgery, one of the questions underlying this project was whether smoking causally influenced treatment outcome. An investigation of the possible causal effect of smoking on prognosis is described below.

The aim of this secondary analysis was to quantify the possible magnitude and direction of any causal association between smoking and orthopaedic infection recurrence, and to ascertain whether there may be a dose-response relationship between the maximal tobacco intake in the three months preceding surgery, and treatment outcome.

Biological mechanisms for the effect of smoking on wound healing, and consistency with other observational data describing the relationship between smoking and surgical site infection, were described in Chapter 2. Reversibility was assumed, as pre-operative smoking cessation appears to improve surgical treatment outcome. Past smoking was not investigated, as only the effect of current smoking was of interest.

Self-reported smoking was recorded for all but two participants in the four cohorts contributing to prognostic modelling. These data were also used for this analysis. However, smoking was assumed to be influenced by participants' age and gender, as it is not evenly distributed in the general population contributing to these data.(Office for National Statistics, 2020) As randomisation for smoking status is impossible, one strategy to make full use of observational data is to create a pseudo-population where every participant has an equivalent chance of smoking peri-operatively. This can be achieved using Inverse Probability of Treatment Weighting (IPTW), as described in Chapter 4. Smoking can be described as the 'treatment' being observed in this analysis. If the factors that simultaneously influence individual smoking status and treatment outcome are known, each participant in the data can be represented in proportion to their inverse probability of smoking, creating a pseudo-population where the relationship between smoking and treatment outcome is not confounded by those factors.(Hernan & Robins, 2020; Pearl, Glymour, & Jewell, 2016)

The proportion of people who smoked peri-operatively was broadly equivalent across different orthopaedic infections and surgical treatment strategies. 136/741 people who had treatment for osteomyelitis smoked (18.4%), compared with 80/435 people treated for PJI (18.4%). 578 of 1005 people who did not smoke had local antimicrobial therapy implanted at the time of their operation (58%) compared to 114 of 206 people who smoked (55%).

Examining crude treatment failure rates among people with different orthopaedic infections, 16.7% of people who did not smoke and had surgery for PJI experienced treatment failure by 12 months, compared with 16.7% of people with PJI who smoked. 13.0% of people who had osteomyelitis and did not smoke experienced treatment failure, compared to 12.2% of people with osteomyelitis who did smoke. At face value, this would suggest no increased risk in treatment failure attributable to smoking. However, it is important to take into account the differences in both the demographic factors influencing smoking in the general population, and the possibility of differential treatment allocation for people who smoked (particularly those who were more unwell).

Age might be expected to influence wound healing and immune function sufficiently to affect the likelihood of orthopaedic infection recurrence. It is included in a prognostic score for orthopaedic infection treated with DAIR. (Wouthuyzen-Bakker et al., 2019b) Study participants in the youngest age quartile were more than twice as likely to smoke perioperatively compared to those in the oldest quartile, however. 5.29 If both factors have a causal effect on treatment failure, their relative distribution might be expected to reduce each other's apparent associations with treatment outcome.

For 1154 of 1213 participants, age, gender and treatment outcome at 12 months were known. Among these, 600 participants were treated at the Nuffield Orthopaedic Centre, Oxford. A logistic regression model for self-reported perioperative smoking against treatment failure, adjusted for age, gender and ASA score, was compared with Inverse Probability Weighted (but otherwise unadjusted) logistic regression models for smoking against treatment failure at 12 months. Age and gender were included in the IPTW model as predictors of perioperative smoking status. The populations compared were 1154 complete cases and 600 participants treated only at one tertiary referral centre in the UK. Among the complete case population, there were 176 treatment failures. Among people treated only at the tertiary referral centre, there were 102 treatment failures.

The plain logistic regression model estimated the odds ratio for treatment failure among participants who reported smoking peri-operatively to be 1.11 (95% confidence intervals 0.59 to 2.01). IPTW models estimated odds ratio for treatment failure to be 0.95 overall (95% CI 0.58 to 1.51) and 1.2 for people treated in tertiary care (95% CI 0.62 to 2.33).

These results would be consistent with no effect or an effect too small to detect. Other explanations could include that smoking was not identified by self-report in all participants who smoked, leading to an underestimate of the true effect. It is possible that other unmeasured confounding factors had opposing associations with smoking and treatment outcome in this group (for example, general ill health). It was not possible to include a general marker of ill health in IPTW without violating model assumptions, as ASA score includes current smoking, and Charlson score was not ascertainable for the majority of participants. Even assuming a true OR of 1.2 for treatment failure from current smoking, with measured recurrence rates in the study population, between 18 and 29 additional treatment failures per 1000 people would be expected to result from peri-operative smoking.

It is important to note, however, that these findings do not rule out a detrimental effect from cumulative lifetime smoking, for example through the increased risk of peripheral vascular disease. An unadjusted logistic regression model for the risk of treatment failure at 12 months for 1134 complete cases showed an OR of 2.7 for treatment failure among participants with diagnosed vascular disease (95% CI from 1.53 to 4.53). If this association were to be assumed to be causal, this would represent between 130 and 203 additional treatment failures per 1000 people treated, from a baseline risk of 10-15%.

A possible dose-response relationship between treatment failure and peri-operative smoking was examined. As already described, recording of weekly tobacco intake varied between study sites. I^2 for peri-operative smoking ascertainment between study sites was 50.8% (moderate heterogeneity). Pre-operative maximum tobacco intake was only recorded at all in a small subset of UK study sites.

There was no conclusive evidence of a dose-response relationship between peri-operative smoking and treatment failure, with the caveat that tobacco intake was self-reported, and available for only a small fraction of participants.

5.11.3 Peri-operative smoking and quality of life

As specified previously, one aspect of the study aimed to investigate the relationships between potentially modifiable behavioural factors, such as smoking in the peri-operative period, and PROMS: change in EQ-5D quality of life score. A linear regression model for 611 participants with data available for EQ-5D quality of life increment over 12 months found no relationship between the magnitude of the increment and peri-operative smoking ($p > 0.1$). Mean EQ-5D quality of life increment was +0.17 over 12 months for people who reported smoking peri-operatively (95% confidence interval -0.55 to +0.89), compared to +0.23 for people who did not report smoking peri-operatively (95% confidence interval -0.48 to +0.94).

5.11.4 Conclusions: what effect does smoking have on treatment outcome?

Even though a causal effect from peri-operative smoking on treatment failure for surgically-treated orthopaedic infection is biologically plausible and supported by some interventional studies,(Thomsen et al., 2010) this investigation was not able to conclusively demonstrate a clinically significant causal effect.

This study had major limitations, namely the incomplete recording of weekly tobacco intake, and that self-reported information was the only variable available. It is impossible to specify the size of a causal effect from smoking on surgical outcome accurately, without resorting to measures such as salivary cotinine testing and carbon monoxide quantification in addition to reported smoking status.

In observational longitudinal studies, many people stop smoking temporarily in the 1-2 days before a major operation.(Nolan et al., 2016) People in this situation might self-define as peri-operative non-smokers, despite evidence to date suggesting 2-4 weeks before surgery being the optimum smoke-free period for reducing post-operative complications.

The Bradford Hill criteria (Hill, 1965) for inferring causal effects from observational data include being able to observe a temporally- and biologically-plausible, large association, consistently across different studies. Experimental evidence must support the causal nature of the association, and biologically similar causal pathways should be demonstrated. A dose-response relationship should be observed, and removing the cause should remove the effect. In practice, not all these findings may apply to a clinically relevant causal pathway. This study investigated whether there was a clinically significant causal effect from peri-operative smoking that was reversible (i.e. removed by quitting smoking peri-operatively) and dose-dependent (greater for people who smoked a greater number of cigarettes peri-operatively). Neither of these findings were demonstrated unequivocally.

Smoking is a behaviour that is closely tied with socioeconomic status. (Office for National Statistics, 2022; Thompson, Pearce, & Bar, 2007) It was not possible to account for differing levels of social deprivation among most participants in this study, and to separate the effect of peri-operative smoking from that of social deprivation. Social deprivation may have confounding effects on surgical treatment outcome, for example through chronic stress, transport access, healthcare access (such as support from GP practice nurses or district nurses for wound care), difficulty taking time off work for convalescence, and micronutrient deficiency. A study evaluating surgical outcomes in people with foot osteomyelitis found that participants experiencing homelessness suffered from a greater incidence of treatment failure.(Barton et al., 2020) It is salient that the participants in the PRIMIO prospective cohort study over-represented those who lived in postcodes with fewer markers of socio-economic deprivation.(DfCLG, 2015)

Though it was not possible to identify a large causal effect of peri-operative smoking cessation among participants in the four observational studies contributing to this analysis, peripheral vascular disease (which is often a consequence of long-term smoking) was strongly associated with with treatment failure at 12 months. The mean age of participants in this study was 60 years, and many may have smoked in the past but reported no peri-operative smoking. Past smoking was not recorded in three of the four contributing datasets, so investigating an association with past smoking in this study was not possible.

Age may have contributed to selection bias in the cohort overall, reducing the observed effect of peri-operative smoking. Differential effects according to cohort age have been observed between smoking and dementia, due to the selection of participants by existing smoking-related morbidity.(Hernan, Alonso, & Logroscino, 2008) This selection bias is not possible to correct through IPTW. It is possible that the cumulative effects of long-term past smoking among people who did not report smoking peri-operatively, outweighted short-term adverse effects from smoking among participants with a shorter smoking history. As shown in Chapter 3, previous observational studies including participants with surgically treated orthopaedic infection showed mixed associations between peri-operative smoking and long-term treatment failure, supporting the findings of this study.

On the basis of these findings, it would not be ethical to withhold surgical treatment for orthopaedic infection from people who smoke. There was no difference observed in the improvement in quality of life in the 12 months after surgery between participants who did and did not smoke in this study, suggesting that people who smoked peri-operatively benefited just as much as those who did not report doing so.

Peri-operative smoking cessation interventions may still be worthwhile, as they reduce early operative complications and long-term risks other than treatment failure.(Thomsen, Villebro, & Moller, 2014; Nasell, Adami, Samnegard, Tonnesen, & Ponzer, 2010) However, other peri-operative strategies with greater marginal gains may have to take priority, if the aim is to reduce surgical infection recurrence and long-term antimicrobial prescribing arising from orthopaedic infection treatment failure. More broadly, interventions that avoid the harms of long-term smoking, such as peripheral vascular disease, may benefit people who may need to undergo orthopaedic surgery in future. The optimum time to stop smoking peri-operatively may be as early in life as possible.

5.12 Conclusions and limitations

This chapter investigated three questions. The first question related to how useful modifiable behavioural factors might be for prognosis, for people about to have surgery for orthopaedic infections. Behaviours of interest included smoking, alcohol intake, blood sugar control and eating in the peri-operative period. These behaviours affected factors that could be measured peri-operatively, including through biometric measures, blood tests or simple clinical scoring systems such as the MUST score.(BAPEN, 2016)

Some of these measures were only available for a small proportion of participants. For example, measures of glycaemic control, including HbA1C and peri-operative blood glucose, were only recorded for people for whom diabetes mellitus had been diagnosed or was suspected, and in people who needed high-dependency care after surgery. This limited the usefulness of peri-operative glycaemic control measures for prognosis in the wider population of adults having surgery for orthopaedic infections. Similarly, MUST scores were easy to record on first clinical contact, but only 3% of participants for whom a score was available had a risk of malnutrition identified on screening. The study population was not large enough to investigate the prognostic usefulness of measures positive for a small fraction of participants.

Other measures, such as alcohol use and smoking, suffered from challenges in ascertainment. Though alcohol use was recorded diligently in two of the prospective studies, making sense of the recorded values proved difficult. The agreement in interpreted weekly alcohol intake, between two clinicians looking at the same recorded values, was poor, particularly at higher levels of intake (that might be expected to have more leverage in a logistic regression model). Peri-operative smoking status was reported by participants and not verified with biochemical markers, so likely underestimated the overall fraction of participants who smoked in the weeks before and after surgery. Using these factors for prognostic modelling would likely contribute systematic errors to predicted risk.

All prognostic variables included in modelling were specified in advance, and the number of variables was appropriate to the sample size. Many prognostic variables were systematically missing in at least one of the datasets contributing to the study. Logistic regression modelling for treatment failure at 12 months confirmed that specific health conditions (immunosuppressive conditions, diabetes mellitus, peri-operative smoking) and biometric measures (BMI) added very little to the discriminative accuracy of a prognostic model for this study population. Some variables that were complete across all datasets, and had a strong association with outcome, were not included in modelling as they were not included in *a priori* list (for example, diagnosed peripheral vascular disease).

A parsimonious prediction model including only age, gender, ASA score and the number of previous operations, performed nearly as well as a better specified model with more predictive variables. This parsimonious model shared factors in common with the Host status section of the BACH and JS-BACH classification systems for orthopaedic infection.(A. J. Hotchen et al., 2019; A. Hotchen et al., 2021) This model could be used for a more reproducible way to stratify people with orthopaedic infections according to host status. Overall, however, the discriminative performance of the prediction model was limited. A points scoring system derived from this logistic regression model performed barely better than chance in internal validation. The risk of treatment failure predicted by the model was not associated with any difference in the increment in quality of life over 12 months.

Finally, an additional investigation was carried out into the possible causal association between peri-operative smoking and treatment failure. The causal factor of interest here, smoking in the immediate peri-operative period, relied on self-report from people included in the study data at the time of surgery. Some people who described themselves as not smoking peri-operatively may have smoked within two weeks of their operation. Analysis using IPTW found no evidence of a strong causal association between self-reported peri-operative smoking and treatment failure. An association may have been hidden by participant under-reporting and other confounding processes that could not be eliminated in analysis. Nevertheless, smoking is known from prior published studies to increase the risk of early post-operative complications, including cardiorespiratory illness and surgical site infections. Peri-operative smoking cessation and other aspects of health optimisation, or 'prehabilitation', in preparation for surgery, will be described in the next chapter.

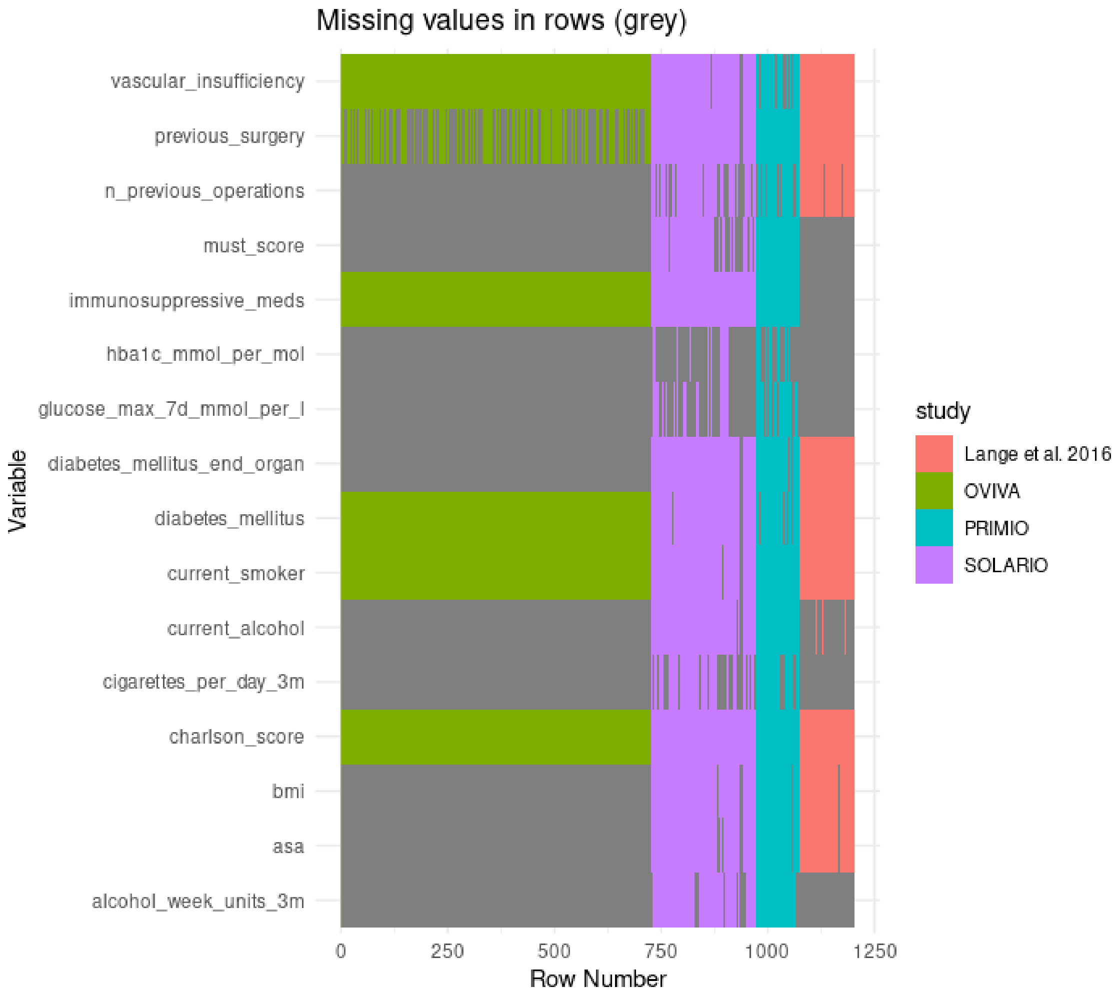

Figure 5.1: Baseline variable measurement and completeness in studies contributing to model development. Grey denotes missing data values, while colours show data values that were available at the time of analysis.

Characteristic	Lange et al. 2016, N = 130[1]	OVIVA, N = 727[1]	PRIMIO, N = 104[1]	SOLARIO, N = 252[1]
Gender				
Female	64 (49%)	251 (35%)	41 (39%)	82 (33%)
Male	66 (51%)	476 (65%)	63 (61%)	170 (67%)
Age at operation (years)	72 (64, 79)	59 (47, 69)	58 (48, 67)	58 (45, 67)
Unknown	1	0	0	0
Affected bone				
Foot	0 (0%)	124 (17%)	15 (14%)	44 (17%)
Hip	130 (100%)	138 (19%)	22 (21%)	25 (9.9%)
Knee	0 (0%)	147 (20%)	36 (35%)	25 (9.9%)
Lower limb	0 (0%)	197 (27%)	7 (6.7%)	36 (14%)
Other	0 (0%)	18 (2.5%)	0 (0%)	1 (0.4%)
Spine or pelvis	0 (0%)	24 (3.3%)	1 (1.0%)	4 (1.6%)
Tibia	0 (0%)	0 (0%)	15 (14%)	76 (30%)
Upper limb	0 (0%)	79 (11%)	8 (7.7%)	41 (16%)

[1] n (%); Median (IQR)

Figure 5.2: Baseline characteristics for participants in modelling study

Characteristic	Lange et al. 2016, N = 130[1]	OVIVA, N = 727[1]	PRIMIO, N = 104[1]	SOLARIO, N = 252[1]
Current smoking	33 (25%)	107 (15%)	20 (19%)	46 (18%)
Unknown	0	0	0	2
Peripheral vascular disease	6 (4.6%)	48 (6.6%)	3 (3.5%)	17 (7.0%)
Unknown	0	0	18	10
Diabetes mellitus	11 (8.5%)	133 (18%)	27 (27%)	54 (22%)
Unknown	0	0	5	7
Immunosuppression	0 (NA%)	27 (3.7%)	10 (9.6%)	13 (5.2%)
Unknown	130	0	0	0
BMI	25 (22, 29)	NA (NA, NA)	30 (25, 35)	28 (24, 32)
Unknown	5	727	1	3

[1] n (%); Median (IQR)

Figure 5.3: Medical comorbidities affecting participants in modelling study

Characteristic	**Lange et al. 2016**, N = 130[1]	**OVIVA**, N = 727[1]	**PRIMIO**, N = 104[1]	**SOLARIO**, N = 252[1]
Operation				
Joint debridement	0 (0%)	0 (0%)	21 (20%)	12 (4.8%)
Osteomyelitis debridement	0 (0%)	502 (69%)	41 (39%)	175 (69%)
Osteomyelitis debridement and internal fixation	0 (0%)	0 (0%)	2 (1.9%)	23 (9.1%)
Other	0 (0%)	0 (0%)	1 (1.0%)	1 (0.4%)
PJI first stage revision	11 (8.5%)	90 (12%)	18 (17%)	41 (16%)
PJI single stage revision	119 (92%)	135 (19%)	21 (20%)	0 (0%)
Local antimicrobials implanted	53 (41%)	318 (44%)	71 (68%)	252 (100%)

[1] n (%)

Figure 5.4: Characteristics of surgical treatment for participants in modelling study

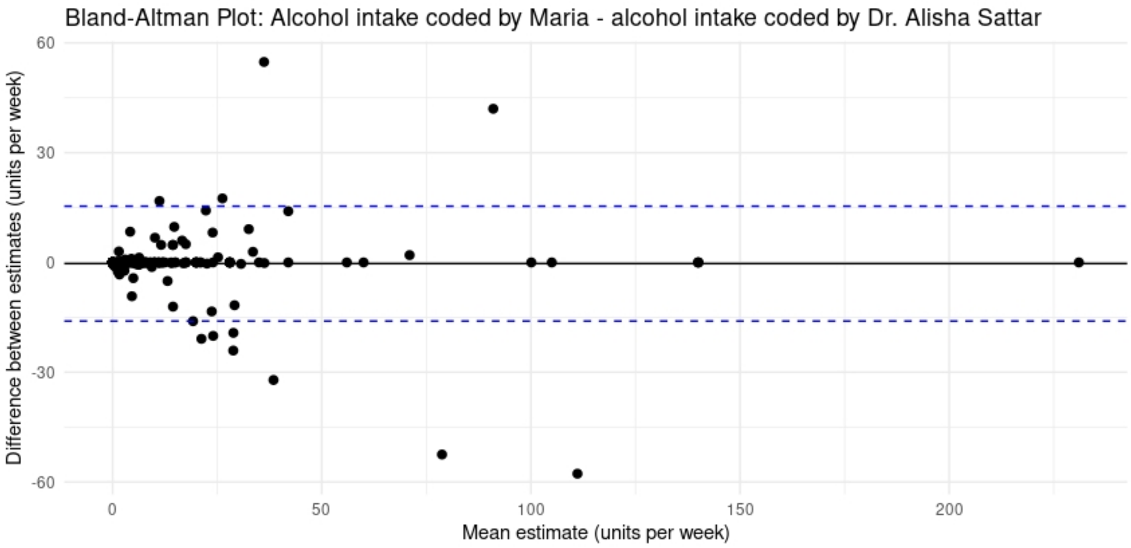

Figure 5.5: Bland-Altman plot showing disagreement between average alcohol intake (UK units per week) between two clinicians interpreting recored results from a research database. Y axis values represent errors in alcohol intake estimation (UK units per week)

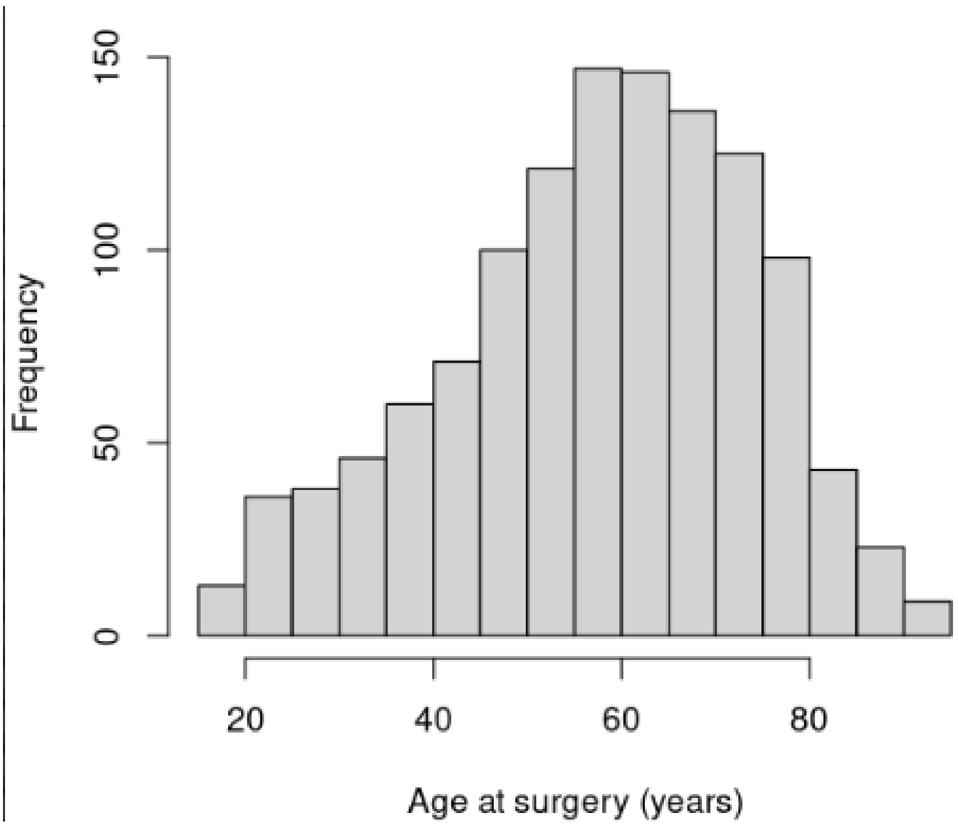

Figure 5.6: Histogram of participant age for participants in four studies contributing to prognostic modelling.

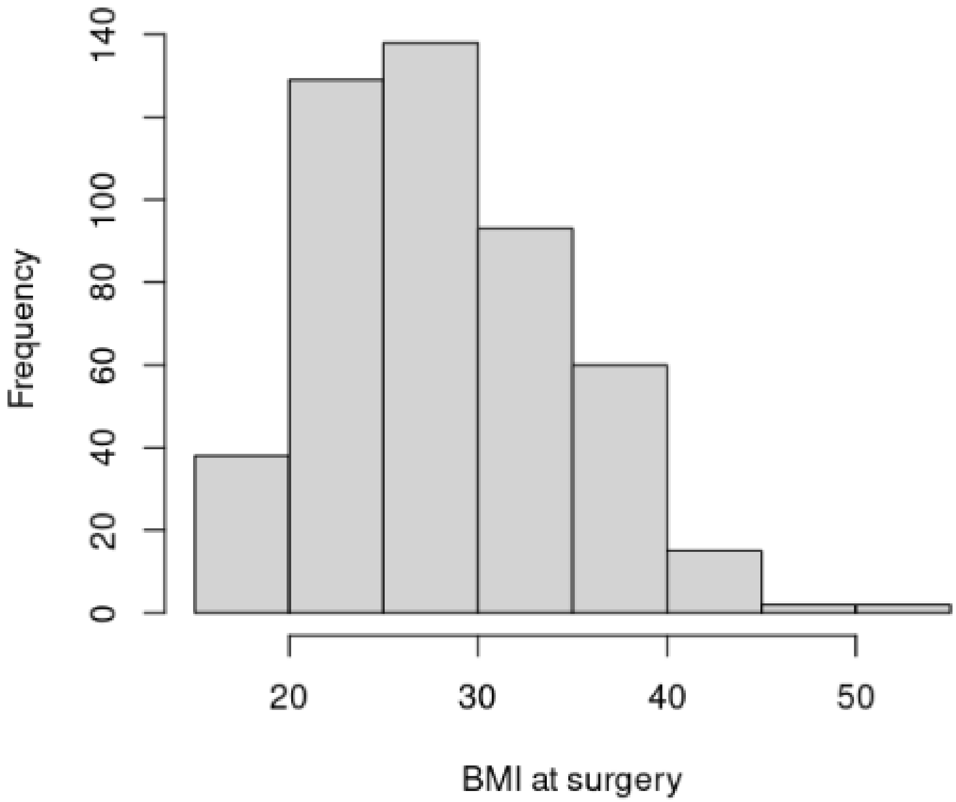

Figure 5.7: Histogram of participant BMI (kg/m^2) for participants in four studies contributing to prognostic modelling.

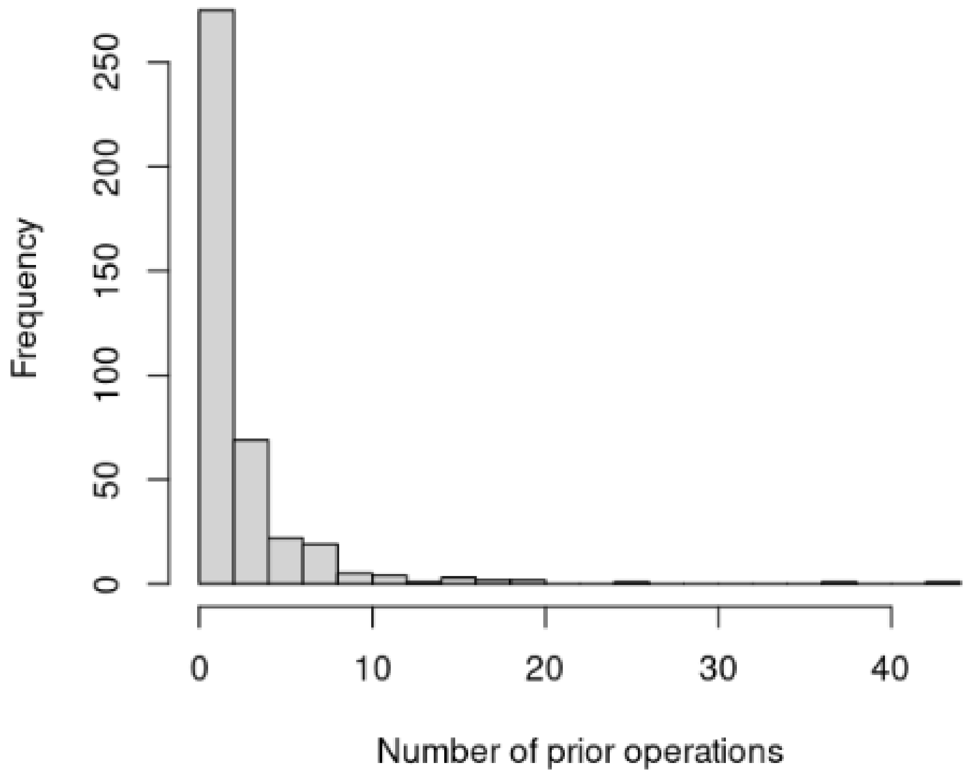

Figure 5.8: Number of previous operations at the anatomical site of orthopaedic infection, including those not performed to treat orthopaedic infection, that participants had undergone prior to their index surgery.

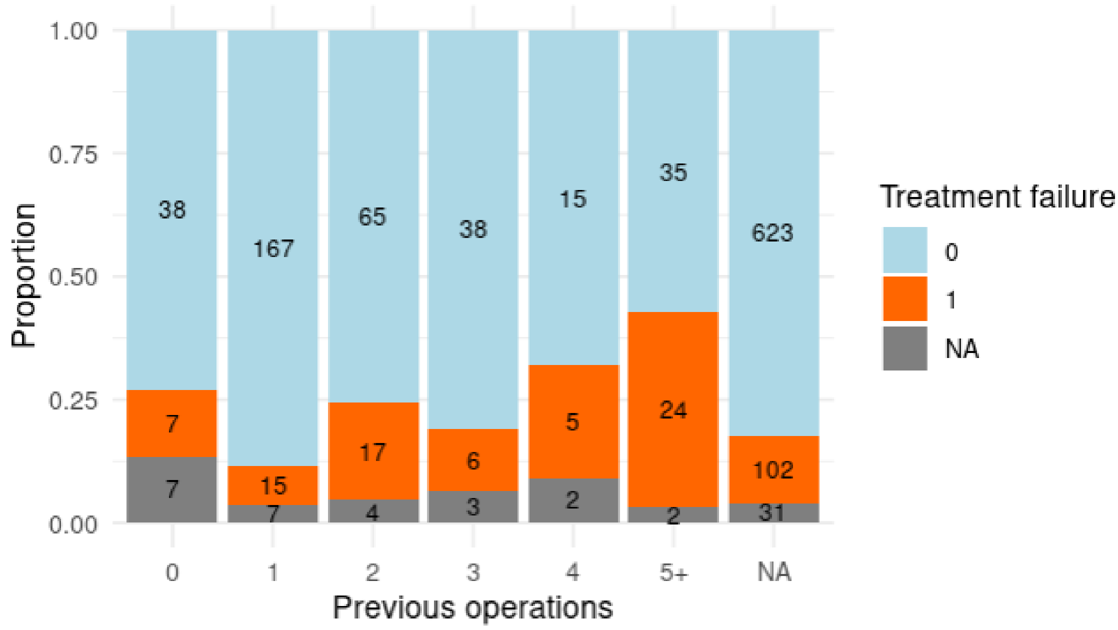

Figure 5.9: Association between categorised number of prior operations at the same anatomic site, and treatment outcome 12 months after index surgery.

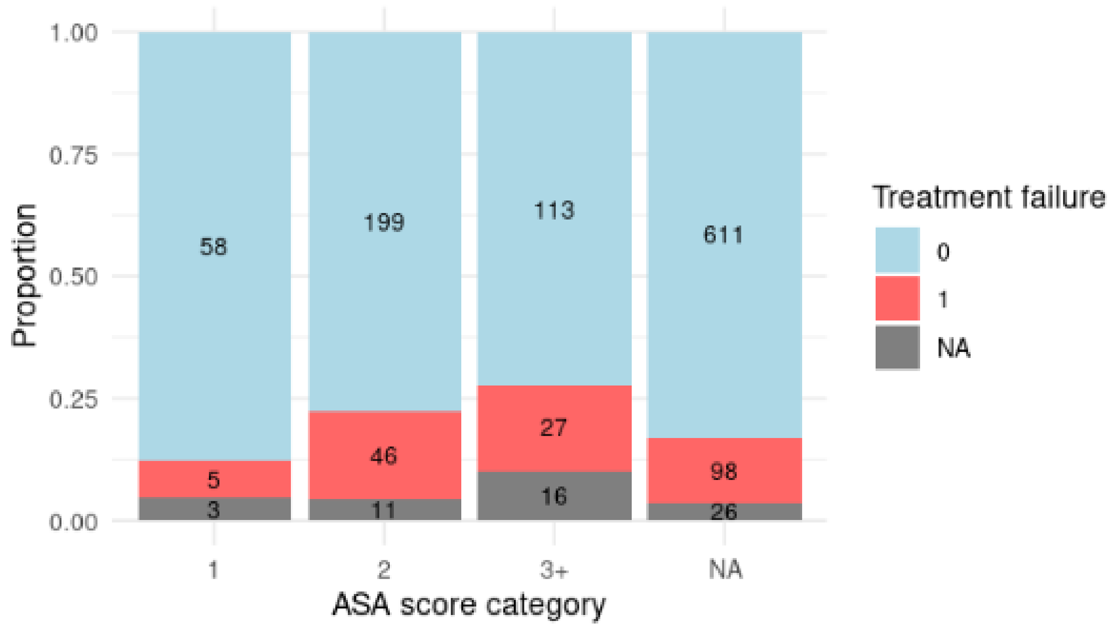

Figure 5.10: Association between categorised ASA score and treatment outcome 12 months after index surgery.

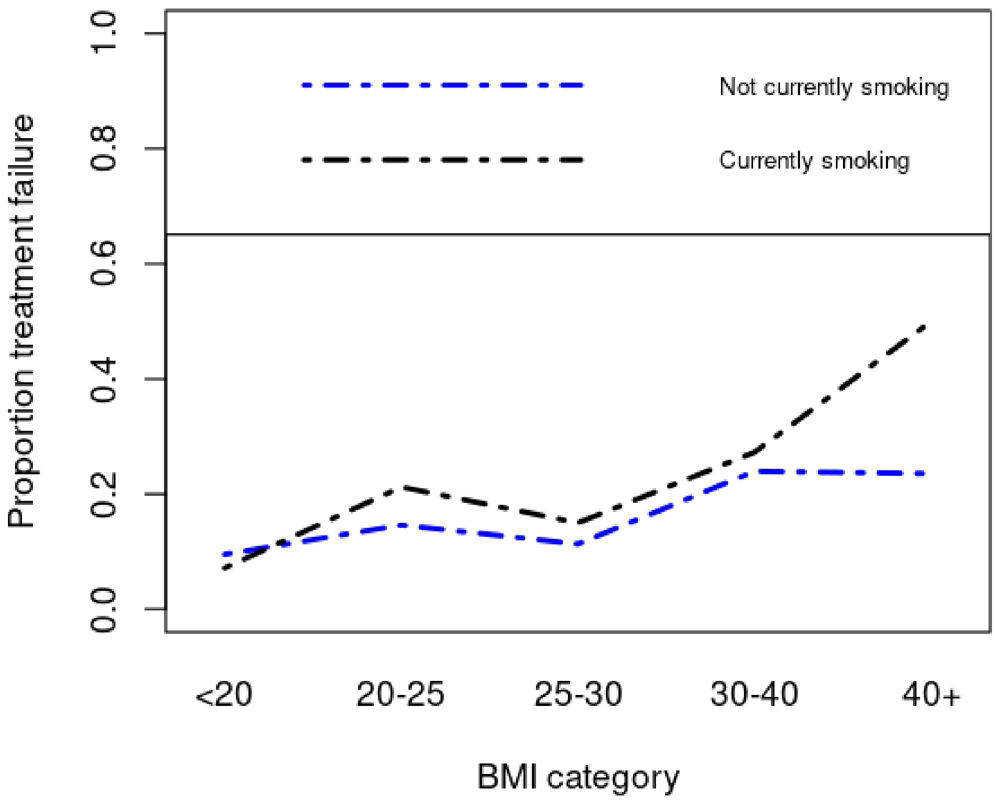

Figure 5.11: Interaction plot for BMI and current peri-operative smoking for treatment outcome at 12 months. Among those with BMI>40, two participants smoked and nineteen did not.

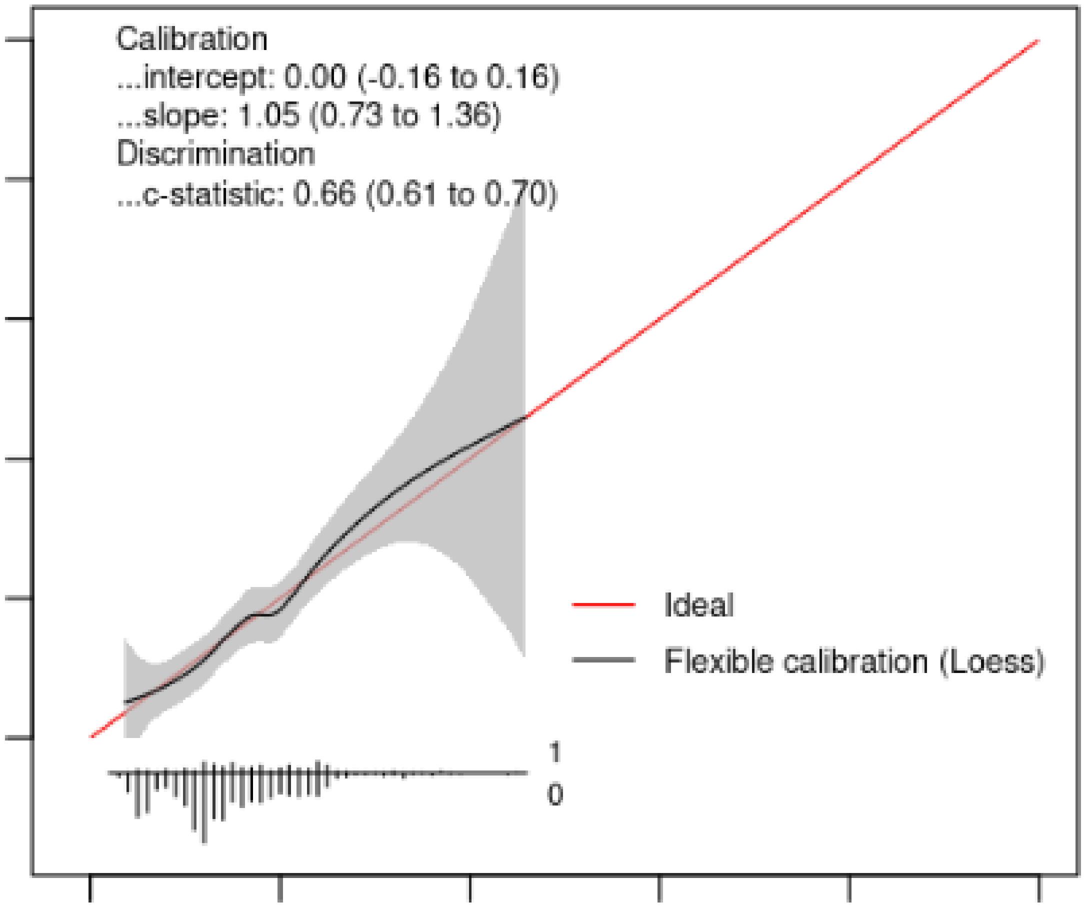

Figure 5.12: Plot showing calibration parameters for pooled full logistic regression model for treatment failure at 12 months.

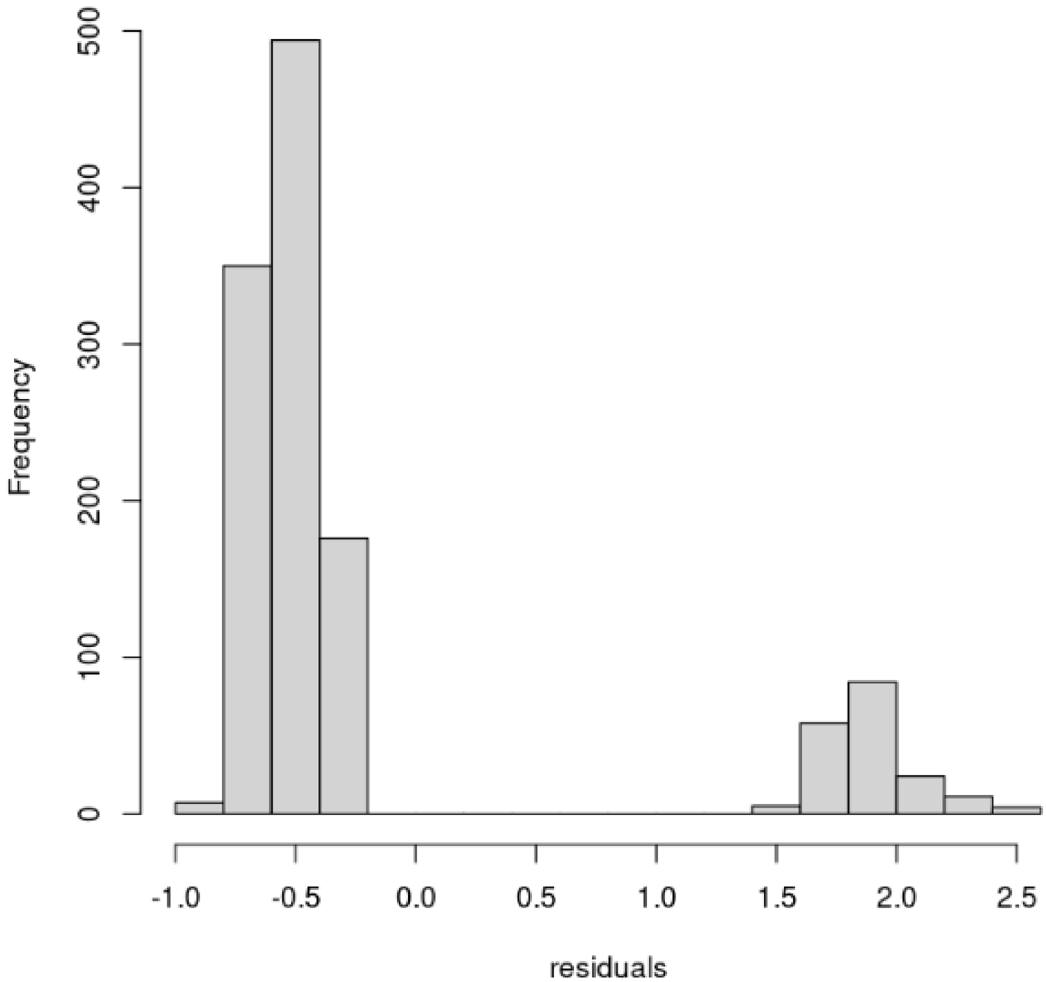

Figure 5.13: Histogram of residuals from parsimonious logistic regression model.

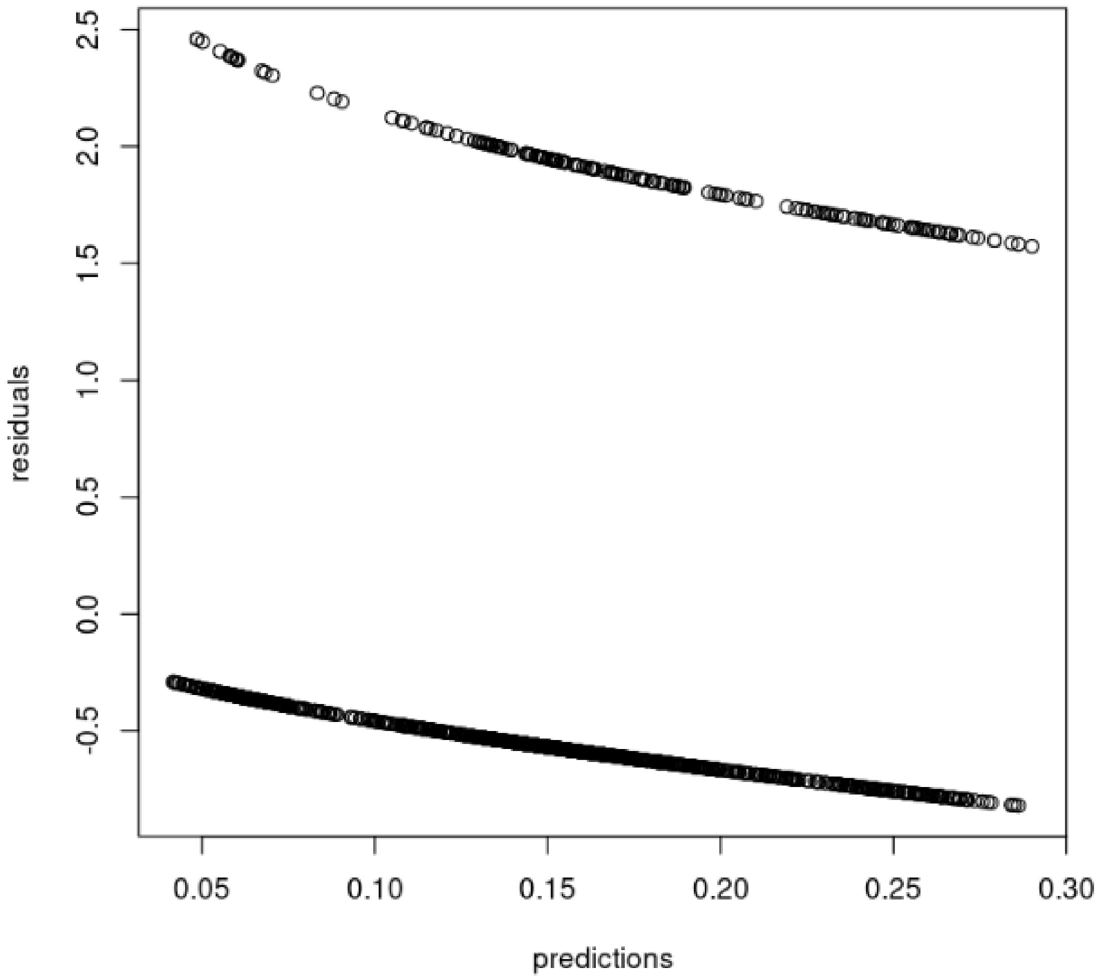

Figure 5.14: Plot of residuals against predicted logit(p) from parsimonious logistic regression model.

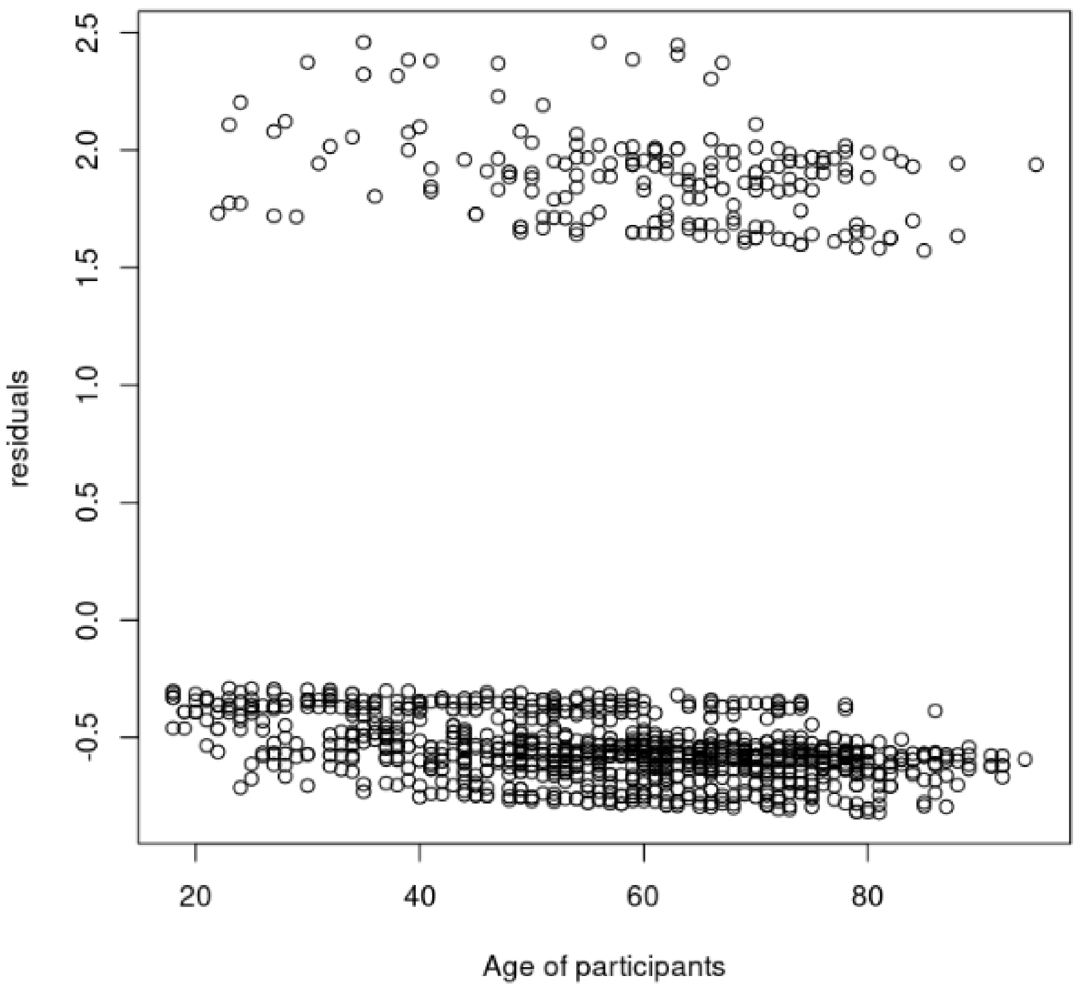

Figure 5.15: Plot of residuals against age from parsimonious logistic regression model.

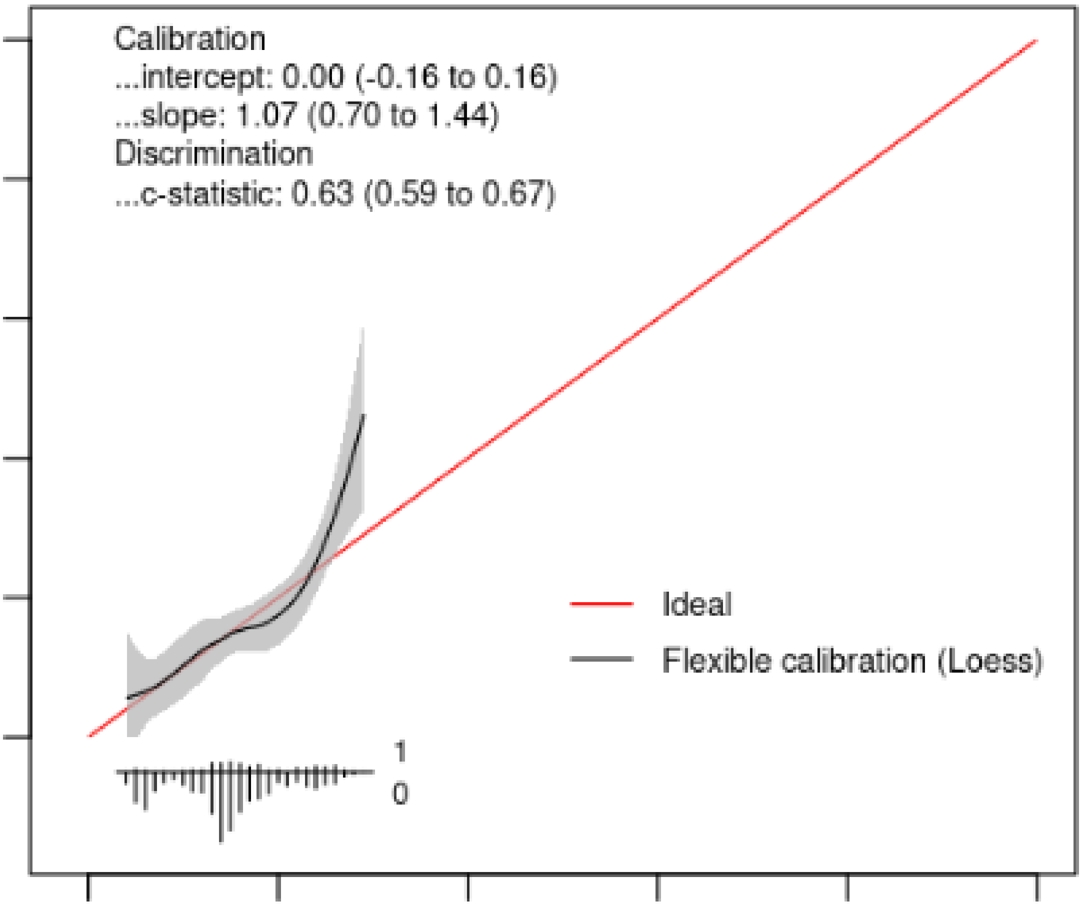

Figure 5.16: Plot showing calibration parameters for pooled parsimonious logistic regression model for treatment failure at 12 months.

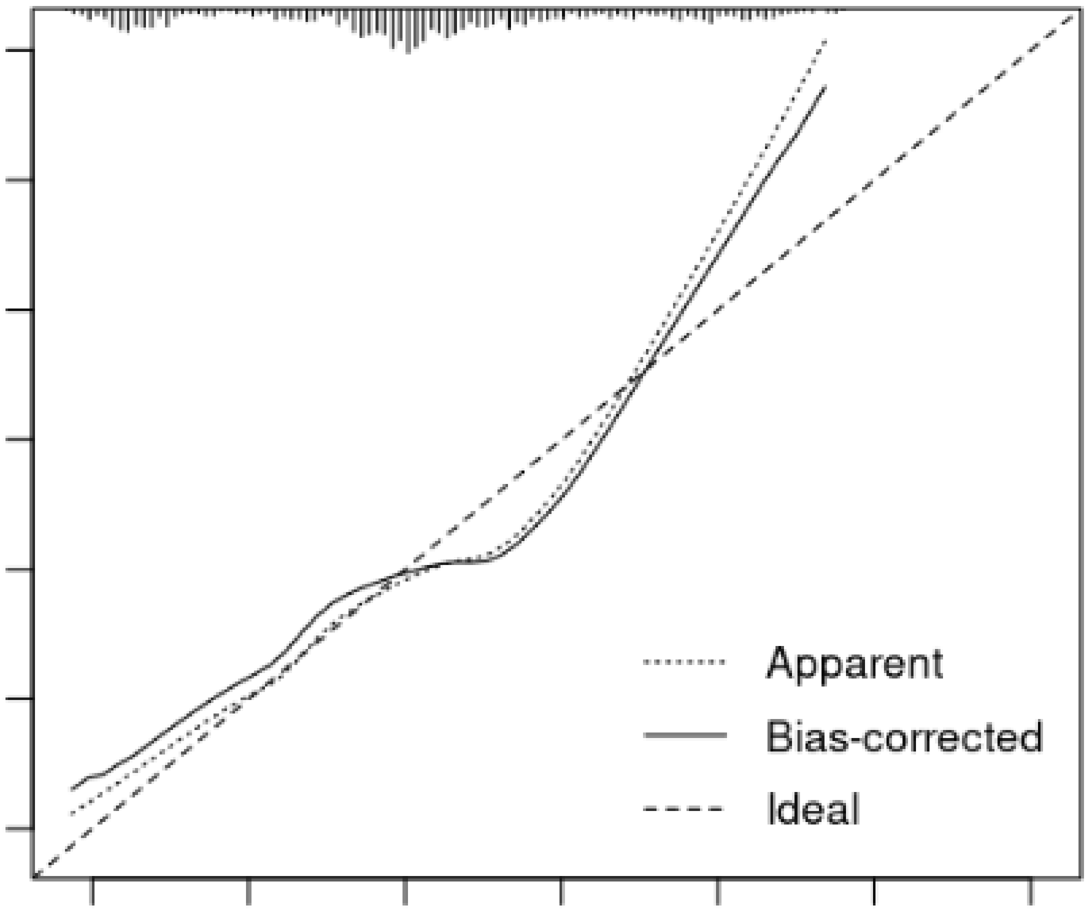

Figure 5.17: Plot showing parsimonious model calibration and optimism-corrected parsimonious model calibration using boration in 200 bootstrap resamples of the original study data.

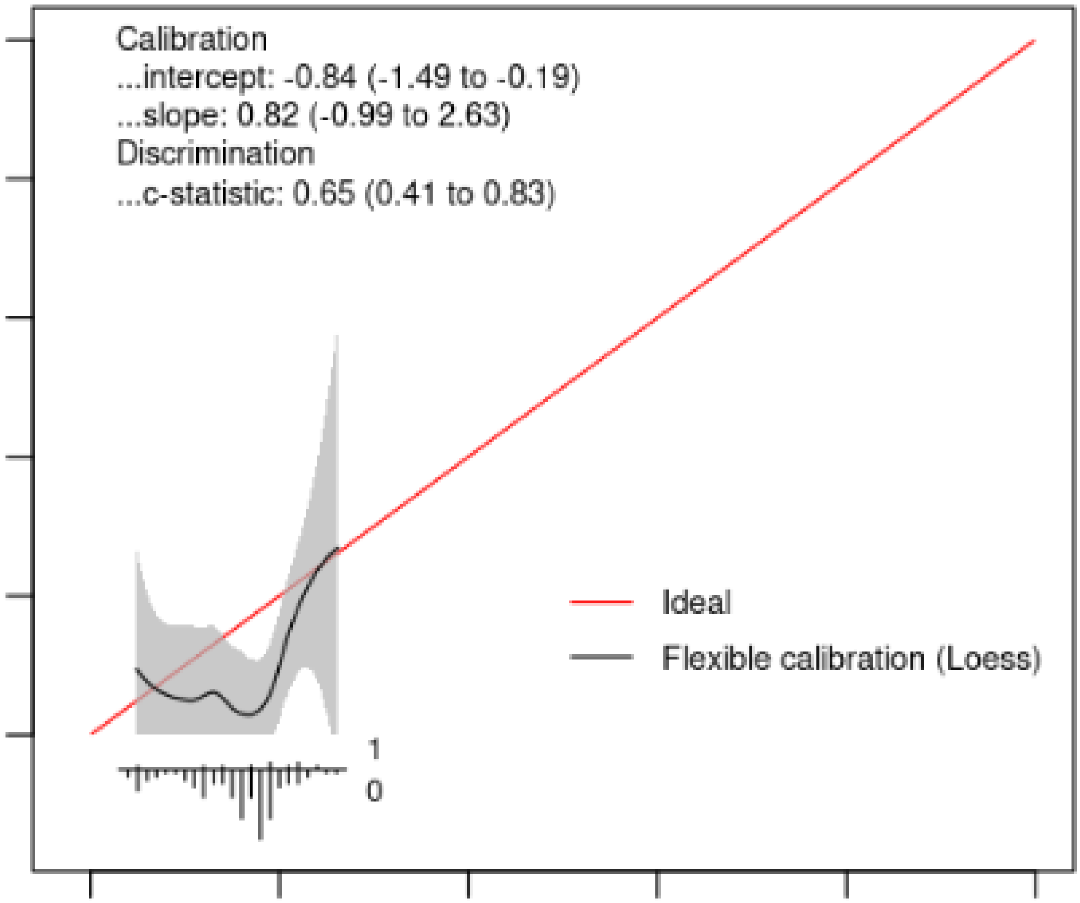

Figure 5.18: Calibration and discrimination of the parsimonious model, elaborated with data from PRIMIO, SOLARIO and OVIVA, and tested against Lange et al. 2016.

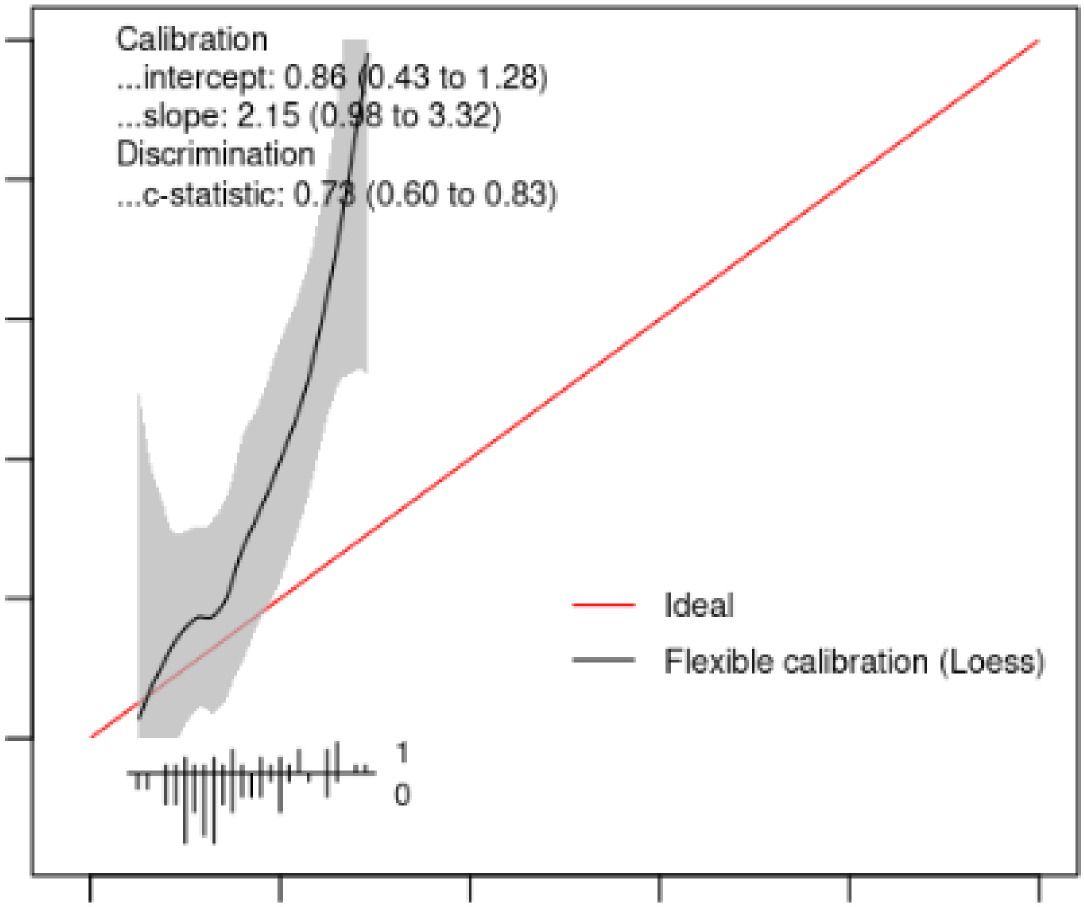

Figure 5.19: Calibration and discrimination of the parsimonious model, elaborated with data from Lange et al. 2016, SOLARIO and OVIVA, and tested against PRIMIO et al. 2016.

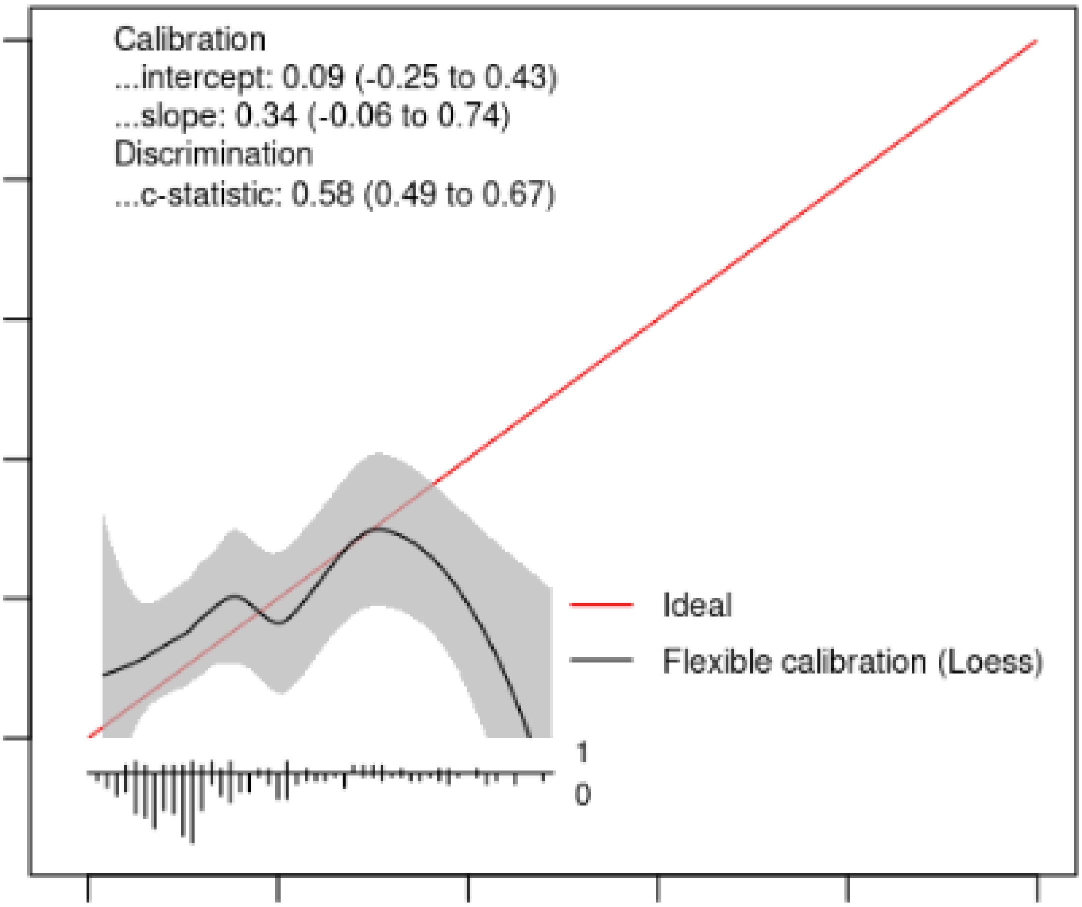

Figure 5.20: Calibration and discrimination of the parsimonious model, elaborated with data from PRIMIO, Lange 2016 and OVIVA, and tested against SOLARIO.

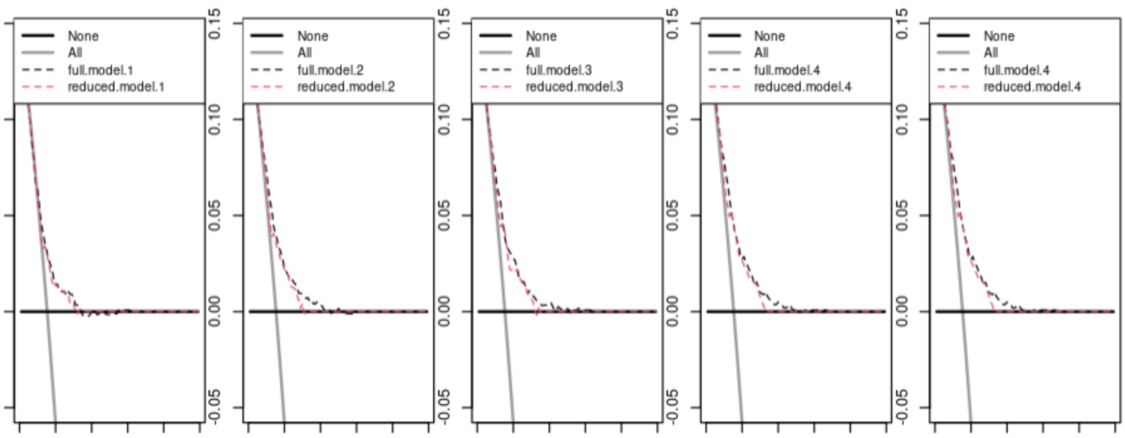

Figure 5.21: Decision analytic curves for the full (red) and parsimonious (black) models, presented in five representative imputed datasets obtained using MICE.

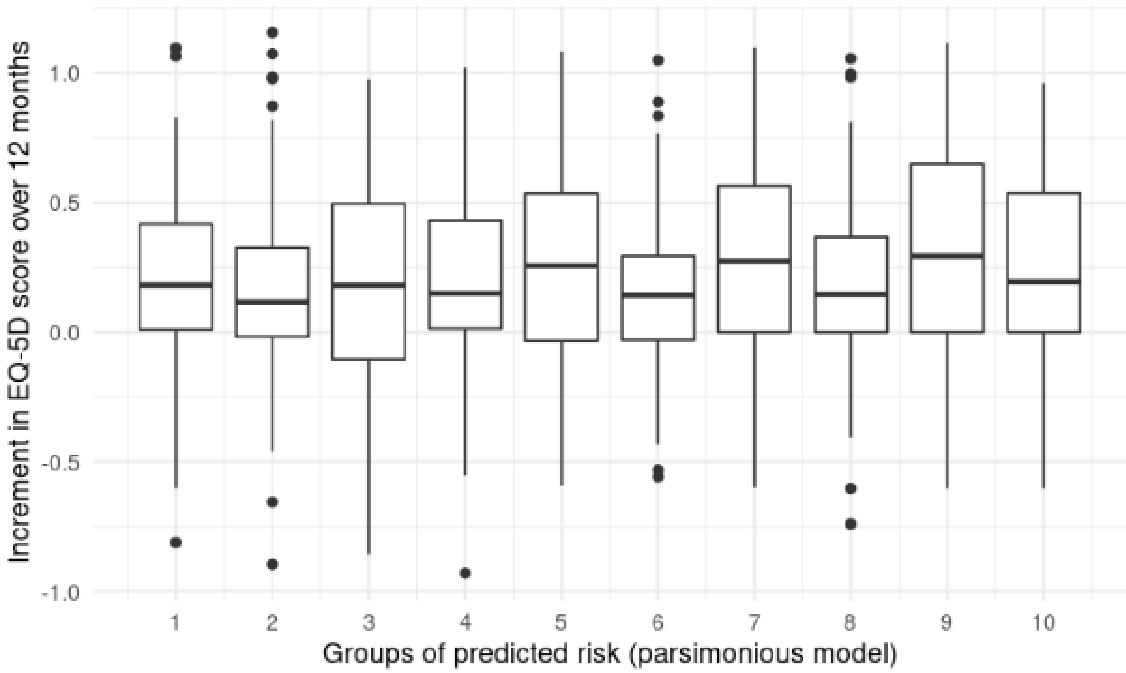

Figure 5.22: 12 month increment in Quality of Life score after surgery, compared across ten categories of pooled estimates for the risk of treatment failure obtained from the parsimonious model.

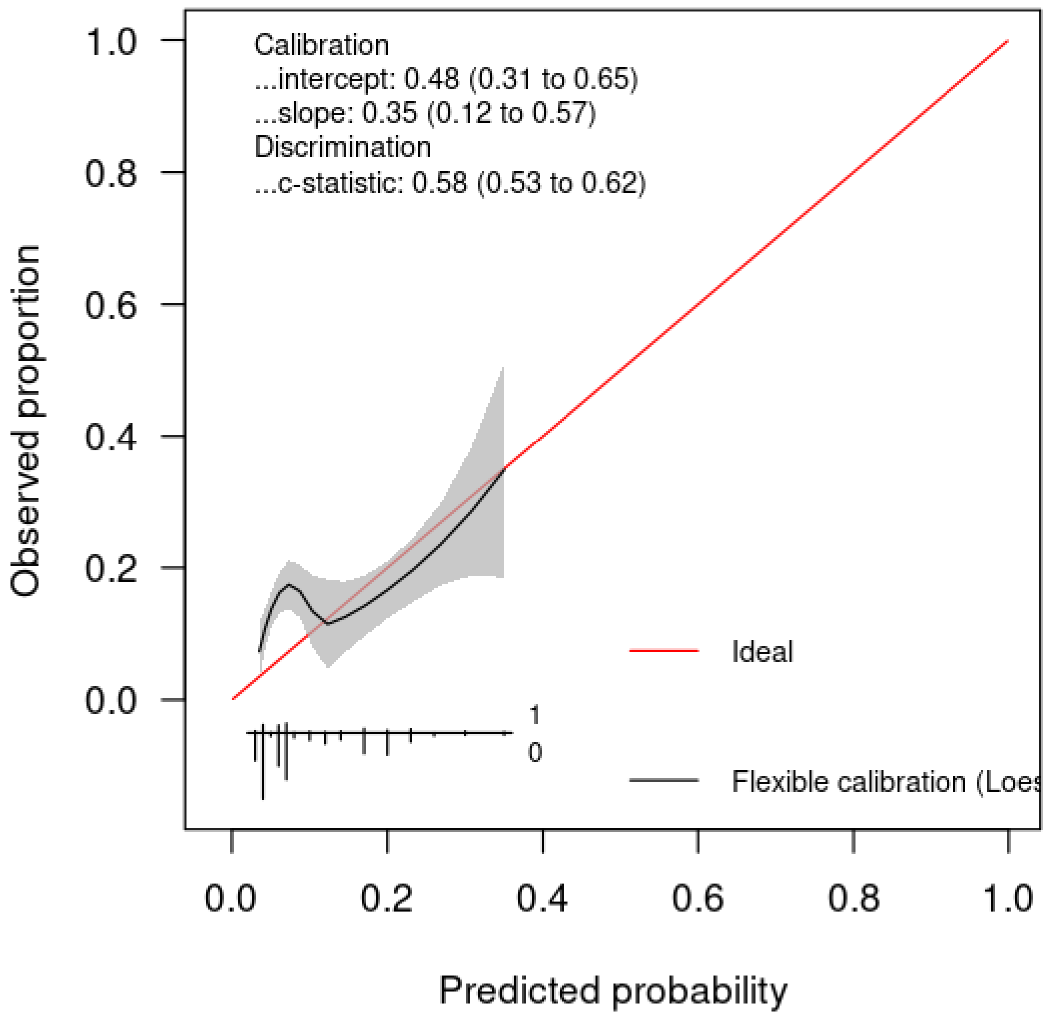

Figure 5.23: Example calibration curve for the points score prognostic model using one of ten multiply imputed datasets.

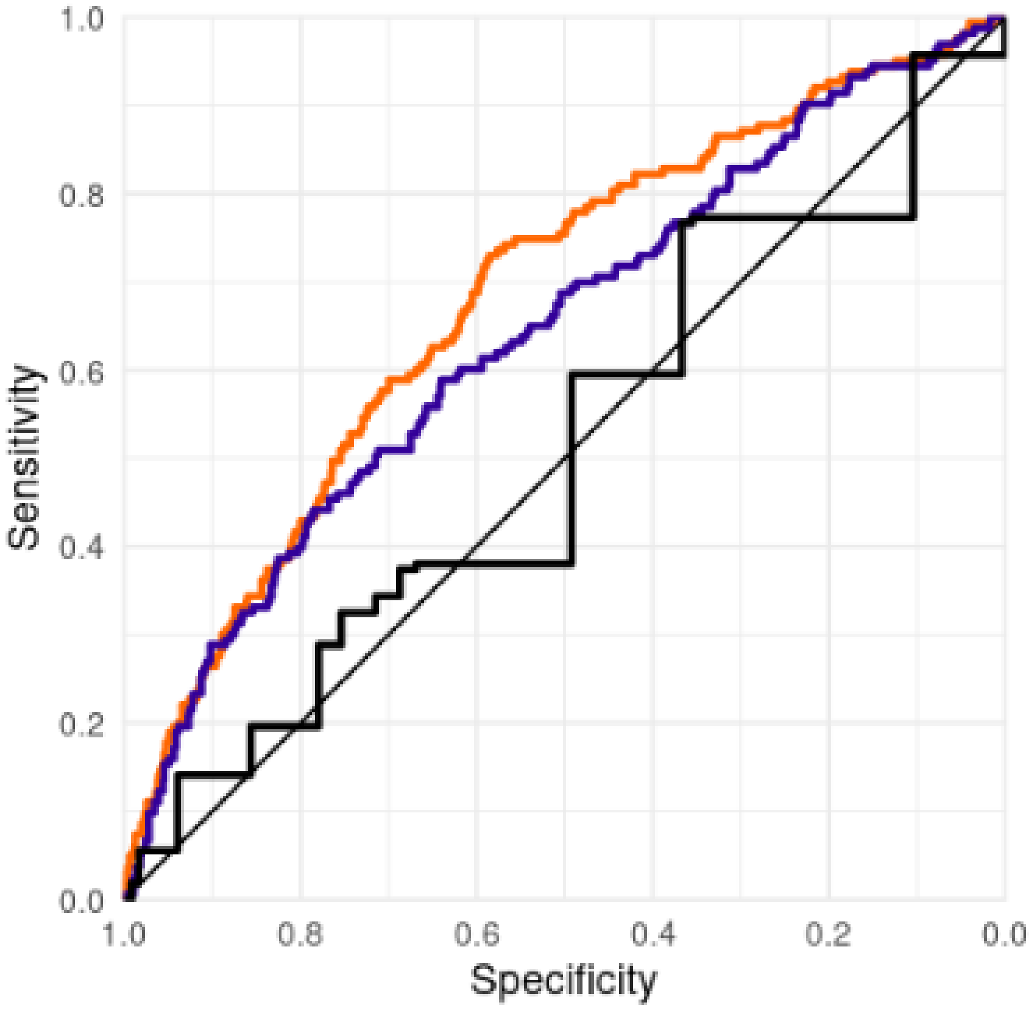

Figure 5.24: Example Receiver Operated Characteristic discrimination plot including the full logistic regression model (orange), the parsimonious logistic regression model (indigo), and the points score developed from the parsimonious model (black).

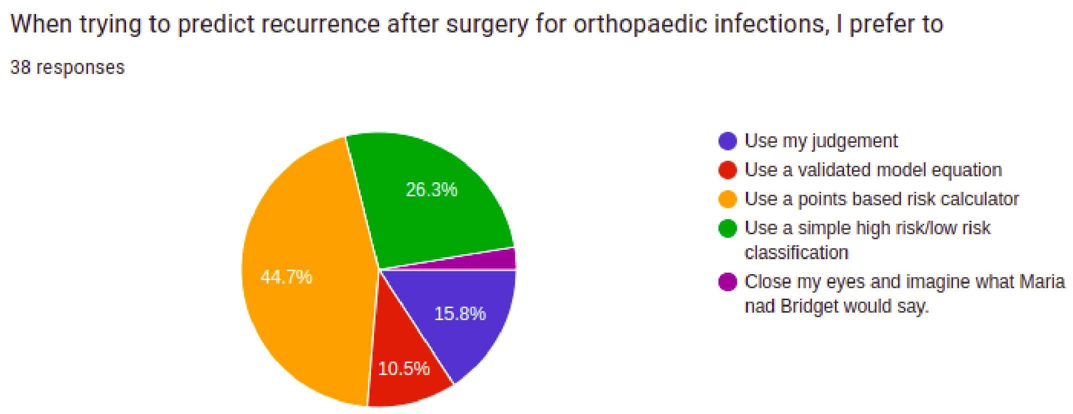

Figure 5.25: Conference attendee preferences for orthopaedic prognostic models. Final segment represents an ’other’ response; the respondent comment is included verbatim. ’Bridget’ likely refers to Dr. Bridget Atkins.

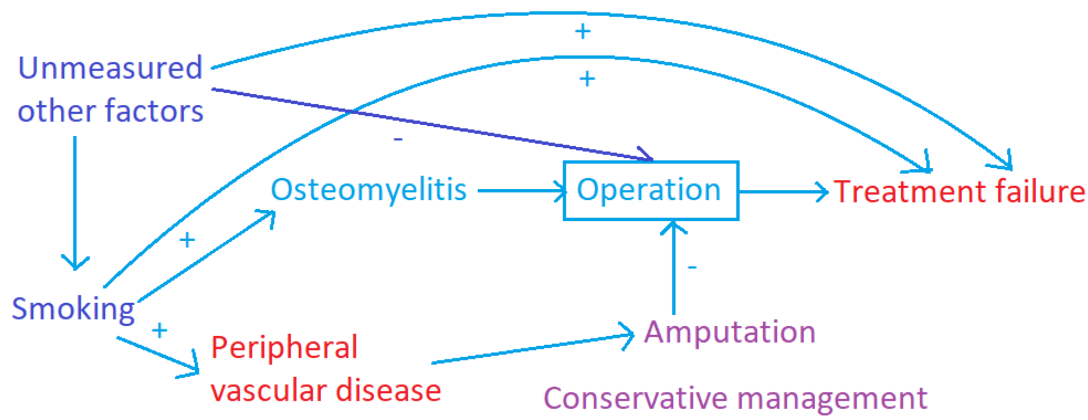

Figure 5.26: Directional Acyclic Graph showing a hypothetical backdoor path through which some, particularly older, people who smoke at the time of their clinic visit might not receive reconstructive surgical treatment for orthopaedic infection. Smoking increases the risk of peripheral vascular disease, which may render surgical reconstruction too challenging or may result in delays to surgery while revascularisation takes place. The index operation is marked as a collider in this path, as only people who have had a reconstructive operation for orthopaedic infection were included in prognostic modelling.

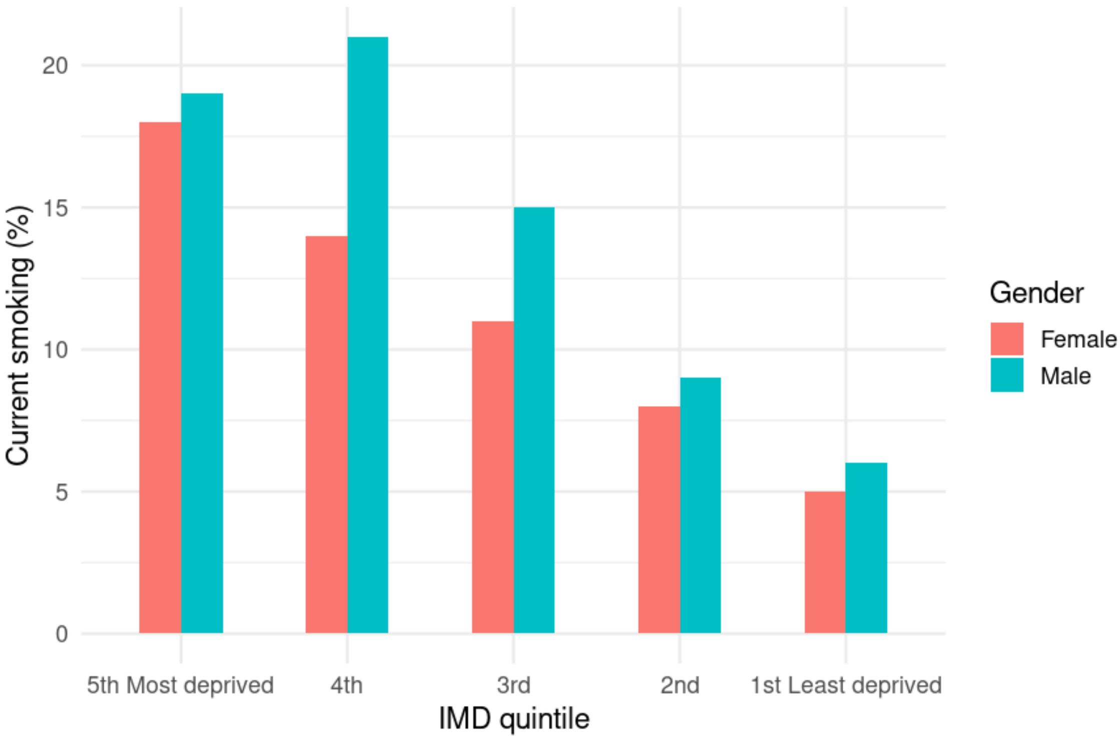

Figure 5.27: Distribution of smoking (%) among male and female participants in the Health Survey for England, 2021, according to quintile of Index of Multiple Deprivation.

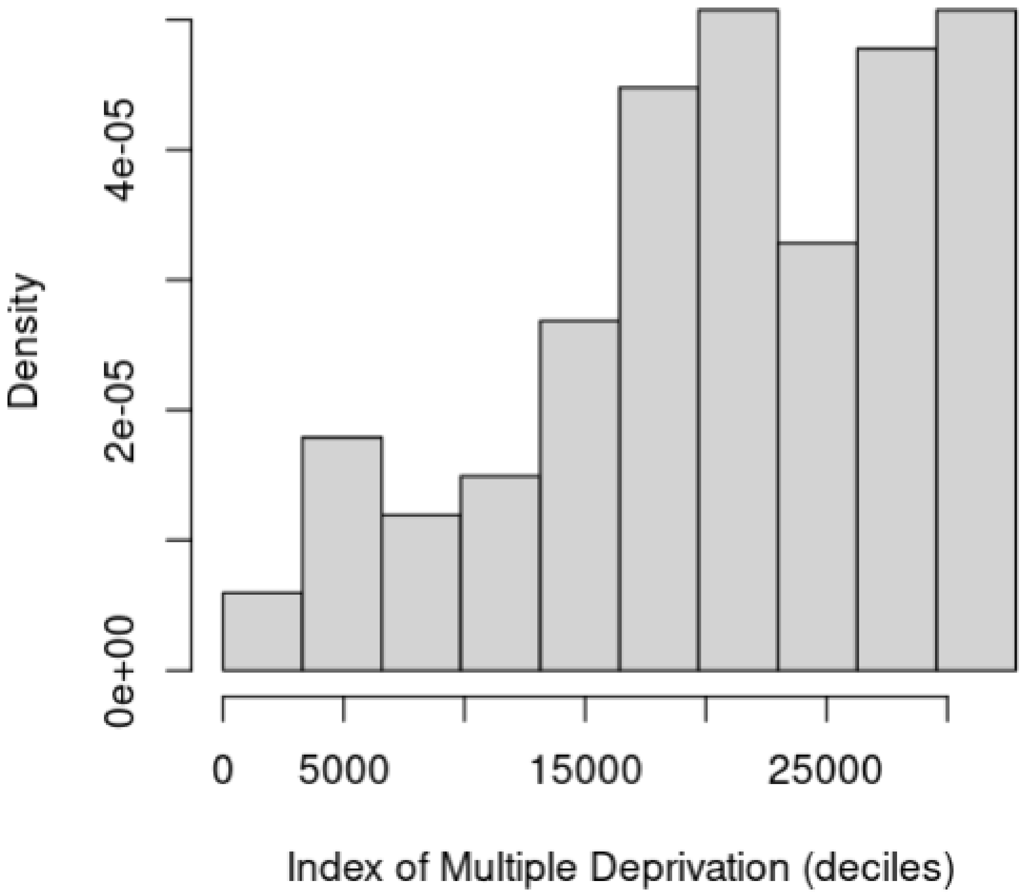

Figure 5.28: Distribution of Index of Multiple Distribution (deciles) for participants in the PRIMIO prospective cohort study.

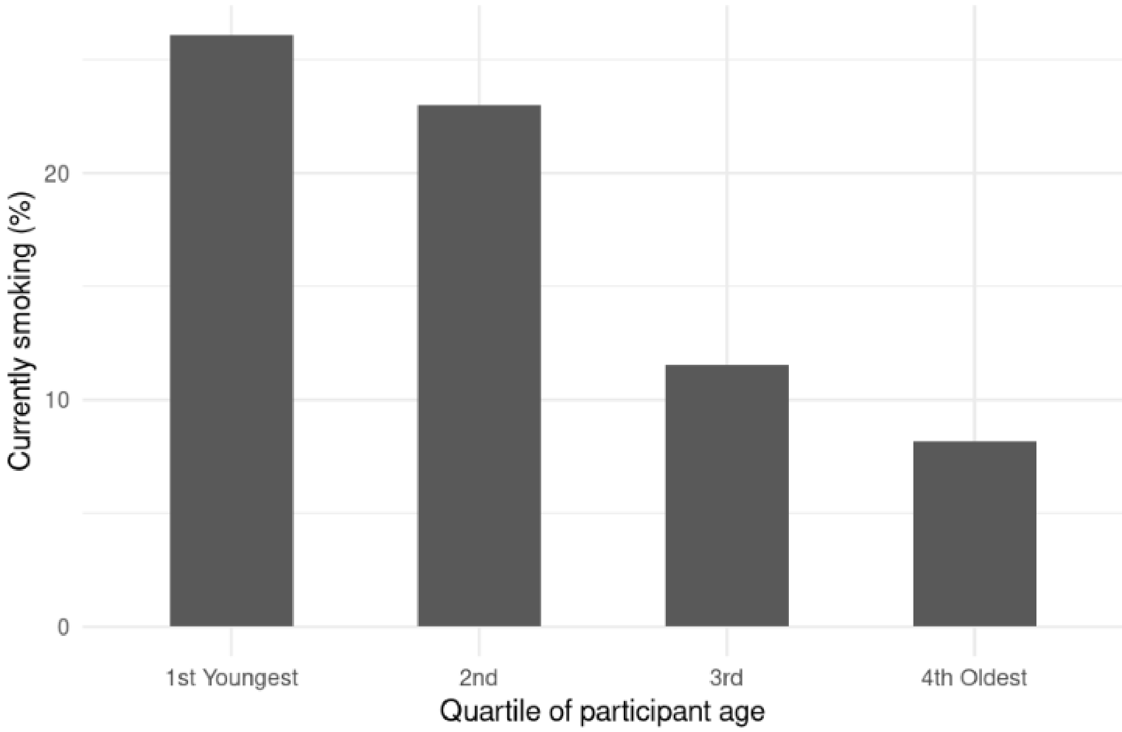

Figure 5.29: Proportion of participants in the 4 cohorts (PRIMIO, SOLARIO, OVIVA and Lange 2016) who smoked at the time of surgery, according to age.

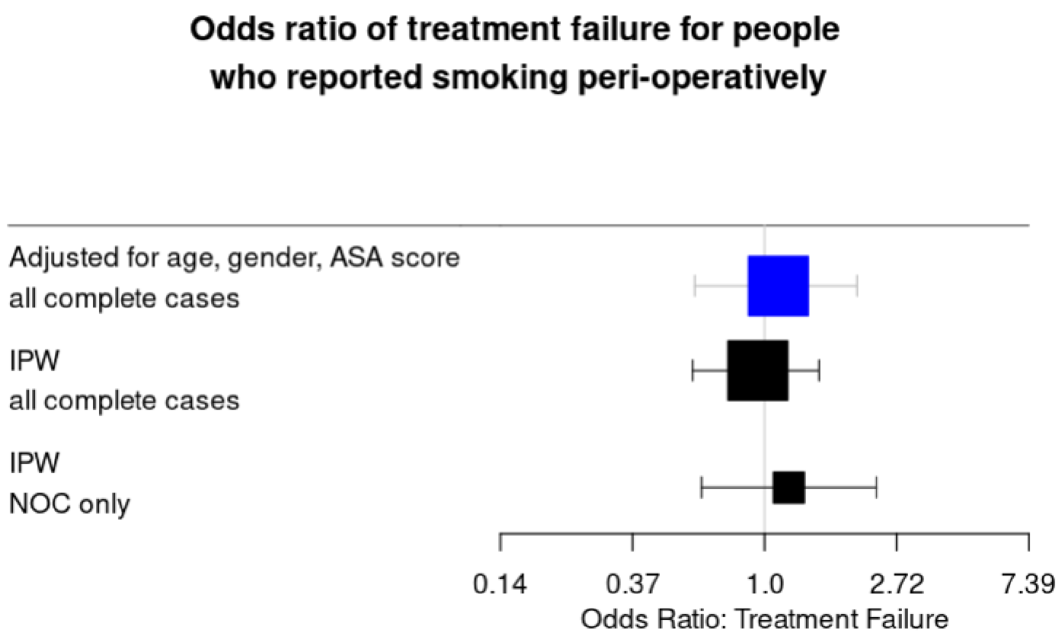

Figure 5.30: Odds ratio for treatment failure for participants who reported peri-operative smoking.

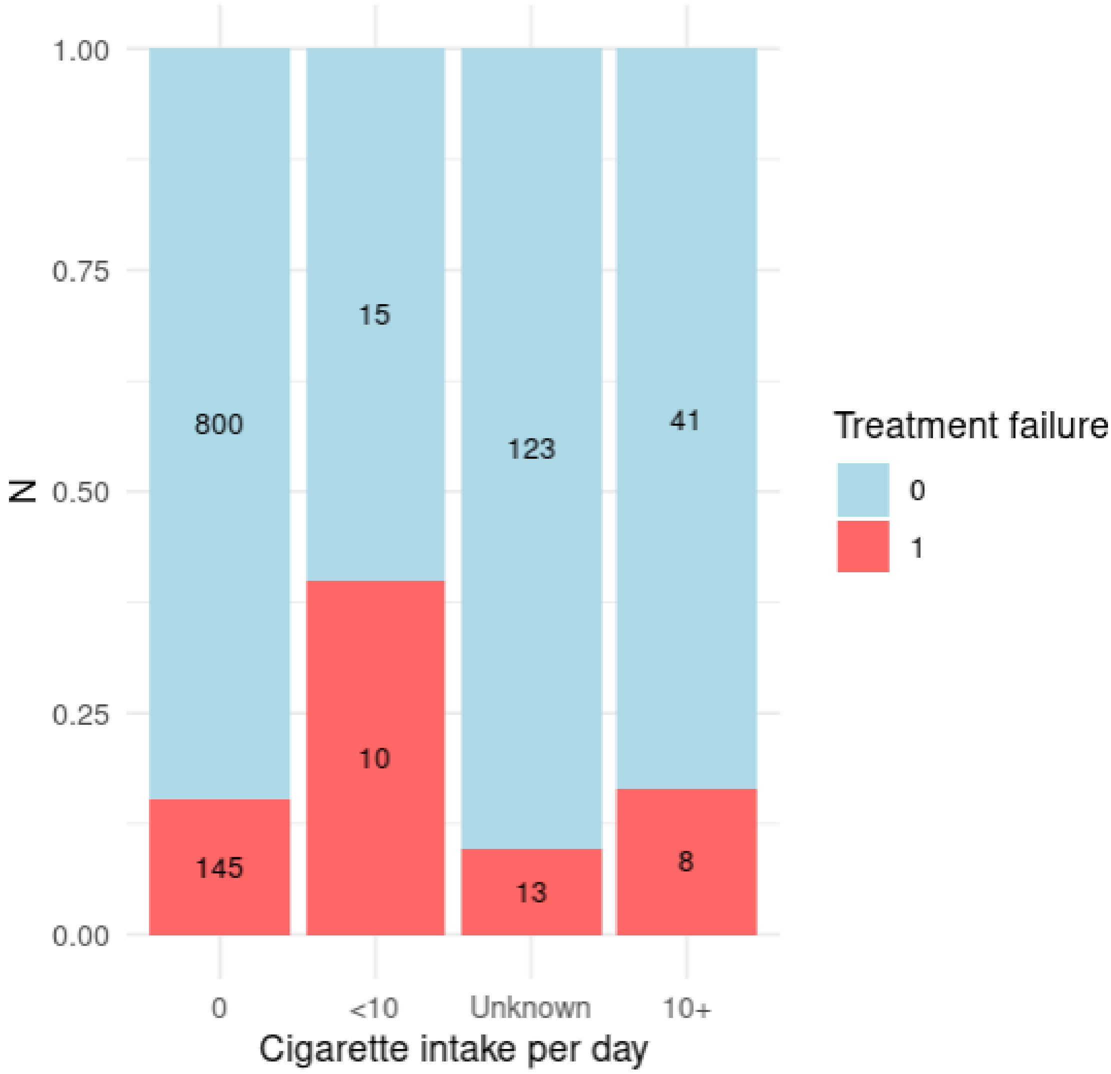

Figure 5.31: Proportion of participants who experienced treatment failure, according to recorded maximal tobacco intake (cigarettes or equivalent) in the three months before surgery.

6 | Qualitative study: Barriers and facilitators to pre-operative health optimisation for adults with orthopaedic infection

6.1 Background and rationale

According to existing observational and interventional studies, smoking, alcohol use, blood glucose control and nutrition may influence the risk of orthopaedic infection after surgery. Pre-operative smoking cessation interventions are cost-effective even for surgery to implant a new joint replacement, where the treatment failure rate is lower than for orthopaedic infection surgery. (Boylan et al., 2019) Reducing alcohol intake and stopping smoking 4-8 weeks before surgery has measurable benefits including reducing surgical complications. (Truntzer, Vopat, Feldstein, & Matityahu, 2015; Toennesen, Nielsen, Lauritzen, & Moller, 2009) This period is similar to the usual waiting time for surgery for adult bone and joint infections, as in most cases emergency surgery is not required. Studies of pre-operative interventions addressing obesity, malnutrition and blood glucose control have also reported improvements in patients' recovery and surgical treatment outcomes.(Thomsen et al., 2014; Hopkins et al., 2017; Delmi et al., 1990; Livhits et al., 2009)

Tailoring pre-operative care for patients with orthopaedic infection is one of the requirements of the National Specialist Orthopaedics Service Specification, and this study aims to address this requirement. (NHS Commissioning Board, 2013) Pre-operative optimization, or pre-habilitation, is part of the strategy to improve surgical outcomes after orthopaedic procedures. (Briggs, 2015) During the course of the COVID-19 pandemic, the need to turn waiting lists for surgery into 'preparation lists', with better access to pre-habilitation interventions, was highlighted as an opportunity to improve outcomes.(Dhesi & Plotkin, 2021) Despite this guidance, existing pre-operative interventions may not be appropriate for people with orthopaedic infection awaiting surgery, so it is important to understand the barriers and facilitators that may affect their uptake.

6.1.1 Pre-operative interventions should be tailored to people with orthopaedic infections

Behavioural interventions to address health factors sometimes work well, but are often taken up by as few as half of the people to whom they are offered. (Thomsen et al., 2014; McHugh et al., 2001; Kaner et al., 2018) Not all behavioural interventions are equally acceptable.(Bartlett, Newhouse, Long, Farmer, & French, 2019) For smoking cessation, some types of behavioural intervention appear to be more effective, though this may vary with context such as the psychological comorbidities of the person receiving them.(Black et al., 2020)

There is a strong consensus among orthopaedic surgeons internationally that pre-operative optimisation plays an important role in preventing orthopaedic infection, and many surgeons report being willing to incorporate prehabilitation interventions into routine care.(Vick, Graham, Henderson, Houston, & MT., 2011; Gehrke et al., 2013) However, variation in the relative effectiveness of different interventions might result from the setting in which they are administered, the time over which they work, the people receiving them, and the relationships and social norms those people experience.(Thompson et al., 2007) The cultural and social context in which an intervention takes place, including healthcare system factors, patient and clinician communication skills, health expectations and beliefs within a community, and political debate around responsibility for illness, may have a major influence on patients' engagement with behavioural interventions.(Chapman, 1993; Lauridsen, Thomsen, Kaldan, Lydom, & H., 2017; Greenhalgh et al., 2011; Carbone & Rosal MC, 2007; Leta, 2018)

People affected by orthopaedic infection have specific needs and experiences associated with their illness that may alter how they engage with behavioural interventions. These experiences include pain and fear for most people with severe infection.(Cahill et al., 2008; Moore et al., 2015; Lerner et al., 1993) People who have previously had spinal surgery were less likely to engage with a preoperative protocol to reduce the risk of surgical infection than those who were having surgery for the first time, suggesting that past experiences of surgery or healthcare contact might influence engagement.(Schaffzin, Mangeot, Sucharew, Beck, & Sturm, 2016) However, few studies have sought to understand and describe the experiences of people affected by orthopaedic infection, and how these experiences may impact healthcare interactions.

Pain, cognitive load and distraction (that might result from having to plan healthcare, travel to a tertiary care centre, make adaptations to daily life to cope with limited mobility, and negotiate financial benefits, on top of existing life tasks) can affect both the decision making around planned behaviours, and the control of automatic behaviours, that affect health.(Allen, Edwards, Snyder, Makinson, & Hamby, 2014; Shiv & Fedorikhin, 1999; Apkarian et al., 2004; Harman & Ruyak, 2005; Tversky & Kahneman, 1974; Allred, Crawford, Duffy, & Smith, 2016) Behavioural interventions can add to cognitive load, which may be counterproductive when the added cognitive load impedes appropriate inhibition of unwanted behaviours, or reduces the introduction of complex behaviours necessary to achieve a health outcome.(Shiv & Fedorikhin, 1999; Hinder & Greenhalgh, 2012)

Existing studies of behavioural interventions in the healthcare context find that only a small proportion of participants make long-term changes, to smoking for example.(West et al., 2015) However, it is clear that many patients may make temporary changes, such as stopping smoking around the time of surgery if prompted.(A. Webb, Robertson, & Sparrow, 2013) This may be enough to influence outcomes after orthopaedic surgery.(Boylan et al., 2019; Truntzer et al., 2015; Toennesen et al., 2009; Hopkins et al., 2017) Improving intervention engagement may be one of the primary sources of improved effectiveness.

This study aimed to explore the experiences of people with orthopaedic infection, from the time symptoms manifested, through the period when the diagnosis was made, and focusing on the period of time between referral for specialist treatment and surgery. It included people affected by primary orthopaedic infection, and people who had orthopaedic operations that were complicated by infection. The COVID-19 pandemic, and its effect on healthcare access and daily life, gave a rare opportunity to observe the importance of context for behaviours relevant to health during this study.

6.2 Aims and objectives

The aims of this study were:

1. To explore the experiences of people with orthopaedic infection in the pre-operative period;
2. To understand the barriers and facilitators to health factor change for people affected by orthopaedic surgery;
3. Alongside Realist synthesis, to understand what behavioural interventions aiming to improve recovery from operations may work for patients awaiting

curative surgery for orthopaedic infection.

6.3 Ethical approval

Ethical approval was obtained from the Health and Social Care Review Panel B (Proportionate review, reference 21/NI/0056), prior to the commencement of the study.

6.4 Behaviours of interest

The primary behaviours of interest were those pertaining to tobacco smoking, alcohol drinking, food preparation and eating, and the management of comorbid illnesses in the pre-operative period. This selection was necessarily broad, as at the outset of the study it was not clear which of these complex behaviours would be most relevant to the success of surgery for orthopaedic infection.

When describing behaviours relevant to health, simple terms can stand for complex patterns. For example, smoking describes acquiring tobacco products, seeking out a particular time and place to smoke, and relational negotiation with co-habitants, colleagues, extended family, pharmacists, doctors and other healthcare providers.

6.5 Methods

The methods for this qualitative study were developed together with a panel of Patient Representatives with experiences of orthopaedic surgery and infection.

6.5.1 Theoretical framework

This study was carried out with reference to a Realist theoretical framework.(Maxwell, 2018) In order to infer causal relationships between interventions and outcomes, the Realist framework allows observations to be used to test hypotheses.(Pawson & Tilley, 1997; Astbury, 2018) However, it is assumed that all observations are affected by the theory inherent in the process of observation – all observation is 'theory-laden'. Thus, 'a realist stance implies a reflective and critical attitude toward one's own beliefs, plans, and actions,' and demands a clear description of reflexivity.(Maxwell, 2018) Hypotheses are formulated as: 'what works, for whom, in what context, and why'.(Pawson & Tilley, 1997) Mechanisms, or 'what works', are only ever indirectly observed, 'as through a glass, darkly'.(Emmel, Greenhalgh, Manzano, Monaghan, & Dalkin, 2018) Mechanisms in the Realist framework are causal processes that only ever operate under certain contexts, for some people, some of the time.

Ray Pawson, one of the founders of Realist evaluation, stated that,

> The things we study – policies, programmes, interventions – are inserted into systems which are already fluid and changing. Interventions are often heralded as instruments for change, but what they actually try to do, all that they can do, is to change the course of change . . . We always need to keep in mind that what would have happened anyway is change.

The Theoretical Domains Framework (TDF) is an iterative grouping of factors from existing psychological theories, that are relevant to understanding behaviour change. It was developed to allow researchers from different disciplines to express research findings in the same terms, with reference to the same underlying theoretical basis.(L. Atkins et al., 2017) It can be seen as an extension of simpler models of behaviour, such as the Capability-Opportunity-Motivation model.(Michie, van Stralen, & West, 2011a) Using the TDF to analyse behavioural interventions is also intended to guide towards elements of behavioural intervention, such as from the Behaviour Change Taxonomy, that have been linked to specific domains of the TDF.(Abraham & Michie, 2008; Michie et al., 2013) Behavioural interventions can be thought of as composites made of elements specified in the Taxonomy.(Beard et al., 2019; Lorencatto, West, Christopherson, & Michie, 2013)

6.5.1.1 Elements of theory guiding observation

A priori, changing aspects of the context for peri-operative behavioural interventions were identified, that were felt to be relevant to the interpretation of the collected data by the research team, including mentors and Patient Representatives.

Using the example of smoking and behaviour change, macro level contextual changes that could affect behavioural interventions include social norms and common knowledge, public infrastructure, and patterns of socioeconomic opportunity or deprivation. The level of existing knowledge most people have about the risks of smoking has changed with time, as have norms around where and when it is acceptable to smoke. Community smoking cessation services are now available in more settings, such that contact with medical professionals is no longer required to obtain nicotine replacement products.(Chapman, 1993; Cummins, Curtis, Diez-Roux, & Macintyre, 2007)

Socioeconomic deprivation is a macro level influence that affects smoking. In the UK, smoking is more common among people who are unemployed or those working in manual unskilled occupations.(Office for National Statistics, 2020) Hilary Graham described the relationship between socio-economic circumstances and smoking in mothers with infants and young children in a UK urban population selected based on the catchment areas of two maternity centres. Higher rates of smoking were associated with a greater caring burden, including looking after adult family members and children with disabilities, and with lower household income.(Graham, 1993) People experiencing a greater burden of care may frame smoking as their only opportunity for self-care, and a factor that allows them to suppress emotional outbursts that may harm others.(Graham & Kelly, 2004; Wells et al., 2017)

Smoking may be portrayed as a behaviour that individuals choose to engage in freely. It has come to be imbued with moral overtones due to its widely known adverse consequences for long-term health. Healthcare professionals may seek to enforce morally-charged norms around behaviours such as smoking, dietary intake and exercise. This exacerbates an imbalance between the healthcare provider and the person who smokes, referred to as 'biopower':

> The underlying expectation is that coercion is unnecessary and that responsible, rational citizens will 'freely' govern themselves in ways consistent with expert knowledge. Rather than being in opposition to the state or independent of it, experts such as doctors, nurses and epidemiologists bring the state into being via the mobilisation of their 'autonomy'. And, it is by means of professions such as these that citizens are governed at a distance by inciting them to govern themselves[,] and biopower is operationalised.

(Thompson et al., 2007)

Socioeconomic deprivation goes hand in hand with exclusion from certain shared activities or entitlements in society. This can limit both resources and opportunities to enact change. So while expectations from healthcare providers may be that all people seeking treatment will have sufficient resources to 'freely govern' their behaviour,

> Economic circumstances produce patterns of social exclusion by limiting an individual's ability to participate in work, family and community life.

p. 62 in: (Siegrist & Marmot, 2006)

The prevailing ideology that behaviours contributing to health outcomes are a matter of personal responsibility, and must conform to standards set within certain socio-economic groups, has been criticised as 'health-ism':

> I think it's pretty clear that 'health-ism' has taken hold. The responsibility for health has now been placed firmly in the hands of the individual, and we have become ever more obsessed with physical health, while we look scornfully at those who put their health at risk, even though we may know nothing about their preferences, or about their opportunities or constraints. (. . .) We're polarised in how we behave, and how we judge those behaviours. [Those judgements] come from middle-class values.

(Dolan, 2021)

Micro level influences on the effectiveness of health behaviour interventions will be considered in the analysis, as both mechanisms and context.

One micro level influence is how people gain skills. Skills may be defined as the acquired behaviours necessary to achieve a goal. People may need particular skills to use nicotine replacement devices effectively. Skills are necessary for negotiating access to healthcare: such as searching for information, communicating with administrative staff, or asking clinicians questions during appointments. The distinction between practical skills and theoretical information for chronic disease management was demonstrated by Trish Greenhalgh and colleagues in a study focusing on narrative. (Greenhalgh, 2013) 'Participants appeared to recognize the distinction between abstract knowledge ('knowing-that') which they said they gained from health professionals, and tacit or practical understanding ('knowing-how'), which they felt they gained from sharing stories. One participant put it like this:

> We learn the facts from you [health professionals] but we learn the meaning and how to do things from one another.

This disconnect between theoretical knowledge and practical knowledge may explain why health literacy may have little influence on chronic disease management in certain patient groups.(Tang, Pang, Chan, Yeung, & Yeung, 2008) A lack of distinction between information and skills may underlie reduced effectiveness for some behavioural interventions:

> [In the healthcare context, people may receive] fictional vignettes or images typically given in educational materials, in which self-managing patients are depicted somewhat blandly as doing context-independent tasks such as 'eating healthily' or 'exercising.'

(Tang et al., 2008)

A further individual level influence in the uptake and effectiveness of behaviour change interventions could be reactance. Proposing an intervention to change behaviour may provoke resistance from people who could benefit from it, if it is perceived as a threat to freedom. Reactance is a motivational process involving negative thoughts and emotions directed towards a forced choice or a loss of freedom, with motivation to restore the freedom.(Brehm, 1966) When reactance arises from an externally communicated threat to freedom, negative thoughts and feelings, as well as aggression, can arise that are often directed at the person or organisation felt to be the source of that forced choice or loss of freedom.(Steindl, Jonas, Sittenthaler, Traut-Mattausch, & Greenberg, 2015)

These factors are only a few examples of changing elements of social context that may affect what works, for whom, and why, that were considered relevant to behaviour change interventions for people having surgery for orthopaedic infection.

6.5.1.2 Interpretation of interview narrative

Narrating the story of their diagnosis and treatment was expected to have additional meaning for participants, other than just conveying factual information to the researcher. It was assumed *a priori* that some elements of the narrative may constitute face-work. This is a concept elaborated by Erving Goffmann that describes the behaviours that ensure a person retains 'face,' a degree of dignity or standing within a group or interaction. Face-work may be supportive of, or orthogonal to, the participants' accurate telling of events as they took place. (Goffmann, 1955, 1956) The construction of a 'responsible identity' in narrative has been observed in previous qualitative research with people who smoke:

> Far from being out of control, resistant and anti-rational, continuing smokers work to produce responsibilised identities.

(Thompson et al., 2007)

Social desirability bias describes the process underlying selective responses to surveys or interviews, where a participant may be embarrassed, or concerned about suffering repercussions, from telling the truth.(Tourangeau & Yan, 2007) Reporting ongoing smoking, 'excessive' alcohol use or illicit drug use may be embarrassing, and might make people concerned about whether their operation will go ahead. I expected some participants to report a smoking cessation attempt or attempt to cut down how much they smoke, that may not have reflected their actual experience.

The structure of the interviews aimed to reduce embarrassment. First, participants were reassured about the purpose of the interview, that responses would not be communicated to their medical team. A passage in the Patient Information Sheet, written by a Patient Representative, explained that the study would use the information given to researchers, without judgement, to help future patients. All interviews started with neutral introductory questions, and gave participants the opportunity to discuss peri-operative factors that could be less morally charged (appetite loss resulting from infection, access to support for existing medical conditions) before any questions about smoking or alcohol use were introduced. This aimed to give the interviewer a chance to build rapport with the participant and signal non-judgemental listening.

Some interviews took place after the orthopaedic operation had already happened, and recall bias could have distort the salience of past events. I had intended to explore the role of recall bias by conducting both pre-operative and post-operative interviews with the same participants, however in practice it was only possible to arrange paired interviews with one participant out of the purposive sample. It was also noted by a Patient Representative that the ability to narrate events could be affected by illness, and that this may affect the quality and completeness of the information gathered. Remote interviews conducted by phone or video call may also have affected the interaction between the participant and the researcher. An absence of face-to-face contact may have liberated some participants to express narrative or emotions that might upset the researcher, including criticism of clinical care.

6.5.2 Participants

Adults referred to a specialist orthopaedic infection clinic for assessment and treatment for bone or joint infection at a national tertiary referral centre were approached for this study.

6.5.3 Sampling

People with differing experiences of modifiable health factors were approached, according to demographic parameters that may affect their experience of the peri-operative period. These included age, gender, ethnicity, employment and education, and Index of Multiple Deprivation of their postcode of residence.

At least 15 participants were planned, approached at different stages of treatment for orthopaedic infection. Recruitment stopped twelve months after the study opened. Sixteen participants were included in the study, including one participant who provided an interview before and after her operation. New themes continued to emerge that were not found across three consecutive interviews in the study, suggesting that thematic saturation was not reached in this sample.(Francis et al., 2009)

6.5.4 Data collection

Semi-structured interviews were conducted by only one member of the research team, though all participants were given the option of a research interview remotely by video link with one of three Patient Representatives who had received training in qualitative interview techniques and contributed to the design of the study protocol and semi-structured interview questions. Interviews were conducted in person in the hospital clinic when safe to do so, or by telephone, at a mutually convenient time. Respiratory pathogen safety was maintained for the study participants and interviewer at all times in line with contemporaneous clinical care standards.

A topic guide for the semi-structured interview started with open questions about experiences and behaviours in a specified perioperative time period, and focused on target behaviours. The timeline from diagnosis to treatment was used as a 'cultural probe' to allow the participant to recall past experiences in context, and was intended to provide a neutral but relevant scaffold around which questions about behaviour and experiences could be structured.(Green & Thorogood, 2018) Focused questions were guided by the Theoretical Domains Framework.(L. Atkins et al., 2017)

6.5.5 Thematic analysis

Interviews were recorded and transcribed to pseudonymised participant records. Transcription was verified by a second researcher for four participant interviews, and all transcripts were reviewed by the second researcher for style, typography and coding accuracy. Potentially identifiable information was masked from the interview transcript to preserve confidentiality.

Transcripts were coded and analysed using reflexive thematic analysis. Codes were applied inductively, deductively and retroductively.(Pawson & Tilley, 1997) Deductive thematic analysis, using the Theoretical Domains Framework, was carried out for each transcript, and discussed within the research team using anonymised excerpts from interview transcripts.(L. Atkins et al., 2017) Emerging themes were recorded and discussed at research team meetings, and were used to further inform the sampling strategy. The effects of reflexivity and participant-researcher relationships were explored contemporaneously. The second researcher pointed out linguistic and cognitive biases affecting the framing of the analysis, and confirmed that the purposive sample was of appropriate breadth.

6.5.6 Reflexivity statement

While conducting, transcribing and coding interviews, I found the degree of antipathy towards clinicians and healthcare experiences upsetting. From the perspective of a person seeking healthcare, the experience of the disease and the experience of interactions with clinicians necessarily co-occur, and may be interpreted as parts of one unpleasant experiential amalgam. From my perspective as a clinician, the ways in which participants described their treatment (and treating clinicians) sometimes felt unfair. However, I actively sought not to inhibit such reactions from participants during the course of interview recording, in order to be as true as possible to participants' recall of their experiences.

6.6 Results

6.6.1 Semi-structured interview study participants

Sixteen participants agreed to take part. All were adults with a clinical diagnosis of orthopaedic infection. Eight participants had osteoarticular infections following orthopaedic operations, including joint replacement procedures; while others had infections that arose in the absence of prior surgery. Purposive sampling allowed interviews to be conducted with a range of participants whose experiences and communication styles differed substantially from each other.

Many people approached for interview declined to take part or did not return the study reply form. In total, 48 people were approached, of whom 14 were women and 34 were men. Thirty-two people did not take part when approached, including five who actively declined consent to participate.

Participants: characteristics	**n = 16**
Gender	11 male, 5 female
Ethnicity	9 white British, 1 Mixed, 2 British Indian/Pakistani
Religious affiliation	9 not reported, 3 atheist, 2 Hindu, 2 Christian
Age (to nearest 5 years)	20, 30, 35, 40, 40, 45, 45, 50, 55, 55, 60, 60, 65
Qualifications	GCSE to undergraduate degree level
Type of infection	8 post-operative, 8 endogenous
Timing of interview	8 before surgery, 8 after surgery
Non-participants:	**n = 32**
Actively declined	5
Passive non-response	27
Gender	23 male, 9 female

Table 6.1: Summary of participants and non-participants approached for qualitative study

6.6.2 Pain and cognitive load in the perioperative period: relevance to behavioural interventions (capability)

Pain featured prominently in nearly all participants' narratives of their experience with orthopaedic infection. Those participants for whom pain did not feature, often had underlying neurological conditions such as peripheral neuropathy. Pain was a pervasive, daily struggle punctuated by occasional extremes, as described below.

Becky:

> I have to take painkillers every day.

Jack Howard:

> I wasn't causing myself the pain that I'm having now, from anything I do. Now I'm just in excruciating agony, it's like mechanical pain, bone against bone, phchh!

Mandy:

And the pain was excruciating again. So, um, he had me back in, and decided to put a plate in. So I'm assuming that's when – all the problems started because the big piece of metal – again, with not being cleaned out properly, because here obviously they take some of the, um, the bad tissue away, and test that, and that's how they know about the infections.

So, and, yeah so that lasted [clears throat] excuse me, that lasted several months. Um, still got the vac pump on, by then. Um, but then I got to the stage where I couldn't move without the pain, was so bad, so I stopped eating, stopped drinking, to save me going into the toilet.

Luke:

Right, so, yeah, so I couldn't get up the stairs either sort of thing, you know, so, yeah, so I know the femur's the biggest bone in the human body, the PAIN is HIDEOUS. The cancer, love, was NOTHING. Compared to that leg. It was hideous. I mean you need to understand I broke the thing. I smashed it all to pieces, sort of thing, you know. And that was NOTHING compared to the pain that that gives you, that bone, if you get that infection in there. It's hideous. Absolutely hideous, yeah, it's unbearable. It is unbearable. I mean I can take, I take, over the years I've done a few things and I can take a bit of pain but this just was just beyond belief really. Does make you howl, sort of thing, you know.

Judith:

Eight months, and I can hardly walk some days, I can hardly lay on my left side, the pain in my hip is horrendous, I don't know what to do with it. I actually got to the stage that I wanted to die.

Jessica:

> it wasn't me really feeling ill in any kind of way, it was just this horrendous pain in my arm.

Grace:

> When it flared up and it was sore, like when you tried to roll on it, you couldn't. You'd wake up cause, you had. And the sore, the pain, was too much.

Paul:

> Oh, well there was a huge swelling, sort of lower, sort of like a golf ball sized swelling, and the pain – I mean, I was in a lot of pain, so. Yeah, it was pretty obvious there was something wrong.

Joseph:

> It's got a very severe burning sensation, Maria. With the infection in my knee, under my knee, under my knee cap, now it's like a miniature lake, an abscess. That's still in there. I hope, well I know, that soon the hospital will be taking that out.

Bill:

> I said, thank you very much(!) You've done a good job, I said. Because, you know, that time I can't say anything. [Yeah.] So, then he [the surgeon] gone. And after, I said, too much pain, because he broken pieces in there. I [have] broken bone in there. Sixth day I'm in bed.

Both pain and analgesic medication sometimes contributed to reduced cognitive capacity in the pre-operative period, as Ian described:

> Er, they gave me all the information and everything that was going on, and gave me all the choices, but at the point where – all of it was happening, erm – I knew what was going on, but I was so – high on painkillers, that everything was just a little bit groggy, I was just – fix it!

Other pre-operative experiences, including effort directed towards healthcare access, may have contributed to participants' cognitive load. Several participants described monitoring changes in their symptoms, repeatedly interacting with healthcare providers, and critically interpreting as well as enacting clinical advice.

Becky:

> Do you know what, it was Christmas time. I think it was, 27th of December. Day after Boxing day. I went to [Local Hospital] [pause], but they sent me home. They said it was just, a bacterial infection. So more antibiotics, but orally. And then it got worse, and then [pause] it came out like a big, like, abscess. So I need help getting in and out of the bath, so my mum put me in the bath, and then by the time I got out it had popped. So she bandaged it all up, woke up in the morning, and it was just awful. The smell. It was horrific. Just the look of it. It was green, went straight back to [Local Hospital], and then they admitted me.

Luke:

> I've had, I had a real problem on a Friday, I can't remember the exact date, and I went to [Local Hospital] A&E and I couldn't even walk. And, um, they pumped me full of painkillers and whatnot and sent me home and (sigh) by Monday it was hideous again, so I did actually ring that [phone] line. But I didn't want to be a load of hassle if

you can understand what I mean. Um, there was a lot going on with COVID, with the cancer as well, there was all sorts of issues with that, which, which muddied the waters to some extent.

Ian:

So, it was – April 2020, I had pain in my right knee, went and had an X-ray done at my local minor injuries unit. They said it was just soft tissue damage. Three days later I then was not able to walk on my leg, I wasn't able to bend my leg or anything. I had to get an ambulance, er, out to my house, and was taken in to A&E, and they then done the aspirations there, took out five vials of fluid from the swelling and everything that had come on from my knee. And from that they then discovered that there was an infection growing, and over the course of five and a half weeks, through antibiotics and everything like that, the infection was not going down, and that's when they discovered that it was septic arthritis.

Jessica:

So that was just through my GP, which – with obviously everything going on took a while for me to actually get an appointment in the first place. I think, if I'd have just not persisted, the first time I would have even spoken to anyone was a telephone appointment that was scheduled on the 4th of October, so if I hadn't persisted that would have been the first time I would have spoken to anyone about it.

Bill:

After that I ring, couple of times after New Year, you know, before New Year, I ring, I say, when it's going to be operation, he say, after

> New Year, then I ring them, then she say Summertime. One of the ladies from reception or whatever it is, she tell me, your operation going to be summertime. I say, oh, too long, because [Surgeon 2] tell me two months or three months or whatever it is good to be healing. I come in next week it's going to be checked. And if it's good then he's going to doing, he can't, otherwise wait I don't know how long.

The daily struggle some interview participants described facing, from the symptoms of their illness and the effort of navigating healthcare services, is relevant context for peri-operative behaviour change interventions for people with orthopaedic infections. Interventions that rely on reflective motivation, or that are cognitively loading in their own right, might be less effective for this group of people.

6.6.3 Smoking cessation in the perioperative period

Thirteen participants discussed peri-operative smoking, and current or past smoking cessation attempts. Three of thirteen participants quit smoking between three and six years prior to their interview, and were non-smokers in the pre-operative period for their orthopaedic infection surgery. Three participants reported never smoking.

Three women and ten men discussed peri-operative smoking. This reflects the gendered prevalence of both smoking and orthopaedic infections in the UK. Around three quarters of those affected by orthopaedic infections, particularly native bone osteomyelitis and fracture-related infections, are male.(Lew & Waldvogel, 2004) In 2020, the Office for National Statistics estimated that around 14-16 percent of adult men and around 10-12 percent of adult women in the UK self-reported currently smoking, and that this fraction has fallen.(Office for National Statistics, 2020)

Ten participants described their experiences of prior quit attempts, before either their final successful attempt, or before the peri-operative period.

6.6.3.1 Nicotine replacement therapy (NRT) and other pharmacotherapy during past quit attempts: Responses to interventions aiming to support behavioural regulation (capability)

Six participants reported using medications, including NRT, in past quit attempts. Participants obtained NRT from their GP in two cases, from smoking cessation clinics in four cases, from pharmacies in four cases (some participants accessed several sources of NRT). NRT is an intervention focusing on behavioural self-regulation, raising capability to choose behavioural alternatives to smoking, by reducing cravings for nicotine and reducing dysphoria associated with nicotine withdrawal.(West et al., 2015) This type of intervention is effective in a number of settings, including in peri-operative care.(Thomsen et al., 2014)

Several participants stated that they were reluctant to use NRT, citing the need to remove nicotine from their body altogether so as not to 'replace one addiction with another.'

Grace:

> There isn't anything else, apart from patches and, like I said, I don't want to replace – one addict for another. Addiction for another. I don't want a vape. I don't want patches when you have to have them all the time.

Ricardo:

> No, because I didn't want to take any, take any nicotine, or shots, or the stickers, the nicotine what do you call them? Nicotine- Maria:

-patches. Yep. Ricardo: Patches. Yeah. Because I just though that that's just, prolonging things, isn't it. I – maybe I might be wrong, but, erm, I had an episode in the past where I, I was prescribed, [sigh] codeine? And I got addicted to it? So I took codeine for approximately two years, and every time I went to an hospital twice, and they were like, you need to reduce the amount of – codeine you're taking before you completely stop taking it.

Judith:

I did got, I have got a vape, and I said to the doctor, because my son got me a vape, he bought it and you can buy different flavours, and I had that for a while. But the doctor said, that's going from one addiction to another.

Some participants who attended a smoking cessation service reported losing touch with the service over time, or not finding help from cessation advisers useful.

John:

Maria: Have you ever been to a stop smoking clinic? To a place-

John: I was. Not help.

Maria: Not helped.

John: Yeah! Yeah, you know, it's nice was, you know. Talk, everything, I not can say. I write, 'helps,' but is not helps, you know. [Laughs] I just nicely do, I finish, you know.

Maria: I see, so you just went through the process, but you don't really feel like it made-

John: Yeah. But I this process try, is not helped. But I know – read,

> or know people who have experience of no how smoke talk, but not this what they give doctor in GP, you know. *[I would prefer to read, or listen to, the experiences of people who had quit smoking.]*

Judith:

> Well I did get them from the clinic, I do two lots [of nicotine replacement therapy] from, one lot of those from the clinic. And I've not heard from them [the clinic]. Or anything. So I just buy them.

Some participants reported that nicotine replacement products were ineffective or unpleasant to use.

> John: What doctor say, you know. This, you know, same gums I want, I – plaisters [patches]. What is plaisters if I normal smoker, give me one milligrams nicotine, which is nothing not help.

Judith:

> Yeah, so I see a lady called [Name] at the stop smoking clinic place, and I spoke to her for a few times, so she sent me the nicotine patches, well they were a waste of time. I did tell her they would be, because I'd be taking them off and eating them. Because that's about as much use as they are. And I can't have the chewing gum because I've had most of my teeth, I've lost. Because of the medication that I've had, it's affected the my teeth coming out. And so, subsequently, I couldn't have that. The – thing, the patches were a waste of space, so I do like the – the tablets. The mints, tablets.
>
> I tried the spray, and for seventeen weeks I was brilliant, it was brilliant. But after the seventeen weeks when I stopped taking it, and my mum passed away, when I started taking it again, it gave me a real

sore mouth, and it gave me blisters, so I had to stop having that. And then there was nothing else I could have, so I just didn't bother.

Karl:

Yeah, because – I used to, I'm on methadone, and I used to have hot flushes, and they [the nicotine patches] would slide off? Yeah so they'd never really stay on my arm. But when I was here, yeah they actually stayed on my arm, and actually didn't crave anything, so-

Maria: So when they stick on they work.

Karl: Yeah. They do, yeah. But last time I tried them I kept on getting hot flushes with the methadone, they kept on sliding off. So I stopped trying. And the lozenges are disgusting. Oh god, I mean, eurgh, it's like chewing a cigarette. [Pause] Um, so yeah I was quite surprised by that.

(...)

Yeah. And I had the spray, mist spray. Which yeah, again, tastes disgusting. And if you swallowed the slightest little bit, gave you really bad hiccups.

Zac:

Yeah, yeah. But I did have [branded nicotine] tablets.

Maria: Right. And how were those?

Zac: I couldn't really, they tasted, tasted, er, not very nice.

In summary, barriers identified to the wider use of NRT among people having surgery for orthopaedic infection included perceptions that smoking cessation services were unhelpful, that nicotine replacement products had unpleasant side-effects, and that addiction to nicotine (rather than the harms resulting from tobacco smoke inhalation) were the primary target of smoking cessation.

Two participants in this peri-operative study described having used non-nicotine-replacement medication (such as varenicline) as part of previous quit attempts. Both described unsettling experiences while using these medications:

Grace:

> I did – try – going through a smo- a non-smoking clinic, through my GP. And they put me on the – medication. But because the medication, and I didn't realise this at the time, because the medication is based on an antidepressant, and I had, erm, post-natal depression, it's not advised. So I could have killed someone. So they soon took me off of that.

Ash:

> I did try smoking sen- cessation a few years ago, they put me on a – medication called Champix [varenicline], which erm is, is – was really helpful. But it gave me some re-eally strange experiences. Because it's one of the few forms of – giving up smoking, where you can give up smoking, with the tablets, and carry on smoking. It was just, it- just an odd mix so I couldn't – I understood how it works. It started to work. It starts making you hate cigarettes and despise them.

Non-nicotine pharmacotherapy with varenicline requires ongoing clinical supervision, because of the risk of unexpected psychological adverse events that may be distressing or dangerous to people attempting to quit smoking.(Myers, McRobbie, West, & Hajek, 2012)

Two of the three participants who had quit smoking years prior to their operation bought unlicensed nicotine delivery devices during their successful quit attempts. Both discontinued nicotine self-administration within a short time of switching from cigarettes to the new delivery device (an e-cigarette or a vape). One of the three participants quit smoking and stopped drinking alcohol through willpower alone, and reported doing so from the same day, a personally significant birthday.

However, one participant who was still smoking while using nicotine replacement therapy (patches) had tried a vape and did not like using it.

Zac:

> No, I've tried a vape but no. Couldn't get on with it.
>
> Maria: Couldn't get on with it. What kind of things did you not like about it?
>
> Zac: Ner - it was horrible.
>
> Maria: Did it not taste very nice?
>
> Zac: No, no.
>
> Maria: Uh huh, OK. Was there something else that you didn't like about it?
>
> Zac: [Pause] [Sigh] You had to keep recharging it. [Right, OK.] Cause it was a rechargeable.

In some cases, prior smoking cessation attempts allowed participants to try out a range of pharmacotherapies and find what worked best for them, and plan to use those options in future quit attempts. As described above in Judith's interview, ignoring these insights about what worked and what didn't, might reduce some participants' engagement with smoking cessation services.

Karl, about nicotine patches:

> But when I was here, yeah they actually stayed on my arm, and actually didn't crave anything, so-
>
> Which amazingly I actually stuck to. It r- I had patches, but they've never worked before, and yeah, I didn't crave a single bit. And as soon as I got out, the first thing I did was have a fag! [Laughs]
>
> So yeah the patches here were the first. The first time in well over thirty years that I haven't smoked, in eight days. So, I was quite amazed by it to be honest.
>
> So, in an environment where it is controlled, I know I can do it. [Sniffs] So it's not, this big scary monster that I always – built it up to be. Yeah so, I know it is possible with patches now, so.

Zac, about nicotine patches:

> They're doing, they're doing quite well.
>
> Maria: Mhm. Have you ever used them before?
>
> Zac: [Pause] Erm, once. Once or twice. But I – I can still smoke with them, that's the thing.

Grace:

> I just want to be able to- and I'm going to do – what worked for me? What I gave up the longest on, which was the e-cigarette, and the minis, the mints. So.

Even within a small number of participants seeking healthcare support in one centre, there is considerable variation in the nicotine replacement products people did, and did not, find helpful.

6.6.3.2 Alternatives to conventional services for smoking cessation (physical opportunity and skills)

Several participants described trying or planning smoking cessation strategies that allowed them to avoid contact with clinical smoking cessation and lifestyle intervention services. Participants shared many experiences of healthcare-associated distress. This may partly explain why vaping was popular, as it is provided outside the healthcare context.

Becky:

> Maria: After, after [Name] spoke to you, did you get any help from anyone to quit? Or did you just do things yourself?
>
> Becky: I just went on a vape. [Pause] That's it. [Pause]

Ian:

> Ian: No. I've not smoked for probably – three, four years now?
>
> Maria: Uh huh, congratulations! That's great. Can you tell me a little bit about, sort of, how you quit really. And what were the circumstances around that.
>
> Ian: Er, so, I – [laughs] decided one day that I didn't want to smoke any more, so I went and bought a vape. And so was, part and parcel, half and- half and half smoking cigarettes to, er, vaping. And then I completely gave up the cigarettes, and increased the nicotine level on the vape itself. Erm, and then slowly, over time, reduced the nicotine level down to zero on the vape so it was completely nicotine-free as well.

John:

Maria: And at the moment, where are you getting the patches from? Where do you get patches, from clinic, from pharmacy, from somewhere else?

John: From [Pharmacy], yeah.

Maria: From [Pharmacy]. And you just buy them yourself.

John: Yeah!

Maria: Have you ever been to a stop smoking clinic? To a place-

John: I was. [It did] Not help.

Luke:

I made a conscious decision to [not] smoke and I did use err, e-cigarettes? Initially? I did use those, which are, they are very useful? They do work? They absolutely definitely do work, now I smoked since I was 14. I smoked a lot. And I loved smoking I must admit, I really enjoy it, I loved it, you know, it's just my sort of thing. But yeah so, so I made a conscious decision so I, I went onto e-cigarettes. Err, which, they are a pretty decent stepping stone sort of thing.

Ricardo:

Maria: And during that time did you get help from any other healthcare providers, so, you know, like a pharmacy, any nursing service like a district nurse, so-

Ricardo: No. No. I didn't have any help, no. I've always made [got] my plasters [patches], and uh – by myself.

(...)

> When Mr. [Surname] spoke to me it was the – the – effects, that smoking does on your, uh, healing, so – it will take you longer to heal, it will be – er, more difficult to heal. It can be more susceptible to, er, infection and all that if you are a smoker. I thought, well I'm going to have to stop smoking, and so the first thing I've done, I erm – I went to an er, one of those vape shops and I reduced the amount of nicotine I was smoking, but that wasn't working too well, so. A month before surgery, erh [sighs] I, yeah, I stopped smoking.

Zac:

> Maria: Thank you. And have you- where did you get those patches from? Did they come from a stop smoking clinic, or did they come from a pharmacy?
>
> Zac: No that come from a pharmacy.
>
> Maria: From a pharmacy. Uh huh. How – how do you think they're working for you at the moment?
>
> Zac: [Pause] They're doing, they're doing quite well.
>
> Maria: Mhm. Have you ever used them before?
>
> Zac: [Pause] Erm, once. Once or twice. But I – I can still smoke with them, that's the thing.

One participant described how trying to self-manage her nicotine replacement therapy through vaping brought her into conflict with medical advice:

Judith:

> Maria: I see, fair enough, so because there weren't other medicines that worked or were OK for you [Yeah. Yeah.] you decided not to try,

> mhm.
>
> Judith; Yeah, but these, things, they are really good. I did like them.
>
> Maria: Have you ever tried a vape or an e-cigarette?
>
> Judith: I did got, I have got a vape, and I said to the doctor, because my son got me a vape, he bought it and you can buy different flavours, and I had that for a while. But the doctor said, that's going from one addiction to another.

Reversed roles were described by some interview participants, where as a patient they perceived their role as that of their own doctor. Two participants described role re-attribution during treatment of bone and joint infection and other chronic disease management, perhaps owing to difficult relationships with, or lack of access to, clinical care.

Jack Howard:

> Maria: It sounds like you've had painful episodes before, that you've sort of dealt with by yourself, because you said this was like a sprained ankle but in your hip, and that it was more like a soft tissue thing, which suggests this wasn't the first time this has happened to you.
>
> JH: Well it's not put me out of action. It's sort of, it didn't affect what I was doing from day to day. So it wasn't there, and by the time I came to question it, like, I wasn't asking the question any more, d'you know what I mean? It wasn't, it wasn't – It's hard to explain how you ignore pain. Or prioritise pain, or what have you, like, you know? To someone who doesn't use drugs, like hard drugs, injecting drugs, it's sort of. Essentially I've been my own doctor for that long. Because I can't get [laughs] any painkillers from a doctor because of previous

> behaviour. When I've used the doctor for various nefarious purposes, i.e. getting the strongest, the sleepers, the downers, whatever, d'you know what I mean, to feed my addiction. Basically I've been my own doctor, so, dealing with my own pain in a way that's become natural to me, over the years, so.

John:

> Maria: No pain. So otherwise you feel OK. Um, all right. And during this time, after coming out of the hospital, who was looking after the arm, and who did you see for your health? Was it your GP? Was it the orthopaedic clinic in your local hospital?
>
> John: Just, just one time I was, no two times was in GP. First give me antibiotics. Which not much helps. And after [the GP] say – say – need [to] wait [for the specialist] appointment. And this appointment I don't know, half year waiting? And me need be, doctor be myself!

Role reversal of this sort might signify a lack of trust or engagement with clinicians, such that relying on behavioural interventions including the 'credible source' behaviour change technique may be less effective.(Michie et al., 2013)

Dysphoric healthcare experiences may contribute to participants' avoidance of clinical smoking cessation services, choosing to buy nicotine replacement products rather than receiving them for free. In line with this interpretation, participants described wanting to leave hospital as soon as possible because of unpleasant experiences.

Karl:

> Maria: Was there anything particular that sort of made you want to leave hospital on the same day? You're not the only one, by the way.

Karl: Oh, uh, yeah it's just hospitals, I think – it's because, I was in a ward with no TV I think as well, and it was – [sigh] I didn't, I'm not very good with – sleep. I like sleep, and being kept up all night by, beep beep! Beep beep! And other people, and very – plus I'm a smoker, unfortunately. [Sighs] So yeah I've always done it, I've always been very impatient when I got to get surgery, always wanted to leave straight away. [Sigh.] But eight days, done me wonders, because put me on nicotine patches, didn't crave nothing, so. It gave me the fighting chance that it needed, I think, to – start off with, so. It's quite good really. Well, I moaned a bit. [Laughs] It did do me some good.

Maria: Yeah, I mean I agree with you, hospital environments can be really really difficult.

Karl: Yeah, they are, especially when you're in a ward, and everyone's coughing all night over there, and he's keeping you up over there, and getting checked up on every two hours, and. Luckily I had my own room this time, so – that was great, you know, felt a hell of a lot.

Maria: In terms of coughing, sorry, do you mean it was the noise keeping you awake or-

Karl: Yeah, people snoring, and things like that, it's just [sniffs]. I'm a very light sleeper. And the slightest thing keeps me- wakes me up. Uhh.

Maria: And then yeah, can be really difficult if you're not-

Karl: It does, and then I get grumpier and grumpier, and it's – I don't

> want to be like that, so, snapping at the nurses.

Luke:

> Maria: I see, so being stuck in hospital was really difficult and isolating.
>
> Luke: It was hideous. It was absolutely, I mean I hated being there, you know. [Sigh] You're not, I mean the thing is you're on a ward where there are many other people on the ward that have not bone ailments – the guy opposite me, two guys in there had clear mental issues. You know, so they're running around like headless chickens effing and blinding and chucking stuff around, um, which is amusing for a couple of days and then gets boring after that. Sort of thing, you know.
>
> Yeah, and you know the pressure aboard to, to nurses to keep us all under control is very difficult, you know. So it's not a very pleasant place to be, I'd rather have gone home and then come back but that was not allowed. [Fair enough.] I'd have just managed and that was it, you know.

Paul:

> Paul: yeah I'd actually discharged myself. Because, th- I was worried about COVID. And I'd heard the nurses talking about other nurses coming in, you know, not coming in in their work clothes, wearing their uniforms into work, and everything. So I just thought there was nothing they could do for me.

Some participants were suspicious of the motives behind clinical smoking cessation services. Moral judgement was sometimes assumed to be an inherent part of the service.

Karl:

smoking is crap and – I can understand where they're coming from because I bet it costs the NHS a fortune. Every year. So I do understand where they're coming from and if they're – they are there to help you, so. I'll always come to appointments, cause I always need to know that my foot's all right. So that outweighs being nagged at for smoking, for a few minutes, in my eyes.

Maria: Obviously everybody's different, so I appreciate you-

Karl: Yeah, yeah. Well that's how I see it, yeah. They've got every right to moan at me, so, it's only a few minutes. I can cope with that.

Luke:

I wasn't particularly sort-of over- you know, crikey, and and then he went on to tell me what a bad person I'd been! That I shouldn't smoke. And I should do more exercise [sing song voice] and you know my diet was bad and this that and the other. There weren't an ounce of sympathy about the fact that I was gonna have to have a major operation. There was NOTHING.

Perhaps you get sick of seeing people that are erm you know sort of doing, that do things to themselves sort of thing, you know. And that's why they've got that attitude. I totally understand it, you know. In that respect, sort of thing, you know.

6.6.3.3 Knowledge of the relationship between smoking and post-operative outcome, outcome expectations, and other influences on the assessment of capability and motivation from narrative

Some participants described understanding the relationship between surgical outcome and smoking, and recalled that this formed part of their conversation with the surgical team.

Grace:

> Maria: I don't know if anybody has mentioned smoking in clinic today?
>
> Grace: Yes, quite a bit about the recovery, and healing, and- so ideally, I'd like to not be smoking when I come for that. That would be the- what I'd aim for. So that I can improve – my chances of not reinfection. So.
>
> Maria: Was any of that a surprise to you.
>
> Grace: No. It's allr- I already knew that.

Karl:

> [It was/You would] say it's daft really, but. [Sniffs] Yeah, so I think, as they kept on saying, that really affected my foot, I smoked loads that first time. [Sniffs] And they kept on saying obviously the foot's far from your heart, that that smoking would be bad. So [sigh] – stupidly I still do. Hm.

Zac:

> Zac: Well, [sighs]. Um. [Long pause] Got to give up [smoking] from the, erm, from the doctors. [Pause] Before I have an operation.

> [Mhm.] Well, can't afford them really. Trying to get on, to the prescription. [Yes, uh huh.] [Pause] Yeah. So I got to give up before an operation.
>
> Maria: Did the doctors explain why that's a good idea?
>
> Zac: Yes.
>
> Maria: Do you remember what they said?
>
> Zac: Yes it's because my – the veins feeding the lower foot, it's — they're very slow. [Uh huh.] So, yeah. That's why I, that's why I [need to] give up.

Ricardo:

> He [the surgeon] told me about my recovery time, he also told me about being in hospital for a week. At this point he discussed with me, giving up smoking, so he told me what benefits it would bring to my recovery. He also asked me about alcohol, if I would drink, I told him I don't drink, well I'm not a drinking person. So on that day [sighs] I took it – all home. Uh. And, well I started to, well I completely stopped smoking.

Participants who continued to smoke mentioned on a number of occasions that they knew about the harmful effects of smoking for other aspects of their health, but that this information was insufficient to allow them to change behaviour.

John:

> Maria: So nobody can help you if you don't understand you have a problem.
>
> John: Yeah! Yeah. You need understand, yeah! I feel strong for my-

self, me not need help [from] everybody, no. If I smoke I do, I know, bad for my health. Everything. Plus for me it's VERY bad. Because [Rheumatological condition], you know. It's VERY bad, I killing myself. [Pause] I understand normally everything! [Laughs] Yeah. [John was still smoking regularly at the time of the pre-operative interview.]

Judith:

Maria: Did any doctors talk about – surgery and smoking? Before you had your hip done?

Judith: No, no. The only one that did say something was the surgeon at the [NHS orthopaedic hospital]. Said that he wouldn't operate because I smoked. But at the end of the day, I take – I do still have the roll ups, the odd roll ups, I do. But I also, instead of having them all the time, I have the mints that I suck. [Pause] So they're all right. They're all right. They're much helpfuller. They're much more helpful than anything else I've taken.

Karl:

[It was/You would] say it's daft really, but. [Sniffs] Yeah, so I think, as they kept on saying, that really affected my foot, I smoked loads that first time. [Sniffs] And they kept on saying obviously the foot's far from your heart, that that smoking would be bad. So [sigh] – stupidly I still do. Hm.

(. . .)

Karl: Well they said so it's the furthest part away from my heart, so it's more likely to get infection if you carry on smoking, because the blood can't get to it because it's so far away. No it's, so. I knew the risks before I came in and had it done. [Sniffs] But because as I say I've had so much surgery where I've always healed quickly, and I've smoked? Maybe it's because I've got a bit older, or something, erm. But this time, yeah, I was well aware of the risks, and never really listened, stupidly.

Maria: It's because you've got away with it in the past, is that-

Karl: Yeah, that more than anything, yeah. Yeah so I've always thought, yeah, it's all right, smoking, yeah, everyone bangs on about quitting smoking, um, but yeah, it was actually true this time. So. It did bite me in the bum, I should have listened.

Luke:

You know many years ago, when I did originally break my leg, my doctor said to me, when it was done, I went to see him, I smoked, and I and she said look, you really ought to give up smoking because it helps your bones knit better. And you're overweight, you need to lose some weight, you need, you know, to help this along sort of thing. It was a regular occurrence.

(...)

I – most of my information comes from [District General]. Hospital. They were very generous in, you know, they'd sit down and go through stuff with me. Explain the issues about the metalwork, you know, and they err – obviously in my case it was through the metalwork where the – he said that when the metalwork was fitted, he goes, the infection was fitted with it. It's quite common, you know, for it to happen. And it's been there ever since you had the metalwork in there, but your body's actually dealt with the infection itself. Without a problem. Obviously the problem that you have is that you've got cancer, you had chemo which lowers your er immune system down even lower, and it's, it's, it's come out to play. And it's creating havoc.

Ricardo:

When Mr. [Surname] spoke to me it was the – the – effects, that smoking does on your, uh, healing, so – it will take you longer to heal, it will be – er, more difficult to heal. It can be more susceptible to, er, infection and all that if you are a smoker. I thought, well I'm going to have to stop smoking, and so the first thing I've done, I erm – I went to an er, one of those vape shops and I reduced the amount of nicotine I was smoking, but that wasn't working too well, so.

Becky:

Becky: Some people go to food, some people go to drink, I went to, I smoked. [Pause] So. [Pause]

Maria: And was there anything different this time, er, in terms of making your decision?

Becky: [Pause] That I don't want to end up losing my foot! [laughs] Really. And I don't want to be in that position, where, I've got to learn to, walk again. [Pause] It took me a long time, it took me nearly, well, nearly a year to, learn to walk again. And [pause] I, to be – I don't want my little girl seeing that ever again. [Pause]

Maria: So sort of the fact that you'd already had that experience, um, sort of set your mind, is that right?

Becky: And I know how hard it is. [Yeah.] And I, and I don't – yeah.

> It's – it's like being a baby again. It's, it's horrible. It's painful, it's not pleasant. (Not pleasant at all.)

Contrasting Karl and Becky's experiences, and their interpretation of medical advice relating to smoking and their orthopaedic problems, one of the factors that appeared to affect their interpretations was whether or not they had had successful surgical treatment previously, and the kind of effort they were expecting to go through during their current recovery. Both Becky and Karl had been through their definitive infection surgery at the time of interview, and had had a chance to reflect. Evidence from more participants may have been helpful to identify whether 'getting away with' a behaviour such as smoking during previous surgical recovery, as a salient event, might be important in some people's reflective motivation to change behaviour.

6.6.3.4 Nosocomial infection and behaviour change (motivation)

Several participants were clear that their infection was hospital acquired, which implied that other factors (such as existing health conditions and behaviours) could not have contributed to it.

Ash: [Attribution of infection to revision surgery]

> And that total knee replacement lasted twenty years. Which was longer than I was told it would last. So the reason I'm here now, in this situation needing a second one, which is called a revision – er, surgery, is because it has literally had its – shelf life was coming to an end, got infected, and it, so things have gone wrong since then, with a second knee replacement. So that was when it began, about twenty years ago, with my left knee.
>
> Because apparently an artificial joint attracts bacteria like a magnet.

And I didn't know any of this. So that's what happened, and it's got to be removed, and it can't be, because I've got a broken femur now.

John:

John: Yeah. After I go hospital, is broke arm. Doing operation. And after, have infection from hospital. It's from hospital is MRSA! Not from anywhere [else]. And, [this hospital-acquired infection was the] start [of my] problems til now!

Maria: Uh huh. And how-

John: [abruptly interrupting question] Sorry I don't know how. [Pause] Two years.

Karl: [also described walking miles to friends' houses within 7 days of foot surgery after leaving hospital against clinical advice]

Karl: Now I can't, can't remember the name doctor, who'd actually done the surgery. But I started seeing some bloke, some blond bloke with curtains? If that makes sense. Can't remember his name. And he came and, and that's when he said, he said I'm walking too much. When I was thinking it was an infection?

Erm. And I also think they set it too straight. Cause now it's been set over? When originally it was like that. So it was-

Maria: So it was pointing along the same line as your foot, whereas now it's pointing a little but further round.

Karl: Now it's in touching a bit more? So I think that was the problem as well? Because I could just not get it in anything, any shoes properly, where now I can? [sighs]

Luke:

It was never really diagnosed as, I mean, I got told all sorts of weird and wonderful things, you know. Obviously the old adage was "I was a bit overweight," I mean, everybody is, erm. Because obviously the issue with the leg went back to 2008 where I smashed it all up basically, had some metalwork in it, and the general consensus was that it was just general wear and tear, but obviously it turned out not to be that. [laughs] Yeah?

(. . .)

But yeah, he was pretty harsh, I'll tell you something else that I find really strange as well.

Maria: Go on!

Luke: Really odd. And I ca- you know, I am perplexed, sort of thing. I am CLEARLY overweight. And I always have been, for, christ, since my early 20s. I'm not GROSSLY overweight. But I'm generally I'd say about a stone to a stone and a half overweight. [Sigh] and d'you know, obviously with these, with the heart condition that's come along et cetera, no one, but no one, mentions your weight.[Pause] No one. I can't understand that bit.

Maria: With the, with the heart condition?

Luke: Well, you can imagine if someone turns up, sees you, and they say well, you've got this heart condition, and they're sitting there weighing x amount of stone, you would probably say to them, d'you not think you're slightly overweight, perhaps we ought to look into that. You know maybe we could help you with your lifestyle. [Sigh]

> No one has ever mentioned my weight. Ever. Through all my, you know the only time my weight has ever been mentioned is about my leg. Yeah.
>
> Maria: Right. Uh huh.
>
> Luke: Which I never thought had an awful lot of bearing on it. I think I was right, in a way. Yeah. Um.

Some instances of overt hostility in the transcripts above (such as abrupt interruptions and raising the voice for emphasis), may be consistent with reactance to perceived or actual recommendations for peri-operative behaviour change, as all interviews were conducted by a healthcare professional. (Steindl et al., 2015; Reynolds-Tylus, 2019)

Many narratives described instances of poor healthcare. Moral licensing or spillover may play a part in some narratives: describing how one has been wronged by a healthcare healthcare provider may grant the participant a degree of leniency towards their own behaviour.(Dolan & Galizzi, 2015) Patients may justify less input towards their own treatment if they receive poor care.

Jack Howard

> JH: Yeah I'm on methadone, prescription via [specialist addictions service]. When I went into [City] hospital this time round, they went, bang! There's your- because they took- I was on 80ml, they've cut me straight down to 60. So they've taken a quarter off me. Without even consult- I mean, I know they do it. Sort of, thing, so. Because that's become part of my pain, you know what I mean. [Maria: Pain treatment?] Uh huh. It's made it, it's been even worse and even harder. [Sigh] To sort of even do anything or function, because, I'm with-

drawing! At a time when I'm in constant pain as well, you know? So I think, yeah, that is not the way to go about things.

(. . .)

Basically I found out there was infection in the bone about twenty minutes ago, like. [Maria: Right.] D'you know what I mean, like when people would talk to me straight and gone, "this is how it is," right. People don't think I've got the capability and the ability, I don't know if that's how I'm perceived, sometimes I would be talked AT and not TO.

Becky:

Yeah, they, yeah, they just kept going, coming back with different answers, of what they were going to do, or they didn't know what was going on, and you just think to yourself, well, I'm sitting here for two and a half weeks, not knowing? And plus my family don't know. They are the ones at home with my little girl, getting different answers every day? So it was just not fair. On anybody.

John:

John: Yes and, yeah, and doctor not give me sick note, nothing. Leaking arm and I go work, it's not normal. [Pause] I'm very angry about all doctors. [Fair enough.] What I see.

Maria: Tell me more. Tell me more.

John: Because not help me. I say, and before when first time I go – I go in [General Hospital], when, first time, when this infection I get. And, how can work like these doctors, if [they] say, I don't know what need[s] do[ing]. And keep at me in hospital. And put,

> you know, antibiotics. And this for me stress by [my having to] say, you do something! [To the doctors.] If you n'understand I not say, all doctors, everything, understand. If you n'understand, I say, WHO understand! Yeah. And me need, shouting, something [I needed to shout, or something]. After [I shouted, it was] OK, [they then] send me in [Local orthopaedic referral centre]. That's – it's not normal, needs shouting, too. You know, be[ing] angry. After [shouting at the doctors], [they] help you. If I [had] not say[d] nothing, I sleep in this bed [in hospital] and [would still be] waiting! Then! I feel very bad.
>
> (...)
>
> I think so in England more better doctors who looking, animals, you know. [Maria: Oh, vets are better!] Because, you know, pets in England is very high [important]. Or, I think so, people second. [Laughs]
>
> Maria: Yes, I've heard that from other people too.
>
> John: Yeah yeah yeah yeah. If you have dog, you go to doctor straight, if have problem, infection in arm. If I have, me need wait half year. [Laughs]
>
> Maria: I see, with a dog you can have it done straight away, whereas with you, you have to wait-
>
> John: Yeah, it's like this!

The context for any peri-operative smoking cessation interventions includes the quality and safety of healthcare, as well as the continuity of care provided both in hospital and in the community. Continuity of care was discussed separately with several participants. Improving the quality and safety of clinical care may improve the uptake of clinical interventions designed to improve treatment outcomes, including peri-operative smoking cessation, through the effect on participants' trust of clinicians, and the value and success of communication and interaction between people affected by bone infection and clinicians treating them, and through the behaviour change mechanism of monitoring (with or without feedback).(Michie et al., 2013)

6.6.3.5 Social context, social and physical aspects of opportunity in smoking cessation experiences

Some participants were very attuned to what they saw as the intentions behind social policy that affected their experience with behaviours relevant to health. For example, Ash was sceptical about changes to cigarette vending.

Ash:

> And all this, they've stopped making packets of ten, they said oh we don't want to make packets of ten, because it stops children from buying them. That's the biggest load of rubbish I've ever heard in my life. It's to force people – no seriously I'm not stupid, and I won't buy into that idea. It's to force everyone to buy twenties, but the good news is, less and less people are smoking nowadays anyway. And I think in a few years' time you'll be made to feel like a complete pariah. If you're smoking, out and about. There are genuinely a lot less people smoking. Vapes are a bit of an issue but that's none of my concern.

Financial restrictions featured in the reflective narratives made about smoking and the benefits of smoking cessation by several participants.

Joseph:

> Maria: You gave it up on the same day, OK.
>
> Joseph: on the [Day of Month] [Year] it was. No, [Year] I think it was, Maria. I used to smoke about sixty cigarettes a day. Embassy number ones I smoked. Or Benson Hedges, whatever I could get hold of. And also I was drinking about a litre, a litre and a half of vodka a day. And I sat, I was in my bungalow in [City], about [Year] it was, and I thought, where's my money going. I looked at my bank statement, looked in my wallet, thought, "bloody hell. I'm not doing very well here." So I went through my outgoings, saw how much I was spending each day on cigarettes and alcohol, so I put a drop on it there and then. And then finances improved. No end.

Grace:

> But also, we think – that – we would have a better quality of life, more money, et cetera.

Ash:

> Well if you think about it, £10 a day is £70 per week. [A lot of money.] £280 pounds a month. [Pause] All right there's nowhere to go, but it's a holiday one day! [Laughs]

The narratives of some participants directly questioned the role of healthcare contact as a "teachable moment" for behaviour change, as alternative explanations for short and long term quit attempts in the healthcare context emerged, including the loss of control over one's physical environment or body due to hospital admission and clinical procedures. Some participants said restrictions to smoking, whether in the hospital or other environments, shaped their smoking behaviour. It is plausible that physical restrictions may have greater impacts than reflective motivation:

smoking relies mostly on habitual, automatic behaviours.

Ash:

> Secondly being in a confined situation in hospital with, attached to a er uh machinery and stuff like that and equipment, I can't smoke. So in a way [laughs] being in hospital has helped. And being an inpatient in hospital has helped me with, erm, not smoking. And not drinking! So bizarrely there's been some positives about being an inpatient in hospital. Uh yes, I've had the occasional cigarette as an inpatient in hospital, but at the moment I can't even walk. So I can't s- get up. Go out on crutches or a wheelchair to the side of the building and have a cigarette, so that's helping me.

Zac:

> Maria: What sort of things did you do, and tell me in what sort of context that happened. Like, what else you were doing at the time, and why you decided.
>
> Zac: Well I was actually in hospital. [Maria: Right.] At the time. So I couldn't, so I couldn't go out. Out of the hospital. So. Yeah. So I gave it up for a bit.

Karl:

> I can't exactly in a hospital bed sp- light up a fag, where as I can set down the side of my sofa to light up a fag. Um, I think that's the thing. Me- down to my – willpower. I suppose? When you're told you can't be- can't do something, and you know you can't, you put it to the back of your mind and say, sod it, I can't, I can't fight it, so – whereas at home, there's nobody to say, right yeah, you ain't getting

out of that bed, you can't go and do it, so. With every week like that, unfortunately. [Pause]

So I think – it was a good thing keeping me in for eight days, although I know it ties up a bed in here for eight days, I think it's better to keep somebody like me in here for a bit longer, personally, but. In my eyes, anyway. Well it was for me, anyway.

(...)

And I think that's another reason he wanted to keep me in for eight days. Cause it meant eight days of me not being able to smoke. Which amazingly I actually stuck to. It r- I had patches, but they've never worked before, and yeah, I didn't crave a single bit.

Luke: about quitting after cardiothoracic surgery

So you're cuddling a tea towel all the time so I didn't kno- after I came out of hospital it was so painful, I was so scared of coughing that it hurt so much that I stopped using the e-cigarettes as well! [Laughs] And that was that!

Ricardo:

Because when I was smoke I cannot smoke, like, in the office, or- and unfortunately some companies still accept, well, ah, it's just a vape, you can vape. Does that make sense? So you're indoors and you're vaping, while before it was –

But the thing is, because- just there, it's mostly, this is not, something I'm affirming one hundred percent, it's just my opinion, but because vaping is there and because you can vape pretty much everywhere, because it doesn't smell, you vape inside the car, you vape at home,

> you vape in the toilet, you vape – anywhere. So, [Laughs] I think it's even worse!

Grace:

> Erm, and, I'll do little things during the day, like- and also we've got a new car and he won't let me smoke in the car. So, erm, that's a – that's a good thing, for me! Because it means that, I leave them at home. So I go and do, the school run, go shopping, and they're not there. So I can't go and smoke. So that's helped me cut down.

Only one narrative, that of Ricardo's discussion with the orthopaedic team, described reflecting on smoking behaviour in the context of illness or healthcare, while not under duress or conflict with healthcare providers, suggesting that it may have been less teaching, and more necessity, that drove changes in smoking behaviour during healthcare contact for most participants. This is in direct opposition to the framing of healthcare contacts as "teachable moments."

6.6.3.6 Social context, the role of personal relationships in smoking cessation experiences

Other people who smoked, including cohabiting partners, spouses and friends, were described as in some cases facilitating and in some cases obstructing quit attempts, such as those who smoked in front of the participant, giving a cue or reminder about having a cigarette. Additionally, benchmarking against norms in a social group or geographic area, where a higher proportion of people might smoke, might make quitting smoking feel less normal.(Cummins et al., 2007; Thompson et al., 2007) As relationship assortment is not random, interventions that target participants' cohabitants and social groups may be more effective than those that target only the participant as an individual.

Zac:

Maria: And can I ask, does your wife smoke?

Zac: Yes.

Maria: She does. OK. Has she ever tried to quit before?

Zac: No. No.

Maria: Have you ever talked to her about quitting before?

Zac: Er, no.

Ricardo:

Maria: Erm, and can I just double check, does your wife, does she smoke? Or did she used to smoke?

Ricardo: Er, she did before, yeah. She stopped two years ago and I couldn't. [Uh huh.] She managed to stop, but I couldn't stop. [Pause] Well when I said I was going to stop smoking, she said, I don't think you're going to make it, but I'll help you. [Uh huh?] But well, I made it! Yay!

Luke:

And obviously my missus hated me smoking anyway. Cause she doesn't smoke.

Maria: She doesn't smoke. Uh huh.

Luke: She does not, no. But I mean she's fair, she's not. 'ooh you can't smoke in the house whatever like that,' you know, I did, I do, I do what I like, fundamentally? Which is nice? Er, but, uh, yeah, she,

she didn't like the idea of me smoking anyway and she thought that it was a jolly good idea that I stopped as well. So yeah.

Ian:

I thought of it myself, because my ex-partner, she was still smoking whilst I was doing it, so that- that made it a bit more challenging. But no, otherwise I done it myself.

Maria: Brilliant. And how did you find the experience? Was there anything that you found particularly challenging?

Ian: [Pause] Not – I suppose when I was out socialising. Erm, that was the more difficult part. Erm, because [pause] a lot of my friends were smokers, and obviously when we were going out and drinking and everything, everyone's going out smoking or smoking at the table we're sat at, et cetera. So that made it a little bit more challenging. But otherwise – no I didn't find anything to be too much of a challenge, I just got very irritable very quickly. [Yes, mhm.] I think other people found ME to be the challenge.

Grace:

Maria: Uh huh. So it sounds like you've tried this before. Can you tell me how that went?

Grace: Yeah. It was great. And then he was at home, and he had a cigarette right in front of me, and I went- I'd given up for about two or three weeks? And I went, oh, one won't hurt. [Pause] And that was it.

6.6.3.7 Commitments to others, social aspects of opportunity

For some participants, commitments or obligations to other people close to themselves provided an incentive to quit smoking.

Becky:

> I don't want to end up losing my foot! [laughs] Really. And I don't want to be in that position, where, I've got to learn to, walk again. [Pause] It took me a long time, it took me nearly, well, nearly a year to, learn to walk again. And [pause] I, to be – I don't want my little girl seeing that ever again.

Grace:

> Um, however, I promised him, I would give up smoking. Before he died. And I'm very mindful that I promised him I would. But also, we think – that – we would have a better quality of life, more money, et cetera. It's been very much since Christmas, that we've gone right, d'you know what, I need to do something about it. Especially with the hike in the prices as well. Erm, and, so we've been making a concerted effort, to cut right down?

The example below highlights the possible concerns about relying on non-professional close relationships to support quit attempts. It also supports the role of nurturing, rather than abusive or disempowering relationships, as providing greater reflective motivation and social affiliative soothing to combat the discomfort of nicotine withdrawal and habit change. (Gilbert, 2017)

John:

> Maria: Yes, so if you don't want to stop-

> John: Yeah, because you're not helping, for- maybe kids, when you training [when you are raising children], you can say stop. I remember, when I time – when I was, I don't know how old. Very young. I try smoke. My father give me, couple times, belt – and straight, I stop. I now can, you know, say, give me now, fifty times belt! No but I won't stop, now not help this. [Laughs]
>
> Maria: "Even if you belt me fifty times, it's not going to make any difference if I don't want to do it"?
>
> John: Yeah! I'd be happy if helps like this. [Laughs]

6.6.3.8 Help-seeking behaviour, personal strength, and social aspects of opportunity

Some participants voiced their own need to be 'strong' or 'stronger' to overcome their addiction to smoking, and in some cases to cope with other aspects of their healthcare experience simultaneously. This drive was in opposition to seeking help from others. For example, John explained:

> You need understand, yeah! I feel strong for myself, me not need help [from] everybody, no. If I smoke I do, I know, bad for my health. Everything.

Ricardo said that personal strength was required to stabilise and reduce the nicotine intake when vaping:

> It helps you, it helps you, but you need to be strong, very strong, and er very, [pause] [sigh] strong-minded person to just smoke that quantity, don't go over that, and be able to, um, reduce, so.

Becky described the need to be strong when undergoing treatment, of which smoking cessation was a part:

> You just got to, get on, with life. Especially when you have little ones. It's hard. Don't get me wrong. I find it really hard. But – what am I to do? [Pause] Cause I've got to be strong for my little girl.

Ash described the internal drive to be strong and deny the help he needed as something in his past that he wanted to avoid, and urged others seeking treatment to avoid as well:

> In my experience, if I may say this, just don't sit there, knowing you want help, need help – the point I'm making is don't be afraid to keep asking. Don't be afraid to keep asking, no matter how small or trivial it is, don't be afraid to ask, because somebody can't help you unless they know what help you need. And I've realised that. I'm literally asking for all the help I can get now. So ask for it, don't bottle it up. Because that's what I used to do, and – that's what they're here for!

The expectation that one has an obligation to demonstrate personal strength, may undermine self-efficacy in smoking cessation attempts. Particularly in situations where these have not led to long-term abstinence in the past, people may see themselves as falling short on this virtue. This framing can act as a social barrier to seeking the necessary help to achieve long-term smoking cessation.

6.6.4 The role of despair and spoiled identity, (de)motivation arising from limited capability and opportunity

Learned helplessness is a behavioural state in which there is reduced motivation to escape a harmful exposure, following failed attempts to escape from it.(Hiroto & Seligman, 1975) This may be relevant for some people in the peri-operative period.

Illness, including infection, and behavioural habits that negatively impact health, can contribute to a person's self-categorization as a lost cause, or 'spoiled identity,' that correlates with reduced motivation to care for the self and avoid both current and future harm.

People experiencing infection with hepatitis C, including those infected through blood transfusion, described a state Susanne Fraser and Carla Treloar observed, that is characterised by

> the internalization of stigma, the acceptance of one's health and identity as irredeemably and utterly spoiled, and the conviction that acquisition of further discrediting attributes cannot make the stigma any worse.

(Fraser & Treloar, 2006)

This mindset may be held by some people affected by chronic orthopaedic infection, particularly if, as many described in their semi-structured interviews, they have already experienced failed treatment on a number of occasions.

Interventions that improve on a person's capability and opportunity to change behaviour might counteract a state of 'learned helplessness' or 'spoiled identity' and the resulting low motivation to avoid harm. Compassionate care can ensure that people retain access to social affiliative soothing, entitled to care despite feelings of shame or spoiled identity. (Gilbert, 2017)

Learned helplessness manifested in some participants' experiences of healthcare, including Becky's:

> I just didn't feel very [sigh] – not important, but just not a – don't know. I don't know, I just can't find the words, really. [Makes sense.]

> I just got to the point in life where – I just turn up and [pause] if they say this is going to happen, it happens.

Becky identified that compassionate care may have improved her engagement with her treatment:

> Maria What do you think is the way that you should feel?
>
> Becky [Pause] Well, cared for really. I hope. I just – [pause] Not just an NHS number. An actual person. Would be nice.

Spoiled identity and social disaffiliation manifested in difficult interactions with healthcare providers, as described by Jack Howard

> I've been living with active addiction for uh, thirty years. And eh, I've been suffering the consequences of the lifestyle.
>
> (. . .)
>
> So I just switch off when the fellow was going to do that, I wouldn't even start listening, because what's the point. But to be talked to and heard, spoken to as a human being and not as a junkie on the blag, or – which is not really where I'm seen, with the pain relief and blah blah blah, you know what I mean.

Karl found himself particularly sensitive to comments from healthcare providers that reinforced his sense of spoiled identity, as someone who used methadone as part of recovery from previous heroin use, and had come to expect them

> Every op- every operation I've ever had, erm, as soon as they know I'm on methadone, like I say the first thing they bang on about is, will we be able to find any veins? Um, [sniffs] And it's just some throw-away comments, in the past, by other hospitals. Like, oh god,

> what is it. "Ah that's just like morphine, that's just like heroin, that's just like, you'll like that." And just, I've had all sorts of throw-away comments over the past. So you do tend to get just get- assume, that that'll happen every time. Soon as you mention methadone, you – ooh, dealing with a drug addict. [Sniffs] erm. [Pause] So yeah, that – didn't feel so much like it this time. So.
>
> (...)
>
> yeah, you do get treated differently. Unfortunately.

Karl compared his primary surgery to his more recent experience having treatment for orthopaedic infection, suggesting that a different approach from clinicians led to a perception of better quality care:

> So it's been good the second time around. The first time wasn't too great, keen on it, but the second time was totally different. [Sniffs] So it's been good.

Other behaviours that impact health, including alcohol use, diligence in taking care of existing medical conditions, and eating, may also be influenced by judgements of moral worth, and may contribute to a sense of spoiled identity.

6.6.5 Alcohol drinking in the perioperative period

Ten of sixteen participants discussed peri-operative alcohol drinking, of whom four did not drink alcohol at all. Because alcohol drinking is a socially normative behaviour in the UK, and because national guidance defining limits of normal alcohol consumption has changed with time, participants' (and the interviewer's) conceptions of healthy levels of alcohol intake were culturally bound and sometimes uncertain. Social norms have a strong influence on both drinking behaviour and self-reporting of drinking behaviour. (Tourangeau & Yan, 2007)

Normative and moral framing, and comparison with other behaviours seen as having an impact on health, were noted during some participants' interviews. Ash referred to alcohol as 'naughty':

> But it started to get – errr, wean myself off, and because I'd spent so much time in hospital as an inpatient it was impossible to drink even though I was a bit naughty and had it a couple of times while I was an inpatient, but not all the time. I weaned myself off, where my tolerance has come right down.
>
> Because [City2] is a naughty city! It sells alcohol twenty four hours a day! And I could buy it! I didn't do it often, but I did! But that's when I couldn't sleep and I was hitting my lowest points.

John compared the relative health impact of alcohol drinking and smoking, as he thought it was perceived by doctors:

> Maria: So you want to quit for good, mhm.
>
> John: Yeah yeah yeah yeah yeah. That I know, fifty grams [of alcohol] in but not smoke. For arteries, you know, like, say all- all doctors, you know? [Laughs]
>
> Maria: It's true, it's true, it's [quitting smoking] the single best thing you can do for your health.
>
> John: But not I mean beer or something, you know. Like vodka! [Laughs] Because arteries psht, all time. I joke, you know, but it's real. All people talking like this.

Social norms around what level of alcohol intake was 'normal' and what was 'excessive' were at the fore of most descriptions of alcohol intake. Participants minimised how much they drank. One counterexample was found in Jack Howard's interview. As someone in a social group with different norms, whom he referred to as 'self-respecting junkie bod[s],' Jack Howard may not have internalised wider social pressure to minimise reported alcohol intake.

Ash:

> But I still drank, but not excessively. I did not drink excessively, not every day like I used to, and as I said my tolerance had gone where – I could hardly drink without feeling a little bit, like, weak and uh giddy and stuff like that.

Bill:

> That time my week I was, one, two cans? Sometimes three cans, but you know, light, not heavy, not strong.

Ian:

> I'm not a heavy drinker. I would drink [pause] on a night out I'd have a few drinks, but, erm, it's not a regular thing.
>
> (...)
>
> Uh with secondary surgery, no. No I didn't have- I wasn't drinking – uh no, probably actually was, once a week, but at home, wasn't going out and having a drinking session, but yeah at home I was probably having er, a few drinks once a week.

Paul:

> Not, no. Less frequently than weekly. A few drinks every couple of weeks when I had visitors, but not, not, not much.

Surgical treatment and medications often forced a reduction in alcohol intake:

Jessica:

> Um, I think – it was only really the first year of uni that I was drinking a bit heav- more heavily, but in this last year I've, I've not been, no. [Pause]
>
> Maria: You've not been – that hasn't been part of your habit. OK. [Jessica: No.] But it's not something that's changed based on the symptoms that you've had recently.
>
> Jessica: No, I mean what with my medications I can't drink anyway.

Ian:

> Errm, r- [pause] way back before the first lockdown. I was, erm, out a lot more, and going out two or three times a d- a week drinking, but nothing, [pause] to an excessive point. But not before the second surgery, no.

For those participants who felt able to discuss alcohol drinking, ease of access to alcohol and a lack of other activities, either because of disability, COVID-19 lockdown, or both, increased their alcohol intake.

Ash:

> It would take me, from my home, get out of my chair, get down my stairs, on crutches. To go to the off license. The walk there was two minutes. It was too easy! It was just too easy.
>
> (...)
>
> Uh, how, how is it possible, that everything else, is IM possible, to do, and yet the EASIEST thing to do, during these periods, for me,

was to buy alcohol. HOW does that make sense. I can't compute – with that. I just can't.

Bill:

Two, two [cans of beer a day]. Sometimes two, sometimes three, like that. Because nothing to do, so. Just I feel like to sit down and – watch TV and just, er – open can and just sit and- that's it. And now from five months, six months, I no[t] drink at all. [Yes, uh huh.] And I not feel like to drink as well. Yes, sometimes when some sign then little bit feel, but I've not to drink it, no. Yeah. Yeah. That's it.

Ian:

So whenever we'd go out to the supermarket we'd – I'd get, I'd buy [sigh] whatever I needed, and there was the occasional purchase of, of the rum, and but I'd always have [Branded Cola] like every day.

Jack Howard:

so I get a taxi to [Supermarket] and spend the twenty five quid. So and, er, end up with a couple of four bottles of sherry. Like four litres of sherry. So I take one with me, and then have the rest of it delivered. That became a cycle. Know what I mean, so it was costing me twice as much, three times as much, to forty, fifty quid a day, but, because where I'd been in hospital I had money on me as well, that became like, ease of access. It wouldn't have happened, because I wouldn't've been able to walk, because I'd have been in too much pain, but taxis, and [Supermarket] deliveries made it easy.

Paul:

Ah. Let me think. So I'd- it's a few years ago since I sort of, vastly

> cut down drinking. You know I was an every day drinker, whereas now I'm just socially when I have visitors or go out. But otherwise from that, I don't know if I've been doing anything differently. I was – cycling more.
>
> Oh something I've found, because I don't know, I've always had depression. And I've found that after, I don't know, two years of [treatment], that started to lift. And I was, yeah. And I can't say, you can never say about cause and effect, but I just noticed that I was feeling better, and I was getting out every day, cycling, but that was only really probably a couple of months, and then I had the fall. And everything's – gone backwards.

In summary, participants described drinking alcohol out of boredom and for short-term emotional self-regulation, but many were attuned to the changes they noticed in their mood and bodily functions as a result of changes in alcohol intake. Pain was not described as influencing alcohol intake by any participants. The facilitator of alcohol use described with greatest frequency was the ease of access to alcohol. This opportunity factor is outside the healthcare remit.(Michie, van Stralen, & West, 2011b)

Social norms for alcohol intake affected how participants described the amount they drank, but it is less clear whether norms and limits were also acting on how much alcohol participants actually consumed. Labelling an activity as 'naughty' may not deter people from engaging in it.

6.6.6 Management of concurrent medical conditions in the perioperative period

The most common medical condition discussed in interviews was diabetes mellitus, which affected four of the sixteen study participants. Due to the heterogeneity in the medical conditions, the intensity of management required, and the relatively small number of interview participants able to share experiences pertaining to a specific condition, the factors specific to concurrent orthopaedic infection were the predominant focus of the analysis. This allowed a limited examination of the management of comorbid illness in people with orthopaedic infection. Thematic saturation in this topic was not reached.

Moral framing was observed in relation to the control of blood glucose for some participants affected by diabetes mellitus. The word "control" was interpreted as "self control":

Bill:

> Diet control? You know? And, I never eat chocolate or anything like sweet. And I control myself. Because I used to, to work weekends in a restaurant, and there is lots of sweet. But I never put sweet in my mouth! [Laughs] I control myself. [Maria: Uh huh!] From that day I always control myself. Hardly, hardly go over ten, hardly. My sugar.

Orthopaedic infection had an effect on glycaemic control in diabetes, and vice versa. This was discussed in detail by Ian:

> No, the main effect of it was that it made my blood sugars higher because, well, I was fighting the infection. Erm, so that made it more difficult to control because – every time I was having insulin, it would bring my sugars down, but then the next time I'd test it, it would be

straight up to being a high number. So that made it more difficult and that made it, actually made my HbA1C level, like the overall – control, go very high. I mean at one point it was like at 15, 16. And now back down to 10. So it shows what the infection could have done to it over the time.

(. . .)

I had a diabetic specialist er come in to see me while I was there, because obviously my control wasn't great, and, erm, throughout the infection time they were, erm, my blood sugars were going low, high, low, high, low, high. The entire time. So they came in and said that [pause] basically with the insulin and everything that I was taking, and the food and everything that I was eating, that I was 'feeding the infection.' So it was linked, obviously, partly to the diabetes through that, because if I wasn't having as much insulin, I wouldn't be eating as much, and then feeding the infection.

6.6.7 The effect of continuity of care on service engagement

I introduced additional questions about continuity of care, after early interviews suggested that this played a major role in the preoperative experience.

Experiences of care continuity were variable. Having to communicate a clinical history anew at each contact may have made people less able to hear and comprehend what clinicians had to say, due to dual-task competition. (Strayer & Johnston, 2001) This is illustrated by Becky's experience:

Maria Did people sort of, seem to be talking to each other and know what everyone else was doing?

> Becky No. Didn't have a clue.
>
> (...)
>
> my GP and consultant was so hard to get hold of, it was either not in, or [pause] we have some doctor phone you back, that hasn't really got a clue about you – they seem to constantly ask like, "oh well tell me what happened four years ago." Not every time, I speak to somebody, I want – to relive it.

For Jack Howard, the lack of communication between his hospital clinical team and his addictions service support worker, provoked acute opioid withdrawal symptoms, which was an additional burden on his self-regulation

> they don't interact with my [specialist addictions service] worker, my methadone prescriber, but before consulting with them, they've gone dumf [reduced the prescription], and then that's it!
>
> (...)
>
> There ain't no one to explain it to and no one to talk to, you know? Just gets ignored, you know? It's really really frustrating.

Judith also experienced treatment delays due to the failure of her private healthcare provider to inform her GP of the complications of her surgery.

> And then I said I reckon they've given me a recycled one, because everybody I spoke to or know, they've had a hip operation, and everything's been fine! I have mine, in a private hospital, and mine goes tits up!
>
> And the thing is, they knew that I'd got this infection. And they didn't even notify the GP. And that, I think, is neglect. I really think it's

> neglect. Where they knew I'd got it, and they left me for ten days with it, it might not have got to the stage it had got to, you know what I mean?

Having multiple providers involved can be confusing, particularly when other cognitively loading symptoms are present, as highlighted by Judith's experience

> So I rang up the hospital at the [General Hospital 2], no, the [Orthopaedic Hospital] and I said, no, this is stupid, I've been waiting since, this has been going on since June. And we are now in February. Eight months, and I can hardly walk some days, I can hardly lay on my left side, the pain in my hip is horrendous, I don't know what to do with it.

Karl saw advantages to continuity of care, to ensure that behavioural contracts were enforced:

> I think, yeah I think it's good to see the same person. Cause then they, they're with you for the whole journey? So they know- cause if you keep seeing different people, they look on the screen and they go, oh we'll try this and, they never really know what – has happened beforehand, so I think – it is good to see the same person, personally.
>
> (. . .)
>
> [The surgeon] – insisted that I come to appointments. And, like [indistinct] – forced me to come. Whereas before go oh, I'll ring them up and I'll come tomorrow or whatever. So it's been quite good, he's been quite strict with me. So.

Judith noted that having a clinician familiar with her over many years meant that a deterioration in her health was quickly recognised

> Yes. I always see Dr. [Surname]. I don't see anybody else, she's lovely, she's really nice. And the day that I saw her, she said, oh my god I've never seen you look so ill, Judith, ten years that you've been with us, I've never seen you look so ill so if I'm going to call an ambulance (. . .)

This stands in contrast with Mandy's experience, and discontinuity in care caused by changing GP practices and due to restrictions in face-to-face clinical review enforced during the COVID-19 lockdown

> It's so difficult because I was in the middle of changing doctors' surgeries, and then of course COVID puts a halt on so many things, you know, and even though I'm down as housebound, which I hopefully won't be – not too long before I'm out and about, but it's obviously always difficult through the COVID situation with a doctor coming out.

Accessibility and co-location also served to improve the experience of accessing healthcare for Ian:

> Yeah, so, I've been in contact constantly with the specialist consultant and his team throughout the entire process, when they've been there by email or phone call whenever I've needed them just give- just phone them up. I also saw the foot specialist in the [Tertiary Referral] Hospital as well. So that's- the care, everything, is under one roof. I've then been backwards and forwards to my GP as well, erm, and been helping with pain medication and everything like that that I've needed.

6.6.8 The experience of uncertainty during the peri-operative period (capability)

On inductive review of all interview transcripts by a second researcher, it was noticed that many participants drew attention to their experiences negotiating uncertainty during their treatment.

Uncertainty places a strain on emotional self-regulation, and can amplify negative affective states. People who are less able to tolerate conditions of uncertainty may struggle to control behaviour due to resulting emotional distress, and may be more likely to turn to addictive behaviours or substances to cope. (Bottesi, Ghisi, Caggiu, & Lauriola, 2021)

6.6.9 The effect of the COVID-19 pandemic

The COVID-19 pandemic resulted in treatment delays for many participants interviewed during this study. Grace described waiting twenty six weeks for her primary diagnostic assessment. Treatment delays had knock-on effects, as Ian described

> I think that before- the worst part about the, the – prior to my first surgery, was obviously with the COVID having just hit, and me having the – gone to my local minor injuries unit, and obviously having to have the COVID test and temperature checked while I was there, I was like – had a very slight increase in temperature, at 37.1. And because of that, it was like, they weren't paying attention to what the actual problem was. They'd done the X-ray, and they were like, oh no it's just a pressure fracture, you have to leave now, and you have to go and get yourself a COVID test. [Right.] They kind of like dismissed

> what the problem was – and – focused on – COVID.

Bill found his primary operation postponed, and done at short notice by a private provider whose care was, in his opinion, of lower quality than would be expected. Judith described a similar experience, saying the private provider did not serve her food during her hospital stay due to kitchen decontamination.

COVID-19 may have increased the disparities in healthcare access experienced by people of differing socioeconomic status. Barriers could be circumvented by those who had family support, were eloquent and felt entitled, as illustrated by Luke's experience:

> And when I made enquiries about an oncology appointment after I had the stoma fitted, there apparently were no oncology appointments for at least a month, and I, I just stood around with this thing growing for some time anyway which, you know, again, was very frustrating, er, only to be told that there's no oncology. Then all of a sudden, my missus had spoke to operations directors and various other people we, which you know personally I don't think we need, you sh – I know, I know that COVID was, you know, an exceptional time, (sigh) but we managed to get one within three days. This is crazy, it was, absolutely crazy, we got one in three days.

6.7 The contribution of Patient Representatives to interpretation of qualitative findings

Interview transcripts were reviewed and discussed with Patient Representatives during the process of transcription and coding. Patient Representatives are lay people with experience of treatment for relevant conditions.

One Patient Representative commented that the people who chose to participate and contribute interviews about their peri-operative experience were a self-selected subgroup of people who felt confident about their decisions. During study recruitment, we identified ways to allow others to contribute their experiences, for example by limiting the duration of the interview, or encouraging family members to stay.

During analysis, the negative impact of the lack of continuity in pre-operative diagnosis and treatment, from one healthcare provider to the next, was described as a burden.

Interactions with clinicians were described in terms of being fraught relationships with many responsibilities on both sides. Mistakes could be interpreted as a lack of respect – examples that were brought up included clinicians or administrators organising online appointments for unsuitable care events, such as a biopsy. One Patient Representative pointed out that there was also a practical obligation for patients to "keep people [clinicians] happy because they have my life in their hands:" that showing dissent or disrespect, particularly in the context of surgery or inpatient care, risked physical danger. These relational tasks contributed to mental load, and had high stakes as usually contact with healthcare was sparse.

Lastly, interventions that relied heavily on close interpersonal relationships with family and friends were considered dangerous, particularly without sufficient oversight from professionals. Spouses nominated as accountability partners for behaviour change, may have felt entitled to play into existing abusive and controlling behaviour.

	Barriers to behaviour change and engagement with interventions	**Facilitators of behaviour change and engagement with interventions**
Capability	Pain Cognitive burden of navigating health system Uncertainty	Continuity of care
Opportunity	Socioeconomic deprivation	Self-directed intervention, such as vaping Restrictions on behaviour
Motivation	Prior experiences of intervention: re-engagement Embarrassment Perception of poor quality or untrustworthy care	Behaviour perceived as outside social norms

Table 6.2: Summary of barriers and facilitators to peri-operative health optimisation identified from in-depth semi-structured interviews with 16 participants with orthopaedic infections.

6.8 Conclusions and discussion

The analysis of semi-structured interviews with sixteen people before and after their surgery for orthopaedic infection identified possible barriers and facilitators to engagement with behavioural interventions in the peri-operative period. Smoking was the target of most of the thematic analysis, but some of the contextual factors identified would be expected to be relevant to other peri-operative 'prehabilitation' interventions.

Pain was described by most participants, particularly before surgery for orthopaedic infection. The executive tasks of living with orthopaedic infection and interacting with healthcare providers may have also placed a significant cognitive burden on participants. These factors were likely to limit their ability to engage with behavioural interventions in the pre-operative period, particularly those that rely on reflective motivation and evaluative cognitive processes. The effect of cognitive load on engagement with a behavioural intervention in the healthcare context was summarised by Gollwitzer *et al.*:

> When people are highly absorbed in an ongoing activity, wrapped up in ruminations, gripped by an intense emotional experience, or simply tired, chances are high that they will not seize an available opportunity to act on their goals, simply because the opportunity fails to attract attention.

(Gollwitzer, 1999)

One behaviour change intervention element from the Behaviour Change Taxonomy that would be expected to work for smoking cessation in the context of chronic pain would be BCT16, or behavioural regulation support, such as nicotine replacement therapy. Several participants in this qualitative study had tried nicotine replacement therapy in the past.

Experiences of nicotine replacement therapy aligned with existing research. Herbec et al. 2018 found that people who did not receive counselling or instructions for how to use nicotine replacement therapy devices such as patches, gum and inhalators, described problems such as sore mouth and inadequate control of cravings. People often abandoned nicotine replacement devices rather than adjusting device use for optimum results. Gaining skills from healthcare professionals was sometimes seen as embarrassing. Participants reported minimising their interactions with the provider if possible. (Herbec, Tombor, Shahab, & West, 2018)

These findings support that vaping was more popular than NRT. Vaping is a nicotine replacement delivery method available outside healthcare, where no advice or monitoring interventions are co-administered. It was found to be more acceptable and effective than conventional NRT in a recent peri-operative trial. Some participants in the trial described that conventional nicotine replacement therapy was embarrassing to use.(Hajek, Phillips-Waller, & Przulj, 2019)

Most participants in this study had previously attempted to quit smoking. Re-engagement, rather than primary engagement, may need to be the main focus of smoking cessation services for people in the peri-operative period. Re-engagement may need to counteract feelings of 'learned helplessness' or 'spoiled identity' inherent in failing to achieve a goal or manifesting illness or behaviour associated with social stigma.(Hiroto & Seligman, 1975; Fraser & Treloar, 2006) Preparing for repeated unsuccessful attempts at behaviour change, may benefit from compassionate approaches.(Gilbert, 2017)

Narratives given by participants in this study were not exclusively to convey information to the researcher. Rubbishing nicotine replacement therapy could have allowed some participants to save face under the pressure of a morally loaded conversation about their ability to exercise self-control and contribute to their ongoing medical treatment.(Goffmann, 1956)

Cognitive dissonance may affect people undergoing unsuccessful smoking cessation attempts. Fotuhi *et al.* found that over time, people who attempted to quit smoking had less conviction in statements about the personal experiential benefits of smoking, such as that it reduces stress. Conviction returned to prior levels if the quit attempt was unsuccessful. Rather than causing behaviour, the degree of conviction in expressed beliefs followed the behaviour. These findings agree with cognitive dissonance theory.(Festinger, 1962) Fotuhi et al. stated,

> We would expect a rebound effect among failed quitters, with these

> individuals again endorsing more pro-smoking beliefs once they relapse to smoking (even if they had previously endorsed more negative beliefs during the time they had quit).

Hostility in some narratives suggested negative emotions and cognitions consistent with reactance.(Brehm, 1966; Sieverding, Specht, & Agines, 2019; Steindl et al., 2015) Appealing to personal freedom in choosing between a range of options, can reduce reactance to behavioural interventions.(Steindl et al., 2015; Reynolds-Tylus, 2019) For example, Bessarabova *et al.* found that reinforcing individuals' entitlement to choose for themselves, reduced the reactance evoked by messages about recycling or mitigating climate change:

> You've probably heard a lot about recycling, even messages similar to this. Of course, you don't have to listen to any of them. You know what is best for yourself. We all make our own decisions and you make your own decisions too. The choice is yours. You're free to decide for yourself.

(Bessarabova, Fink, & Turner, 2013)

Reactance was less prevalent among students given messages where there was a choice between two options for how to monitor skin damage and how to prevent it, compared to those given messages that only suggested one option.(Shen, 2015)

Clinicians may find better engagement and less reactance in their discussions of perioperative smoking cessation with patients if they take existing experience and preference into account, and reinforce the patient's entitlement to choose what works best for them.

6.9 Limitations

This qualitative study was limited by the small number of participants included, and by the low participation rate. Possible reasons for low participation may have also included the amount of time interviews were expected to take (most lasted for at least forty minutes), the fact that topics for discussion may have been considered sensitive by some people, and the reluctance to extend contact with a clinical researcher in the aftermath of COVID-19 contact restrictions. Thematic saturation was not reached in this study.

Some participants, particularly those interviewed after their operation, noted that their recollection of pre-operative events may not have been accurate. This was indeed supported by the one participant interviewed before and after surgery. Observation of a separate group of people going through the pre-operative period, or analysis of participant diaries, would have allowed triangulation with some of the themes identified, but was not possible within the scope and resources of this project.

7 | Realist synthesis: engagement with pre-operative behaviour change intervention for adults with orthopaedic infection

This chapter synthesised the findings of Chapter 6 with broader research in behaviour change. The aim of this work was to identify what actions could promote the uptake of smoking cessation interventions in the pre-operative period. The identification of intervention components, Behaviour Change Techniques, that are most relevant to changing particular behaviours in particular contexts is an area of active research at present, outside the scope of this synthesis.(Beard et al., 2019; Michie et al., 2013)

7.1 Background and rationale

Smoking cessation was chosen as the focus of intervention in this section. Smoking cessation is feasible within the current waiting period for elective orthopaedic surgery, and supported by evidence of efficacy in that timeframe.(Truntzer et al., 2014)

Nicotine replacement therapy has an effect of predictable magnitude in the healthcare context, including the pre-operative period. Myers et al. described the magnitude of effects from smoking cessation interventions, as part of a review contributing to national guidance.(Myers et al., 2012) This has been used as a framework for this chapter. West et al. enumerated the cost-effectiveness of nicotine replacement therapy and other pharmacotherapies for smoking cessation.(West et al., 2015) Both studies highlighted engagement as one of the principal contributors to real-world efficacy for the behaviour change techniques. In addition, engagement with smoking cessation interventions was identified as among the areas requiring greatest improvement by the 2021 British Thoracic Society Inpatient Smoking Cessation Audit,(Devani & Evison, 2021), together with the identification of people who smoke during hospital admission.

Uptake of interventions is a challenge in behavioural intervention research, particularly for smoking and alcohol interventions. Cochrane reviews of both smoking and alcohol interventions to date, included studies with high non-participation and attrition rates.(Thomsen et al., 2014; Kaner et al., 2018)

Identifying contextual elements that affect engagement with behavioural interventions in the peri-operative period, was the primary aim in this Realist synthesis.

7.2 Aims and objectives

The specified aim at the conception of this study was to ask: what factors affect intervention uptake or engagement, for people planning to undergo elective orthopaedic surgery, and why?

The review was initially intended to focus on interventions addressing malnutrition, smoking, alcohol use and glycaemic control, as these factors could be amenable to change in the few months before elective surgery for bone and joint infection. However due to the breadth of sources required to address only one of these factors, the primary focus became smoking cessation, as this was estimated to affect around one in five people treated in tertiary care for orthopaedic infection.(Li et al., 2019)

7.3 Methods

7.3.1 Searches

Published studies were sought from the following electronic bibliographic databases: The Cochrane Library, MEDLINE, EMBASE, CINAHL and PsycINFO. 'Grey literature' including policy recommendations, guidelines, evaluations, reports, and other secondary documents were sought, where relevant to behaviour intervention uptake. Meetings with stakeholders with experience in behaviour change leadership guided and refined the analysis of documents identified in the study, and synthesis with qualitative research findings from Chapter 6.

7.3.2 Study inclusion

In Realist evaluation, all study designs may be relevant to explaining and predicting what interventions support behaviour change engagement, in what context, and for whom. This includes studies with qualitative, quantitative, and mixed methodologies. Documents, such as patient-facing materials and healthcare organization practice or policy documents, that are not reports of original research, were included if they contained information needed to develop and refine the programme theory.(Emmel et al., 2018; Pawson, 2013)

7.3.3 Target behaviours and interventions, study population and study settings

This study focused on interventions targeting engagement with existing behavioural interventions in the peri-operative period, particularly focusing on smoking cessation interventions.

The target population were adults (18 years or older) who were referred for, and were awaiting, elective day case or inpatient orthopaedic surgery. Pre-operative interventions used in other elective surgical settings were later included owing to the limited scope of relevant studies in the orthopaedic setting alone.

7.3.4 Analysis plan and data synthesis

The main focus of this synthesis was to inform the understanding of mechanisms, i.e. causes operating in a particular context for a particular group of individuals at a particular time, that may underlie the acceptability and engagement with pre-operative interventions for smoking cessation.

I screened study titles and abstracts for inclusion in the analysis, and identified further studies from lists of references and forward citation searching. The decisions to include studies was based on their potential to offer information pertinent to programme theory development and hypothesis testing. Decisions to include studies were discussed with the research group and a wider group of stakeholders with experience of peri-operative care and smoking cessation.

Documents selected for inclusion were coded: information about study methodology, sample size, participation and drop-out rates, participant characteristics, outcomes, and measures of effect. I performed all data extraction. Documents were selected and assessed according to their relevance to the study question, i.e. their potential to contribute to theory development; and the rigour of study methods in relation to the question the study set out to answer, i.e. the credibility and trustworthiness of the methods. The aim of data synthesis in this review was to develop and test the programme theory through iterative analysis of available sources. Data coding included deductive (i.e. where sources contribute to testing hypotheses in the developing programme theory), inductive (arising from the available information contained in sources), and retroductive (based on interpretation of the data in sources, where that interpretation relates to mechanisms, using strategies such as counterfactual reasoning). This was informed by the assessment of sources' rigour and relevance.(Wong, Greenhalgh, Westhorp, Buckingham, & Pawson, 2013)

An example of how rigour and relevance can be evaluated may be briefly defined as follows.(Abrams et al., 2018)

Relevance: are the data in the source relevant to the development of programme theory for the review question?

Rigour: are the data in the source sufficiently trustworthy to use in making changes to the programme theory or adding understanding?

Interpretation of meaning: if the source is relevant and trustworthy in the methods used, can the data in the source provide evidence of the context, mechanism or outcome of causation, relating to the review question?

The COM-B model of behaviour change informed data interpretation: the capability, opportunity and motivation elements of this model are elucidated in the Theoretical Domains Framework. (Michie et al., 2011a)(L. Atkins et al., 2017) Where sufficient information was available in the source document, interventions were coded using the Behaviour Change Taxonomy,(Michie et al., 2013) with the plan that CMOCs that applied to particular intervention taxa would be analysed. However, in practice, many interventional studies did not include sufficient detail to reliably classify BCTs contained in an intervention. It is also understood that BCTs applied in practice may diverge from those described in study methodology, with reference to smoking cessation interventions.(Lorencatto et al., 2013)

7.4 Results

The sources contributing to this Realist synthesis included seventeen semi-structured interviews described in Chapter 6, 60 written sources, and 16 sources identified through reference lists and stakeholder suggestions. After assessing sources for relevance and rigour, 54 published sources were retained. Results from thematic analysis were interpreted alongside semi-structured interviews.

7.4.1 Initial programme theory

In order to do something, a person needs

> the skills necessary to perform the behaviour, a strong intention to perform the behaviour, and no environmental constraints that make it impossible to perform the behaviour.

(Michie et al., 2011a)

A person's social group norms affect standards of behaviour and expectations of health.(Siegrist & Marmot, 2006) Living with someone who smokes makes it more difficult to quit, as described by participants in the qualitative study presented in Chapter 6, as well as earlier studies.(Graham, 1993) Hope for the future and a person's rating of their quality of life may affect how much they value future health, so how motivated they are to adopt healthy behaviours.(Graham & Kelly, 2004; Fraser & Treloar, 2006)

In decision making, "people are limited in their capacity to process information, so they take shortcuts whenever they can."(Fiske & Taylor, 1991) This is relevant to the capability to engage with behavioural interventions. People waiting for surgery for orthopaedic infection may already be coping with pain, fear and restriction of movement as a direct consequence of their illness.(Moore et al., 2015; Cahill et al., 2008; Lerner et al., 1993)

Appraising the risks and benefits of doing something requires cognitive capacity (thinking space). This is adversely affected by existing cognitive load (things that are already being dealt with mentally). The choice between a 'healthy' and 'unhealthy' snack was affected by cognitive load: cognitively loaded students were more likely to choose chocolate cake than fruit salad, while for students with thinking space, the reverse was true.(Shiv & Fedorikhin, 1999) Musculoskeletal pain, like cognitive load, impairs decision making.(Apkarian et al., 2004; Harman & Ruyak, 2005)

People use different 'mind tools' (heuristics) to solve problems depending on the context. Commonly-used heuristics can lead people to make errors in interpreting information.(Tversky & Kahneman, 1974) People under cognitive load may use heuristics that are faster but less accurate, leading to systematic biases in interpreting visual information, for example.(Allred et al., 2016) Learning more accurate heuristics can improve how people interpret risk and probability information to make decisions, however teaching a new heuristic to someone who is already under cognitive load may be prohibitively challenging.(Hoffrage, Krauss, Martignon, & Gigerenzer, 2014)

If people are given less time to make a decision, or are distracted by noise, they take less information into account when making the decision.(Wright, 1974) People under time pressure spent less time considering the outcome of a safer action, and considering the possible negative consequences of a riskier action.(Maule, Hockey, & Bdzola, 2000) Disadvantaged people in the UK experience more time pressure, and may also experience more distraction and cognitive load in everyday life, for example from negotiating caring responsibilities in the context of limited resources, and working longer hours.(Chatzitheochari & Arber, 2012)

Motivation to change behaviour, or to engage with behavioural interventions, is context-dependent. What is at the forefront of a person's mind, or how much a problem matters to them (its salience), will change how a person might approach it.(van Schie & van der Pligt, 1995) Whether the outcomes of a decision are framed in terms of loss or gain can affect motivation.(Tversky & Kahneman, 1974) The salience of a decision about health depends on norms and relationships in a person's social group.(Thompson et al., 2007; Chapman, 1993; Cummins et al., 2007) During discussions with participants in the clinical research context, several people suggested that the salience of decisions around health behaviours depended on life stages they were going through, such as deployment in the army, or reaching 'middle age'.

7.4.2 The contribution of Patient and Pubic Involvement to developing programme theory

Three Patient Representatives, who had had experience of orthopaedic procedures and access to secondary healthcare, were involved in the design, running and analysis of the qualitative study described in Chapter 6 and the parallel realist synthesis.

Patient Representatives highlighted that the study had to be structured in such a way as to avoid 'victim-blaming', namely the unfair attribution of responsibility for a poor outcome on the person who experiences the poor outcome.(Crawford, 1977) Postponing surgical treatment until after behaviour change had been achieved, or after an attempt had taken place, was felt to disproportionately worsen treatment outcomes for people at greatest risk of adverse outcomes.

Patient Representatives suggested ways of improving healthcare engagement, following from participant experiences in the qualitative interview study in Chapter 6. One of the recommendations was for better support for mental illness in parallel to the treatment of the orthopaedic infection.

7.4.3 Audit of Key Inpatient Indicator Recording: identification of people who smoke in secondary and tertiary orthopaedic services, as context for offering behavioural interventions

In order for smoking cessation interventions to be offered peri-operatively by a surgical pathway, people who smoke must be correctly identified. A service audit in tertiary care for the completion of Key InPatient Indicator data (KIPI) was assessed to obtain an estimate of the level of engagement with Brief Intervention for people admitted for orthopaedic treatment in one hospital in 2019. This audit of routine inpatient care was approved by the Institutional Review Board (OUH QIP6780).

KIPI data is routinely collected during inpatient admission. KIPI data analysed in this audit included the following information:

- Whether people admitted for elective orthopaedic care were asked about smoking;
- Whether people reported smoking currently or in the past when asked;
- Whether people who reported smoking were willing to discuss smoking;
- Whether people who reported smoking and were willing to discuss it, were offered brief intervention for smoking cessation, and referral to a smoking cessation service.

Other information routinely recorded in KIPI related to alcohol use and diagnosed diabetes mellitus. Referrals for inpatient smoking cessation and alcohol withdrawal support, through specialist inpatient support teams, were made automatically upon completion of these data fields on the hospital Electronic Patient Record.

Data were available for 10,077 anonymised admissions to hospital during 2019. Whether the patient smoked was recorded in 5502 instances, 54.6% of admissions to hospital. In most cases (4575 admissions out of 5502), no reason was given for why smoking was not ascertained. The patient being unable to answer, as a reason for not ascertaining smoking status, was only recorded for 35 admissions. Of the 5502 admissions where smoking was enquired about, the patient was recorded as being 'able and willing to discuss smoking' in 1088 cases.

Throughout the year, 675 admissions identified people who currently smoked (6.7%). This is roughly half the prevalence in the general population in the UK in 2019.(Office for National Statistics, 2020) This suggests that there may have been hundreds of missed opportunities per year to identify smoking through this pathway with automatic referral for cessation support. Further analysis of whether certain demographic groups were less likely to be approached, showed that the proportion of people for whom smoking status was ascertained did not vary with the gender, ethnicity, or recorded religious affiliation of the person admitted to hospital. People aged 80+ or under 20 years were less likely to be asked about smoking at admission (Chi^2 test, $p<0.01$).

The reasons for missed opportunities were not possible to specify. However, for interventions in orthopaedic care to be successful, even when they are integrated as defaults in hospital admission pathways, barriers must be elucidated and mitigated. Doing so may increase referral for smoking cessation support up to twofold in this context. These findings agree with those of the British Thoracic Society national audit (2021), that highlighted patient identification as one of the primary targets for improvement in smoking cessation interventions for people requiring inpatient care.

7.4.4 Development of programme theory: engagement as context, Behaviour Change Techniques as mechanisms

Behaviour Change Techniques (BCTs) are elements of behavioural interventions, and could be thought of as non-divisible, unitary mechanisms for the purposes of this analysis. (Michie et al., 2013)

These mechanisms have different efficacy depending on the context in which they act. One salient element of context that changes the efficacy of any BCT is engagement with it. Engagement is committing oneself to an undertaking. It includes people deciding to seek interventions, going to them, agreeing to them when offered, paying attention to them, and applying them.

’Attending’ an intervention does not necessarily mean ’attending to’ it, as described by John during a semi-structured interview referred to in Chapter 6:

> John: Uh, hss, always doctors say, "stop smoking," everything [sing-song voice].
>
> Maria: Mhm. And how do you react when doctors say that?
>
> John: [Sighs.] I, when I smoke, I not listen to you. Know, how. I listen, but, how I say, psht – psht.
>
> Maria: In one ear and out of the other!
>
> John: Yeah, yeah. And that’s it.

Maria: Does it ever annoy you, particularly, when, what you've gone through with doctors-

John: No, you know what is problem, why I listen like this. Because you see I always go to doctors I have stress. There, because I have different problem, and what – I have stress, I go outside and smoke! And that's it.

7.4.5 Engagement as a mechanism necessary for intervention efficacy: challenges in comparing interventional study effects

Contextual factors that affect the degree of engagement with an intervention may act in different ways, such that comparing interventional studies may help to untangle them.

Paradoxically, studies with lower participation rates may show greater effects for the study intervention, due to more interested participants. This means that the engagement may not always be reflected in the effect size reported, and that studies may not be easily comparable. (Emmel et al., 2018; Rycroft-Malone et al., 2012)

7.4.6 Contextual factors that affect intervention engagement as a mechanism: organisational factors and intervention settings

Several factors relating to the setting in which intervention took place were directly relevant to clients' engagement.

Bauld et al. reported that a lack of integration between different healthcare providers for people who smoked during pregnancy,

> together with frequent organisational changes, inhibited the adoption and delivery of a cohesive approach to smoking in pregnancy and increased the chances of pregnant women being exposed to 'mixed messages.'

Suggestions for ways to overcome barriers between organisations included sharing reports on progress and achievement, and face-to-face meetings between service providers from different organisations.(Bauld et al., n.d.) Another way to reduce 'mixed messages' and other consequences of provider fragmentation could be to co-locate surgical and smoking cessation services, as recommended by Farley, et al. (Farley, Aveyard, Kerr, Naidu, & Dowswell, 2016) This hypothesis could also be supported by the findings of Beard et al., that behavioural interventions implemented in non-standard settings (outside primary care) were more likely to be cost-effective.(Beard et al., 2019)

Waiting until after discharge for people to be seen in primary care smoking cessation services (SSS), was a missed opportunity:

> Smokers were expected to engage with support themselves after discharge or at best they could be referred to the local SSS who may manage to contact the patient after discharge to discuss options. This contact though was often outside the window of opportunity, as the smoker was back in their home or work environment with associated smoking cues and triggers and often by then had recommenced smoking.

(Bickerstaffe, 2014)

Some organisational factors may be more challenging to address. The guidance writing team for the National Institutes of Health and Care Excellence group evaluating smoking cessation interventions in secondary care, described this challenge to recording smoking status:

> Our own experience at the Royal London Hospital illustrates some of the barriers encountered in the NHS. The hospital computer system there was commissioned from a private company which charges tens to hundreds of thousands of pounds for including any new item. Questions regarding smoking status, and an option to refer were eventually included, but they had to conform to an unsuitable and clumsy format, and had to be hidden in an area several screens away from the front screen. Staff needed training in how to use the system, which proved impracticable. Despite a series of meetings of senior management, PCT and SSS, computerized referrals to the specialist working in the hospital remain at a negligible trickle. The bulk of referrals is by phone and e-mail from a few keen members of staff.

(Myers et al., 2012)

7.4.7 Contextual factors that affect intervention engagement as a mechanism: timing

Nolan et al. found that the greatest reductions in both smoking and nicotine replacement use occurred in the two days preceding major surgery, and thereafter nicotine use gradually rose in the post-operative period.(Nolan et al., 2016)

Prestwich et al. identified that the immediacy of the target cessation period is something that may affect willingness to engage with peri-operative interventions:

> Interestingly, in an unpublished service evaluation that we have conducted, interviewed patients suggested that they wanted the emphasis to be on cessation during the pre-operative period and not the longer

> term. Thus, while one of the potential benefits of helping patients to abstain from smoking during the pre-operative period is that they are more likely to quit long-term, emphasizing longer-term abstinence at the onset of the intervention may actually lower engagement.

(Prestwich et al., 2017)

Pre-operative clinic may be the time when surgical treatment is planned, and the last contact between medical professionals and the people they treat until the admission for surgery. However, this was identified by a paricipant in Newhall et al. to perhaps not be the best time for introducing smoking cessation:

> "Don't throw in a pitch to be in a smoking program in with your diagnosis. When you are getting your diagnosis you are not happy. You are scared or sad or whatever."

(Newhall et al., 2016)

7.4.8 Contextual factors that affect intervention engagement as a mechanism: reactance and perceived freedom of choice

Messages perceived as repetitive or restrictive were found by other studies to evoke the negative emotions and cognitions characteristic of reactance.(Reynolds-Tylus, 2019) For example, Wells et al. presented quotes to illustrate the frustration felt by people who smoke, when badgered by their family members:

> 'I think a little bit of it is so many people saying "Stop", that your mind is saying, "No, I'll stop when I want to". I'm not having people telling me to stop.' (P31-Head&Neck-Smoker)

> 'But I'll have my cousins and that saying "You shouldn't be smoking anyway" . . . and I just go "Yes, whatever". But, no, each to their own

> really.' (P54Gynae-Smoker)
>
> 'I'm damned if I'm going to be told what to do by them [family members].' (P8-Colorectal-Smoker)

(Wells et al., 2017)

Providing choices from a range of options was seen by people waiting for vascular surgery as a way to improve engagement, and is also an effective tactic for reducing the perceived freedom restriction of an intervention, and thus the reactance it provokes:(Newhall et al., 2016)

> "I think the more options you can give people, the more you're going to have people participate because everybody's different." When asked about timing of the intervention, another noted, "You have to ask 10 people and get nine different answers." One patient summarized the idea of individualization, even within the context of a clinical trial, and noted "For the four of us or 100 people, it's going to be a different way for each individual and the studies usually try to find one that helps everybody and I don't think you're going to because its not just your health but your lifestyle and your raising and how you think of things."

One of the factors that Hajek et al. identified to explain the differences in acceptability between vaping and nicotine replacement therapy in an interventional trial, was freedom to adjust the dose of the intervention:

> It is paradoxical that smokers can select their nicotine levels freely while they smoke, but once they enter NRT treatment this autonomy is removed and nicotine dosing is placed in the hands of those who treat them.

(Hajek et al., 2019)

Paradoxically, a lack of freedom arising from changes in physical opportunity may be a factor that achieves smoking cessation for some people. In the semi-structured interview study in Chapter 6, Karl described his own (not very willing) experience with smoking cessation:

> "When you're told you can't be- can't do something, and you know you can't, you put it to the back of your mind and say, sod it, I can't, I can't fight it"

Reactance may paradoxically turn to acceptance when it is clear that there is no other option. (Steindl et al., 2015) This may well be the case for some people admitted to hospital, but has little relevance to other pre-operative contexts.

Nasell et al. attributed difficulties in recruiting participants with acute orthopaedic trauma, to the introduction of a smokefree policy in participating hospitals. Of 298 people who were approached for the study, 183 refused to participate, while only 104 people completed the study. They noted in their study report,

> A major reason for the enrollment slowing down was the introduction of a nonsmoking policy at the participating hospitals, which probably, as a result of an increased awareness of the negative effects of smoking, negatively affected the patients' interest in participating in a study (...) we estimated that 18% of all smokers were included, 32% declined to participate.

(Nasell et al., 2010)

7.4.9 Contextual factors that affect intervention engagement as a mechanism: the role of stigma

Thomsen et al. reported a qualitative study alongside a pre-operative smoking intervention. This identified a feeling of persecution among some of the 11 women receiving the study intervention prior to having surgery for breast cancer. Women

> felt under constant pressure to stop smoking from family. They also described feelings of persecution and being looked down upon because they were smokers.

This interpretation was supported with a quote from a participant, who came almost to the point of describing herself in non-human terms:

> I think it's easier to be a non-smoker. It's easier because we smokers are a little pressured group, probably hunted by almost everyone. And I couldn't stand the thought of crawling down with iv's and drains [to smoke outside the hospital]. That worried me a little so that's why I thought I might as well go for it [stop smoking].

The choice of health promotion messages in everyday life may affect the degree to which people feel able to engage with smoking cessation interventions. If smoking confers a 'spoiled identity,'(Fraser & Treloar, 2006) there would be no point in stopping smoking after the damage had already been done. Some messages may reinforce this, as identified by Chapple et al.:

> Those who produce images of 'dirty lungs' rightly aim to put young people off tobacco, but such images may upset people with smoking related illness. In contrast, publicity about the Machiavellian role of the global tobacco industry may resonate with young people while avoiding further victim blaming of those with lung cancer and other

> smoking related diseases.

(Chapple, Ziebland, & McPherson, 2004)

7.4.9.1 Contextual factors that affect intervention engagement as a mechanism: compassion and other reactions from clinicians

Evers-Casey et al. identified that clinicians exhibit implicit emotional associations when evaluating illness in people who smoke:

> (...) the most striking discrepancy observed [between implicit associations for hypertension, and those expressed for smoking, were] in the number of times clinicians expressed frustration.

(Evers-Casey, Schnoll, Jenssen, & Leone, 2019)

In order to show compassion to people who smoke, clinicians may have to perform emotional labour to suppress feelings of frustration. Wells et al. presented the experience of a clinician who was able to show compassion in the smoking cessation advice they delivered:

> One staff member, a surgeon, recognising the potential sensitiveness of smoking cessation, saw this as an impediment to the patient moving on in the care pathway and attempted to 'de-moralise' the issue quickly.
>
> "Some say "This is my entire fault doctor" I don't care whose fault it was, we are going to move on from this. This is not about blame, it's not about preaching, it's not about telling you you're a bad person, it's about what is best for you. So I try and keep it self-directed and pragmatic and try and remove any moral or value overly from it because I think it gets in the way." (S19-Medical Specialist)

(Wells et al., 2017)

This 'de-moralising' framing allowed the clinician to maintain affiliative rather than exclusory dialogue with the people they treated, providing social soothing as part of compassionate care for people who smoke. Soothing can improve the patient's emotional self-regulation during the consultation, and thus enhance their ability to attend to both the intervention and the rest of the consultation.(Gilbert, 2017)

Newhall et al. also identified the importance of a compassionate interaction in the experience of people awaiting vascular surgery who were referred for smoking cessation support as part of their treatment: (Newhall et al., 2016)

> All stakeholders identified the tone of the patient-physician conversation as a key aspect of successful smoking cessation. Patients noted the importance of a positive, sympathetic tone in, as one noted "[Surgeons with negative advice] come off that way like if you don't stop smoking, what we do is going to be totally useless." Patients focused on the tone of the advice, rather than the length or strength of the counseling. One patient recalled a successful physician intervention: I'd have a question like with the Chantix and stuff, he [the surgeon] would always answer my questions, 'you just let me know if you want to. I'm not bossing you but if it's something you might want to try and let me know' and that put it so this man's not pressuring me but he's giving me an option to try, so I tried the Chantix.
>
> Surgeons similarly noted importance of their tone in these conversations, and identified the need to be "sympathetic witness" to the patient, rather than, "the old days when we said, 'you are going to either give up smoking or your leg'." Other stakeholders echoed the

> sentiment that although surgeons should address smoking cessation, the tone they use is paramount, one tobacco counselor noted the importance of "really good positive language around understanding their motivations."

Laurisden et al. reported a quote from a participant in a peri-operative behavioural intervention study targeting smoking and alcohol use, for whom a compassionate and freedom-emphasising approach made the difference between engaging with the intervention or continuing to smoke:

> For me it's positive that she's such a nice person. She doesn't say you can't do this or you're not allowed that because that would make me become stubborn and say I'm going to smoke regardless (laughing) (P9, smoking intervention)

(Lauridsen et al., 2017)

Paul Gilbert highlighted the importance of compassionate approaches in healthcare, particularly in situations that could evoke shame in a person receiving care, to improve engagement:(Gilbert, 2017)

> Whereas shame is an experience that separates, segregates, marginalises and disengages people, caring and compassion facilitate integration, (re)connection and support.

Attentiveness to clinicians' demonstrated compassion shone through in several semi-structured interviews conducted during the study reported in Chapter 6, particularly in relation to how doctors discussed smoking cessation:

Karl:

> before the first operation, because they bang on to me that I have to stop smoking before I had the operation?

John:

> Uh, hss, always doctors say, "stop smoking," everything [sing-song voice].

Luke:

> I met this, I can only describe as a horrible doctor, but in his defence he was, he, he was, you know, he did what was necessary. [Sighs] And explained to me my failings, as a human being. And where I got to in this particular s-state of affairs sort of thing.
>
> (. . .)
>
> and then he went on to tell me what a bad person I'd been! That I shouldn't smoke. And I should do more exercise [sing song voice] and you know my diet was bad and this that and the other. There weren't an ounce of sympathy about the fact that I was gonna have to have a major operation. There was NOTHING.

The degree of control over clinicians' verbal and non-verbal communication, and emotional labour performed in order to avoid being perceived as 'horrible', may be difficult for clinicians to sustain, particularly in a low-resource, high-workload environment.

Expressing the attributes of compassion is particularly challenging when clinicians providing care for people who smoke may be more likely to emotionally disengage when dealing with a problem that they do not perceive themselves as being able to influence, where 'meaningfully improving quit rates' in the pre-operative period is seen as impossible. (Newhall et al., 2016) Gilbert echoed the situations in which compassion may be stifled:

> actually a great many inhibitors of compassion [may exist,] such as

> interfering with support systems (eg, not enabling teams to settle and support each other), overworking people, downgrading and limiting opportunities for personal and skills development, and creating punitive bullying contexts. All these are well recognised in modern health services.

7.5 Scope and limitations

This chapter necessarily drew on a range of sources across many disciplines, seeking to identify aspects of care that were often locally-relevant, observational rather than experimentally confirmed, and sometimes difficult to specify.

I found Realist synthesis principles challenging to apply. It was not possible to easily eliminate studies based on methodology, participant population, study setting or level of evidence. Even after reading more than 60 documents in depth and coding often tangential references to elements of intervention context, I could not consider the synthesis to be complete, or independent of other findings that were not included.

Statements about intervention Context-Mechanism-Outcome configurations (CMOCs) were inductively inferred from sources which in many cases were non-experimental. Nevertheless, Realist synthesis focuses on context in a way that may not be easily amenable to experimental study. As stated by Roy Pawson:

> To rule out plausible hypotheses we need situation specific wisdom. The lack of this knowledge (whether it be called ethnography or program history or gossip) makes us incompetent estimators of programme impacts, turning out conclusions that are not only wrong, but often wrong in socially destructive ways.

(Pawson, 2013)

The application of inductive reasoning to the analysis of causal pathways is a matter of epistemological uncertainty. As Karl Popper elucidated,

> The empirical basis of objective science has thus nothing 'absolute' about it. Science does not rest upon rock-bottom. It is like a building erected on piles. The piles are driven down from above into the swamp, but not down to any natural or 'given' base; and when we cease our attempts to drive the piles into a deeper layer, it is not because we have reached firm ground. We simply stop when we are satisfied that they are firm enough to carry the structure, at least for the time being.

(Popper, 1992)

This synthesis may provide an indication of possible interventions to select for future in-practice evaluation, but the scope to make generalisable inferences about intervention effectiveness is very limited.

7.6 Conclusions and recommendations for practice

This Realist synthesis aimed to combine a diverse but relevant group of sources, to specify what actions could be taken to improve engagement with peri-operative behavioural interventions, particularly to enable people waiting for surgery to stop smoking within the 4-8 weeks most likely to benefit surgical treatment outcomes.(Truntzer et al., 2014)

Firstly, improving the identification of people who smoke in the pre-operative pathway, as recommended by recent British Thoracic Society multi-centre audit, is relevant to the context of orthopaedic tertiary and secondary care.(Devani &

Evison, 2021) Understanding reasons why clinicians and people receiving treatment do not feel able to discuss (or record) smoking, may be helpful.

Secondly, providing integrated behavioural intervention services co-located with surgical assessment clinics may be the best way to reach people accessing specialist orthopaedic care, who may live far away, and have limited access to (and tolerance for) long distance transport to multiple hospital visits. Co-locating surgical clinics with pre-operative behavioural interventions may allow intervention to be perceived by service providers as the 'default option,' and could reduce the cognitive load of both intervention provision and receipt.(Perry, Chhatralia, Damesick, Hobden, & Volpe, 2015)

Providing a range of options including supporting vaping,(Hajek et al., 2019) and personalising the approach to each client through face-to-face intervention,(Lorencatto et al., 2013) may both be contextual factors associated with greater intervention engagement and efficacy.

Thirdly, compassionate care may help people re-engage with behavioural interventions. Many participants in the qualitative study in Chapter 6 described previous attempts to stop smoking. Engaging people after previous quit attempts is just as important as engaging people who have never attempted to quit in the past. A compassionate approach can provide affiliative soothing during the healthcare encounter, that may counteract the stress and embarrassment of being affected by illness and engaging in stigmatised behaviour. (Gilbert, 2017; Chapple et al., 2004; Moore et al., 2015)

8 | Conclusions and directions for future research

The studies included in this thesis spanned several questions and aims, all of which related to providing equitable, effective treatment for people with orthopaedic infections, while considering non-intuitive ways to reduce antimicrobial consumption that could conceivably be added to the growing repository of GIRFT interventions.(Briggs, 2015)

Chapter 3 reviewed existing studies to identify prognostic factors that could help select those who may benefit from additional treatments for orthopaedic infection, who would otherwise be at higher risk of treatment failure. Chapter 4 examined possible differential effects from treatments in routine clinical use, including antimicrobial strategies, on outcomes in different groups of people affected by Fracture-Related Infection. Chapter 5 developed a new prognostic model that upheld the Host Status classification of a multi-disciplinary risk assessment tool for people with Fracture-Related Infection and Prosthetic Joint Infections. This model could be used to assess Heterogeneity of Treatment Effects in future interventional studies for people with orthopaedic infections, but could not predict the improvement in quality of life after surgery.

Chapters 6 and 7 integrated experiences of behavioural interventions shared by people having treatment for orthopaedic infection, with existing behavioural intervention research, to develop recommendations for surgical prehabilitation. Findings from these studies challenged the assumption that healthcare contact is a 'teachable moment', and reinforced that interventions other than 'teaching' may be more effective in achieving peri-operative behaviour change.

8.0.1 Recurrence in orthopaedic infection is not straightforward to predict: pathogen, host and treatment factors

The limited predictive accuracy of the logistic regression model described in Chapter 5, and the models reviewed in Chapter 3, underscores the complex and heterogeneous nature of orthopaedic infections. Patient factors had limited predictive power for surgical treatment failure.

The biology of orthopaedic infection may explain some of this unpredictability. Orthopaedic infection involves micro-organisms with very different metabolic chemistry and pathogenesis.(Lew & Waldvogel, 2004) Not all form biofilm, some exist in polymicrobial communities, and some evade attempts at identification due to innate or acquired metabolic adaptations.(Krut et al., 2004; Tuscherr et al., 2016; Tan et al., 2018; Hamad et al., 2022) Aspects of host immune response that are not easy to measure clinically, including minor polymorphisms in immune response that may contribute to (or suppress) inflammation in orthopaedic infection, might influence the clinical course of the disease, including perhaps when and whether infection recurrence becomes clinically apparent.(Asensi et al., 2004; Veis & Cassat, 2021)

Furthermore, using data from interventional studies, where treatment selection and effectiveness may vary systematically, influences the accuracy and relevance of prognostic modelling. (Pajouheshnia et al., 2017; Kent et al., 2018) The extent of bone involvement in surgically treated orthopaedic infection predicts outcome, and simultaneously restricts the choice of surgical treatment.(A. J. Hotchen et al., 2020)

A better understanding of the differential efficacy of treatment modalities for orthopaedic infection is essential: for example, the duration of systemic antimicrobial treatment, and the choice of surgical approach.(Dudareva, Kumin, et al., 2019; McNally et al., 2022) Routinely collected clinical and microbiology data may help identify the most efficacious treatment modalities for patients for whom interventional research data otherwise sparse, such as those with specific combinations of pathogens and host factors, and those who are not well represented in clinical trials. Data analysis stratified using classification systems that predict outcome, such as BACH, may identify differential treatment effects for patients with more severe disease, when differences in efficacy are otherwise obscured in large unselected populations.(Kent et al., 2018; A. J. Hotchen et al., 2019) This may serve to guide treatments offered to patients at the outset of their therapeutic journey, and reduce disease recurrence.

However, such improvements rest on the development of accurate and easily applied classification systems for disease severity. Improved understanding of the interplay between micro-organisms, immunity and healing processes in orthopaedic infection may point towards new treatments, and novel diagnostics to identify infections with increased risk of recurrence.(Hamad et al., 2022) Measurement of the impact of patient referral and treatment pathways, including sociodemographic and comorbidity factors that may affect treatments offered to people with orthopaedic infection, and factors affecting trial participation, will be essential in guiding the analysis of both routinely collected and interventional data.

8.0.2 The association between behaviour and outcome in orthopaedic infection: smoking and infection recurrence

Surprisingly, the cohort studies reviewed in Chapter 3, and work described in Chapter 5, did not demonstrate a large association between pre-operative smoking and the outcome of surgical treatment for orthopaedic infection. This may be due to no effect, or complex opposing effects on inflammation and healing, arising from smoking. Conversely, this lack of association may result from inaccurate ascertainment, as smoking was measured through self-report in this project and many other studies in orthopaedic infection. It may also result from patient selection for surgery, as was suggested from an analysis of pathways from referral to treatment in Chapter 5. Previous epidemiological work examining the relationship between smoking and other conditions highlighted the crucial role of participant selection in determining the size of the associations observed.(Hernan et al., 2008)

This project supports the need to offer high-quality clinical care to people with orthopaedic infection, regardless of existing illness, age or gender. Host factors included in the prediction model in chapter 5, including co-morbidity, age and gender, as well as smoking, failed to predict the increment in quality of life at 12 months after surgical treatment for orthopaedic infection. From a position of fairness, it is reasonable to provide equitable access to treatment, to all those who may benefit.

8.0.3 Closing remarks

High quality clinical care affects engagement, and is essential for building a foundation of mutual trust between people seeking treatment and clinicians, where both see each other as collaborators battling disease, rather than as adversaries. John Rawls described this foundation in relation to perceptions of justice and fairness:

> (1) Besides a capacity for a conception of the good, people have a capacity to acquire conceptions of justice and fairness (which specify fair terms of cooperation) and to act as these conceptions require; (2) when they believe that institutional practices are just, or fair (as

> these conceptions specify), they are ready and willing to do their part in those arrangements provided they have reasonable assurance that others will also do their part; (3) if other persons with evident intention strive to do their part in just or fair arrangements, people tend to develop trust and confidence in them; (4) this trust and confidence becomes stronger and more complete as the success of shared cooperative arrangements is sustained over a longer time; and also (5) as the basic institutions framed to secure our fundamental interests (the basic rights and liberties) are more firmly and willingly recognised.

(Rawls, 1987)

This project, in aggregate, has sought to incorporate the experiences and voices of people in need of healthcare that is just and equitable. As summarised by Lokugamage *et al.*,:

> Ultimately, toppling endemic power imbalances in medicine requires the input of people who have experienced the cognitive dissonance of confronting personal and healthcare structural biases, so that those providing healthcare fully comprehend the lived realities of the individuals they seek to serve. This is work that cannot be avoided.

(Lokugamage, Simpson, & Chew-Graham, 2021)

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