

THE ROLE OF EVIDENCE-BASED HEALTHCARE IN IMPROVING OUTCOMES FOR LOWER LIMB OPEN FRACTURES

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Abstract

Introduction: Lower extremity open fractures are severe, limb-threatening injuries. To improve outcomes, a multidisciplinary approach has been advocated. In the United Kingdom, their treatment is standardised following clinical guidelines. However, management of these injuries globally is unknown. The aim of this thesis is to address this gap and optimise the uptake of evidence to improve the management and outcomes of patients with open lower limb fractures.

Methods: I used a mixed methods approach for my thesis research, which included a large multinational survey of outcomes, comparing results in settings with and without guidelines; an evaluation of available guidelines based on a systematic scoping review; a qualitative study exploring attitudes toward, barriers to, and limitations of developing guidelines for open extremity trauma; and a Delphi study to validate a framework to aid introduction of evidence-based practice into settings with no guidelines.

Results: The INTELLECT study included 2,694 cases of open fractures treated in 16 countries. Patients managed in settings with clinical guidelines were more likely to present better outcomes. A systematic scoping review identified only five countries that currently had clinical guidelines for open lower limb fractures. A reflexive thematic analysis of twelve interviews involving senior orthopaedic and plastic surgeons in countries with no guidelines was used to conceptualise a framework to aid in implementation of guidelines. This framework was later validated by a consensus of members of an international panel consisting of forty-three orthopaedic and plastic surgeons using Delphi methodology.

Conclusion: Significant international variability exists in open lower limb fracture management. Evidence-based clinical guidelines for these injuries are rare on a global scale. Clinician, team, system, and cultural factors should be considered by stakeholders planning the implementation of clinical guidelines to optimise the uptake of evidence in management of open fractures. The proposed framework summarises these elements.

Acknowledgements and Declaration of Authenticity

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Declaration

This dissertation is submitted in partial fulfilment of the requirements for the degree of Doctor in Philosophy. Except where otherwise indicated, the research presented is the result of my own work. I am author of all the figures included in this thesis, and for figures adapted from external sources this is clearly indicated and referenced. I have acknowledged all researchers who granted assistance above, with a detailed list of contributions available in Appendix 22. This thesis complies with the Department of Continuing Education regulations, including word limitations for DPhil submissions, with a total word count of 46,805. The views expressed in this thesis are my own and not necessarily those of my supervisors, AO UK&I, Kellogg College, The University of Oxford, the National Health Service or The University of Texas Health Science Center at San Antonio.

Publications and Presentations

Publications Arising from Thesis Research:

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List of Abbreviations

AGREE	-	Appraisal of Guidelines Research and Evaluation
ATLS	-	Advanced Trauma Life Support
BAPRAS	-	British Association of Plastic, Reconstructive and Aesthetic Surgeons
BAPS	-	British Association of Plastic Surgeons
BOA	-	British Orthopaedic Association
BSSH	-	British Society for Surgery of the Hand
CUREC	-	Central University Research Committee
EQUATOR	-	Enhancing the Quality and Transparency of Health Research
GRADE	-	Grading of Recommendations Assessment, Development and Evaluation
GDPR	-	General Data Protection Regulation
GDP	-	Gross domestic product
ICOPLAST	-	International Confederation of Plastic Surgery Societies
IL	-	Interleukin
INTELLECT	-	International Lower Limb Collaborative
IQR	-	Interquartile range
ISRCTN	-	International Standard Randomized Controlled Trial Number
KIMS	-	Dutch Federation of Medical Specialists
LINEAGE	-	Limitations to the Implementation of Open Trauma Guidelines
LMIC	-	Low- and middle-income countries
LEAP	-	Lower Extremity Assessment Project
MCS	-	Mental Component Summary
MTC	-	Major Trauma Centre
NCEPOD	-	National Confidential Enquiry into Patient Outcome and Death
NICE	-	National Institute for Health and Care Excellence
PROMS	-	Patient-reported outcomes
PCS	-	Physical component summary
QOL	-	Quality of life
QUINTET	-	Quality of Life after Open Extremity Trauma
RSTN	-	Reconstructive Surgery Trials Network
REC	-	Research Ethics Committee
SF-12	-	Short Form 12
SECOT	-	Sociedad Española de Cirugía Ortopédica y Traumatología

SICM	-	Società Italiana di Chirurgia della Mano
SICPRE	-	Società Italiana di Chirurgia Plastica Ricostruttiva ed Estetica
SIM	-	Società Italiana di Microchirurgia
SIOT	-	Società Italiana di Ortopedia e Traumatologia
STROBE	-	Strengthening the Reporting of Observation Studies in Epidemiology
TARN	-	Trauma Audit Research Network
TNF	-	Tumour necrosis factor
UK	-	United Kingdom
USA	-	United States of America
VAS	-	Visual analogue scale
WHO	-	World Health Organization
WOLLF	-	Wound Management of Open Lower Limb Fractures Randomised Clinical Trial

Chapter 1 Background and Rationale for Thesis Research

The purpose of this first chapter of my thesis is to present a concise overview of the overarching themes, controversies, and unanswered questions that form the basis of my doctoral research. I therefore structured the chapter to include descriptions of the concepts and scholarly literature relevant to the research in narrative form so as to provide a context for the work presented later in this thesis.

This background chapter begins with a succinct discussion of the impact of trauma, on a global scale, from an epidemiological and public health point of view. Following this synopsis, I proceed to discuss the pathophysiology of fractures, the definitions relevant to open fractures, the effects that this type of injury has on the patients who sustain them, and current concepts related to the management of open fractures of the lower extremities.

The chapter next discusses the emergence of evidence-based healthcare, with its reasoned approach to clinical decision-making, and its impact on improving patient outcomes in recent decades. Also, I highlight the successful implementation through clinical guidelines of evidence-based concepts for the management of open fractures within specific contexts.

Throughout this chapter, gaps in the body of literature are highlighted, and the chapter concludes with the primary goal of this thesis, which is intended to fill some of these gaps, and the four objectives defined to attain this goal.

1.1 The Global Impact of Trauma

1.1.1 Epidemiology of Trauma

Physical injuries remain one of the leading causes of morbidity and mortality worldwide, especially among children and young adults in both developed and developing nations. It is estimated that over 5 million trauma-related deaths occur annually worldwide.[1] Injuries account for approximately 8% of mortality globally, surpassing malaria, tuberculosis,

and HIV combined, with an estimated 57.4 deaths per 100,000 population.[2] According to the World Health Organization (WHO), road traffic accidents are responsible for 29% of these deaths, followed by suicide and falls at 16% each and homicide at 11%.[3]

Men are more than twice as likely to die from trauma as women, with 77.6 deaths per 100,000 male population versus 36.9 deaths per 100,000 female population. Younger men are the group having the highest risk, with road traffic accidents the leading cause of death for males between 15 and 29 years of age and the second highest cause of death for men aged 30 to 49 years of age.[3]

For every trauma patient who dies, many more survive but with significant rehabilitation needs and possibly disability. This is reflected in the injury pyramid[2] shown in Figure 1.1, where the top of the pyramid represents the small proportion of patients suffering fatal injuries and those with the least severe injuries situated at its base. Regardless of their severity, all traumas lead to lost quality of life (QOL) and economic burden; worldwide, it is estimated that 16% of disability is attributable to trauma.[4,5] Moreover, those affected by trauma and their caregivers incur not only the direct costs associated with healthcare but also the indirect costs comprised of lost productivity and lost earnings.[2] In the United States alone, the cost of road traffic accidents is $300 million USD, equivalent to 1.6% of the US gross domestic product (GDP).[6]

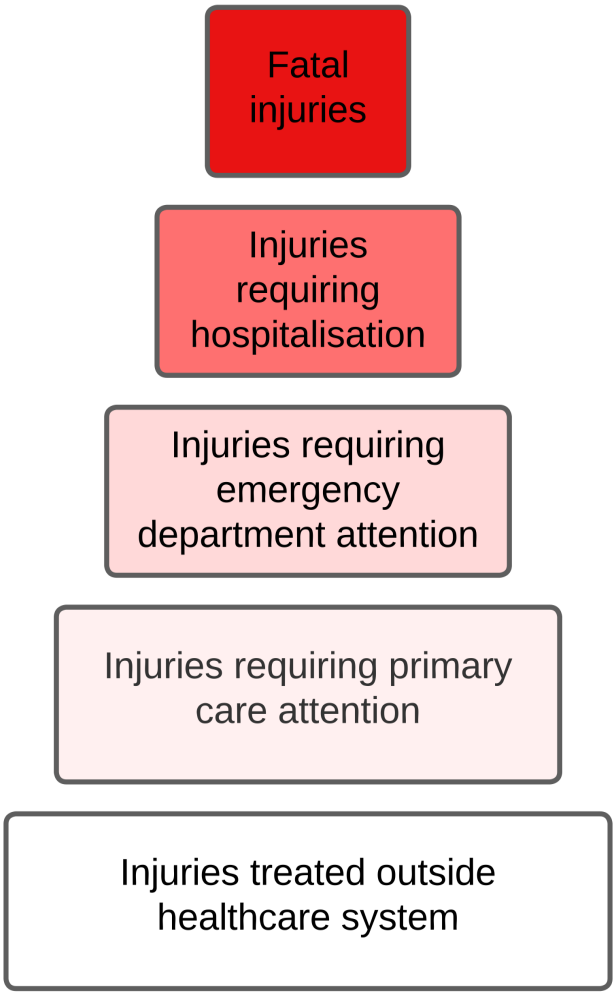


Figure 1.1: Injury Pyramid. Adapted from "Injuries and violence: the facts 2014" [2]

1.1.2 Global Inequalities in Trauma Prevention and Care

Over the last 50 years, developed economies have been able to consistently reduce morbidity and mortality associated with trauma,[7] primarily due to improvements in transportation safety, building regulations, and health and safety policies.[1] However, morbidity and mortality due to trauma in low- and middle-income countries (LMICs) have not followed this trend (**Table 1.1**).[8]

Table 1.1: Injury death rates by WHO region and income. Adapted from *The Global Burden of Disease*, 2004 update.

WHO Region	Injury deaths per 100,000 population	
	High-Income Countries	Low- and Middle-Income Countries
African	-	98,8
Americas	55.4	74.1
Eastern Mediterranean	60.1	95.4
European	45.6	126.8
South-East Asia	-	116.6
Western Pacific	58.2	70.2

The treatment of traumatic injuries in resource-constrained settings presents several challenges including but are not restricted to deficient and poorly maintained infrastructure,[9] unreliable supplies of clean water[10] and electricity;[11] restricted access to operating theatres and surgical supplies;[12] limited training opportunities for healthcare professionals together with poor workforce retention;[13] and lack of standard operating procedures for surgical interventions.[14,15]

Currently, more than 90% of trauma-related deaths occur in developing nations.[2] According to estimates, improving access to timely and cost-effective medical attention could dramatically reduce this.[16] Moreover, the societal burden of injury and resulting disability is particularly important in LMICs, where social welfare and rehabilitation systems may not be available.[17]

1.2 Open Long Bone Fractures

1.2.1 Bone Fractures and Healing

Bone fractures are severe injuries defined by loss of osseous continuity following a traumatic insult.[18] Fractures can be classified as *closed* or *open injuries*. In the former, although the soft tissues around the fracture may be injured, there is no communication

between the fracture site and the external environment, whereas in the latter, the soft tissue injury leads to tearing of the skin and underlying soft tissues.[19]

Fractures can heal through either primary or secondary bone healing. Secondary, or indirect, bone healing is the most common mechanism, as it does not require an anatomical reduction of the fractured fragments or rigid fixation.[20] In this process, following haemostasis and clot formation at the fracture site, multiple inflammatory mediators are released, including tumour necrosis factor (TNF) and Interleukins (IL)-1,6, 11 and 18.[21] This initial inflammatory phase is characterised by neutrophil chemotaxis and infiltration and increased macrophage activity.

Following the inflammatory phase is a proliferative phase involving mesenchymal stem cell recruitment and angiogenesis. Increased fibroblast and osteoblast activity results in the deposition of a collagen-rich matrix called callus, which bridges the fracture site.[22] This soft callus then undergoes calcium deposition, gaining rigidity and gradually recovering the capacity to resist deforming forces.[23] Finally, the callus is remodelled, guided by external stimuli that regulate osteoblast and osteoclast activity, with preferential deposition of bone along weight-bearing vectors.[24]

Primary, or direct, bone healing is uncommon without medical assistance, as it requires anatomical reduction and rigid fixation to provide absolute stability, which usually requires surgical access of the fracture site and internal osteosynthesis. Primary bone healing entails no callus formation, but rather direct repair of the cortices mediated by the cutting cones of Haversian systems traversing the fracture site.[20]

The bone healing process requires the close interaction of biological and mechanical factors. The “diamond concept” of fracture healing summarises these interactions, identifying the roles of vascularity, host factors, mechanical stability, availability of osteoprogenitor cells, adequate scaffolding and the presence of growth factors, all acting together in a biological chamber.[25] If any of these factors is affected, such as vascular inadequacy or the presence of

infection, the bone healing process may be impaired, resulting in delayed healing or non-union.

1.2.2 Definition and Relevance of Open Fractures

Open fractures are severe injuries in which the fracture site communicates with the external environment. The disruption on the soft tissues adversely affects the biological chamber that promotes bony healing, due to the associated impairment of vascularity, and reduced availability of osteoprogenitor cells and necessary growth factor.[26,27] Furthermore, communication between the fracture site and the exterior can lead to ingress of microorganisms and subsequent infection.[28]

The incidence of open fractures has been estimated to be 30,7 per 100,000 adults per year, representing approximately 2.6% of all fractures.[18] These can be life-changing injuries as the consequences of the resulting physical and psychological trauma can take years to resolve.

Restoration of the soft tissues around the fracture site is required in order the re-establish the biologic chamber needed for the bone to heal. In less severe injuries, direct closure can achieve this. However, when this is not possible, a flap reconstruction may be required.[29] If bone healing is delayed, not achieved, or complicated by infection, QOL is often impacted, primarily due to effects on the ability to mobilise pain free and to return to previous life roles.[30] It has been estimated that the incidence of non-union and amputation for patients requiring a soft tissue reconstruction following an open fracture is as high as 17.9% and 7.3%, respectively.[31]

The financial burden resulting from trauma for the patient and for health systems has been investigated in recent years. According to a systematic review, the cost of initial hospitalisation and treatment in the United Kingdom (UK) can vary between £9,401 to £13,855; in the United States, this reaches £126,479.[32] Whilst 89% of those included in the review were working prior to sustaining an open fracture, only 60% were able to return to

their previous occupation following their injury, and 17% had to change occupation following the injury. Moreover, healthcare expenditure and productivity losses increase if infection delays fracture healing and secondary procedures are needed. In the UK, France, and Germany, this societal cost one year post-injury has been estimated to be between €44,757 and €50,197.[33]

Chung et al. (2009) used data obtained for the Lower Extremity Assessment Project (LEAP study)[34] to calculate the lifelong costs of complex limb salvage versus amputation. For patients undergoing reconstruction, the cost was approximately $163,282 USD, with half expended in the first two years following injury. For patients requiring an amputation, the initial cost was lower, an estimated at $91,105 USD. However, the lifelong expenditure for amputation was higher than for reconstruction, reaching $509,275 USD, due primarily to the acquisition and maintenance costs of prosthesis.[35]

The most feared complication following an open fracture is infection due to the ability of certain microorganisms to adhere to and form a biofilm on the injured bone, soft tissues, and internal fixation material.[36] *Staphylococcus aureus*, the most commonly isolated bacteria in bone infection, expresses adhesins that allow it to form such attachments. This microorganism is also capable of evading the immune response by secreting capsular polysaccharides and can even promote endocytosis by osteoblasts, surviving inside them for prolonged periods of time.[37] Coagulase-negative *Staphylococcus* is another microorganism commonly associated with bone infection following open fractures due to its capacity to create a biofilm around implants and thereby making its eradication with antimicrobial therapy alone almost impossible.[38]

Although there are no universally accepted classifications of fracture-related infection, time of onset can be used to reflect the extent of biofilm formation and its impact on wound healing (**Table 1.2**),

Table 1.2: Bone infection following open fractures. Adapted from *Standards for the Management of Open Fractures*[39]

	Time of onset	Clinical manifestation	Pathophysiological features
Early infection	Less than 2 weeks	Swelling, redness, and pain around the fracture site that can also involve discharge and pyrexia.	Virulent pathogens, such as *Staph aureus* in the context of immature biofilm
Delayed infection	2-10 weeks	Clinical manifestation can resemble early infection, but usually with less intense signs and symptoms	Infections commonly due to less virulent pathogens, such as *Staphylococcus epidermidis*. Mature biofilm is more resistant to antimicrobials. Bacterial bone invasion can affect fracture healing.
Late-onset infection (osteomyelitis)	More than 10 weeks	Subtle clinical signs, rarely displaying systemic manifestation	Fracture healing may be complete or incomplete. Low-virulence organisms cause local inflammation and osteolysis that can lead to fixation instability. Local periosteal reaction leads to the formation of involucrum.

Established osteomyelitis can lead to persistent fracture instability, delayed recovery, and, potentially, amputation in severe cases.[40] It requires a multidisciplinary treatment to optimise the host's response, reduce the bacterial load at the focus of infection, identify the responsible pathogens, and select the right antimicrobial regime.[39] This treatment also involves meticulous excision of the infected bone and soft tissues, along with multiple tissue samplings for microbiological cultures. Targeted antibiotic therapy and reconstruction of any resulting bone and soft tissue defects usually follows.[41] Even if the limb is salvaged and union is achieved, failure to eradicate the infection may lead to intermittent reactivation characterised by recurrent bouts of local inflammation and chronic sinus discharge.[36]

1.2.3 Patient-Reported Outcomes and the Psychosocial Impact of Open Fractures

Patient-centred care is an approach to delivering healthcare services that encourages active collaboration and shared decision-making.[42] It encourages the participation of the patients and their families in their care, while taking their preferences, culture, values, and financial circumstances into consideration. Ensuring that patients take an active role in health promotion and illness recovery has shown to improve patient experience, safety of the care delivered, and clinical effectiveness.[43]

From a clinical research perspective, two main strategies have been used to investigate patient experience following an open fracture: qualitative research methods and analysis of quantitative, patient-reported outcome measures (PROMs). The former is an umbrella term that includes ontological and epistemological positions on the nature of truth and how it can be studied, especially that regarding subjective experiences. Qualitative research strategies also permit detailed information to be obtained from individuals or groups through observation or interviews. Data are analysed inductively to develop patterns and themes from the interaction between observation and the researcher,[44] allowing formulation of frameworks to understand complex interactions and generation of new hypotheses that could be addressed by future quantitative research methods.[45]

PROMs, on the other hand, are instruments that aim to capture the individual and subjective perspectives of patients in relation to a predetermined condition or treatment.[46] These are usually presented in the form of a questionnaire to which patients are asked to respond; their answers to the questions posed result in one or more scores that can then be analysed quantitatively. Developing a PROM involves a rigorous multi-step process involving both qualitative and quantitative research methodology.[47]

First, patients' views are gathered through interviews or focus groups, allowing the researchers to identify, define, and understand what needs to be measured. Once these items

are defined, the questions needed to best subject responses related to them are developed and then tested on subjects to assess their comprehensibility and appropriateness. Prior to conducting the research, a pilot may be conducted in which the draft questionnaire is administered to a small sample of subjects to assess the questionnaire's reliability and validity and that of the scores obtained through it. The draft questionnaire may then be revised and administered to the full sample selected for analysis.

The psychosocial repercussions of open fractures and its impacts on QOL have been measured in recent years using both qualitative research methods and PROMs. Tutton et al. (2018) interviewed 20 hospitalised open-fracture patients 12 days following their first operation for the fracture.[48] Employing a phenomenological approach, the researchers asked patients to describe their experience of an open fracture. These patients' descriptions of their perspectives on the experience revealed vulnerability as a common theme that went beyond the physical harm sustained after the injury.

In addition, study participants described experiencing emotional fragility secondary to the psychological work required to make sense of the traumatic event along with psychological shock derived from being informed that they had suffered a limb-threatening injury. These feelings intertwined with panic and reluctance to accept the effects of the injury and its impact on body image. Another theme developed from the interviews was their realisation of having to live with their injuries over the long term. Occurring some time after the accident during the patient's recovery, this realisation involved dealing with both their immediate disability and the persistent uncertainty this generated.

In terms of long-term recovery, Rees et al. (2019) interviewed 25 patients who had undergone treatment for an open fracture two to four years previously.[49] Also utilising a phenomenological approach, the authors investigated patient experience while rehabilitating from injury. The patients interviewed consistently reported struggling to recover, including the need to renegotiate their ways of living to accommodate their new reality. Along with

physical limitations and the inability to move as freely as prior to their injury, themes of disempowerment, of needing to rely on others, and of uncertainty about their futures marked patient experience in this group.

Although from a quantitative perspective, studies measuring PROMs following an open fracture have yielded similar findings. The Wound Management of Open Lower Limb Fractures (WOLLF) Randomised Clinical Trial compared disability, deep infection rates, and QOL among patients treated with negative pressure dressings compared to those treated using conventional dressing care following initial debridement.[50] Employing the EuroQol 5-dimension, 3-level questionnaire and the Short Form-12 to measure health-related QOL among patients who had experienced an open, lower limb fracture, the authors reported severe drops in health-related QOL in some patients to scores equivalent with being dead. Similar findings were reported in studies measuring QOL after such injuries in patients recruited in the United States.[51] However, a recent systematic review by Schade et al. (2020) was unable to identify any studies that reported PROMs for patients who sustained their injuries in low- and middle-income countries.[52]

Another systematic review of lower limb open fracture outcomes identified a wide variability of outcomes, potentially increasing risk of reporting bias. This article emphasised how reporting psychological measures and physical functioning assessments remain uncommon in the literature.[53] Using this systematic review as a starting point, Aquilina et al. (2023) conducted a thematic analysis followed by an application of the Delphi process to establish a core outcome set for lower limb fractures. The consensus meeting that included clinicians, researchers, patients, and carers identified a four-core outcome set that included: "walking, gait and mobility," "being able to return to life roles," "pain or discomfort," and "quality of life."[54] Although no single validated, currently available instrument assesses all four sets, the same research group recommended using the Lower Extremity Functional Scale in conjunction with the EuroQol 5-dimension, 3-level questionnaire to do so.[30]

1.3 Management of Open Fractures

1.3.1 History of the Management of Open Fractures

The relevance of open fractures and the importance of decontaminating such injuries is well documented in both ancient Egyptian and Greek records.[55] This key concept persisted through the Middle Ages into modern times with the rise of barber-surgeons, predominantly in times of war.[56]

Even though Pierre Joseph Desault (1744-1795) is believed to have first introduced the concept of *debridement*, [55] the term did not gain its current meaning until the contributions of Carl Reyher (1846-1890) and Antoine Depage (1862-1925), i.e., the systematic, mechanical cleansing and active removal of necrotic tissues to prevent infection of traumatic injuries.[57]

Prior to the introduction of aseptic surgery and antibiotics, early amputation was considered a life-saving intervention for patients sustaining open fractures by reducing these patients' risk of deadly sepsis.[58] An estimated 60,000 amputations were performed during the American Civil War (1861-1865).[59] However, despite this aggressive surgical management, a high mortality rate was nonetheless reported for open fractures of the lower extremities. German surgeon Theodor Billroth (1829-1894) documented a mortality rate of 49.5% for his cohort of 93 patients treated in Zürich between 1860 and 1876.[60] Not until the introduction of antibiotics did mortality rates for open fractures decrease.[61,62] Early administration of antimicrobials also proved beneficial in reducing infection rates, especially when associated with copious irrigation, adequate debridement, and skeletal stabilisation.[63]

During most of the 20th century, open fractures that were not amenable to direct closure or could not be reconstructed using local tissues would be treated conservatively for long periods of time. This approach eventually concluded with the wounds healing either by secondary intention or by application of a delayed skin graft. Due to the associated high rates of osteomyelitis and non-union, this latter method resulted in a 15% delayed amputation.[64]

1.3.2 Emergence of Orthoplastic Surgery

During the first half of the 20th century, orthopaedic and plastic surgery developed into separate surgical specialties, a process accelerated by the demand in expertise to treat wounded military personnel during the First and Second World Wars.[65,62]

Even early in their development and despite their different practices, plastic and orthopaedic collaborated fruitfully.[66,67] However, it was not until towards the end of the last century that the concept of "orthoplastic surgery" emerged, defined as *"a treatment approach that requires the principles and practices of both specialties of orthopaedic surgery and plastic surgery to be applied to clinical problems simultaneously."*[68] This resulted from parallel advances in both specialties in the field of limb salvage, including the development of contemporaneous skeletal fixation methods and the advent of microsurgery. The latter allowed soft tissue transfer to reconstruct wounds that previously could only be managed conservatively.[69]

The orthoplastic approach for open fractures advocates for a joint assessment of the fractured bone and injured soft tissues performed by orthopaedic and plastic surgeons.[39] The severity of the injury may not be apparent until a thorough wound excision is performed.[70] The National Institute for Health and Care Excellence (NICE) recommends that consultants from each specialty participate in the extension of wounds using safe incisions, careful removal of any devitalised soft tissue, and delivery of bone ends for assessment and irrigation. This approach allows for shared decision-making and so can aid in later planning of definitive skeletal fixation and soft tissue reconstruction, which should ideally be performed together if internal fixation is being used.[71,72] Ultimately, for these interventions to occur at the right times and by surgeons having the necessary expertise, patients who have sustained open, long bone fractures should be treated at specialist centres having both plastic and orthopaedic capacities.[73]

1.4 Evidence-Based Medicine

1.4.1 Definition and Levels of Evidence

Evidence-based medicine, commonly viewed as a paradigm shift in clinical practice, emerged in the last decade of the 20th century.[74] Traditionally, decision-making in medical practice was based primarily on clinical experience, pathophysiological knowledge, and common sense. In this model, high value was placed on expert opinion, whether to understand the prognosis of a condition, estimate the efficacy of a treatment strategy, or assess the reliability of a diagnostic test.[70] In contrast, evidence-based medicine recognises the importance of clinical experience and of understanding the underlying cause of disease. However, although it encourages clinicians to search and appraise the original literature, it places less emphasis on expert opinion within a field. Evidence-based medicine has been described as

> *the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.*[75]

Preceding the emergence of evidence-based medicine was the concept *levels of evidence*. In 1979, the Canadian Task Force for Medical Examinations proposed a system for rating available evidence that could then also be used for grading clinical recommendations.[76] The concept levels of evidence relies on the premise that certain study designs are better at controlling for confounding factors and limiting the effect of bias than others. For example, randomised controlled trials are an application of levels of evidence. Through randomisation, they distribute confounding factors evenly among study groups, thereby reducing systematic error. Recommendations arising from randomised controlled trials are therefore assumed to provide a higher level of evidence than those derived from non-randomised studies. In contrast, expert opinion is assumed to assign the lowest level of evidence, as this typically results from unstructured observation in clinical practice.[77]

To illustrate these concepts, the pyramid shown in **Figure 1.2** is used to portray the hierarchy of levels of evidence.[78] Study validity is high at the top of the pyramid, whereas, inversely, risk of bias is high at its lower levels. Accordingly, pre-clinical studies are located at the base, followed one level up by expert opinion and case reports. Above these fall primary research studies, comprised first of both retrospective and prospective observational studies and second of randomised controlled trials. Above primary research studies at the tip of the pyramid sit secondary research studies, starting with systematic reviews and meta-analyses.[79]

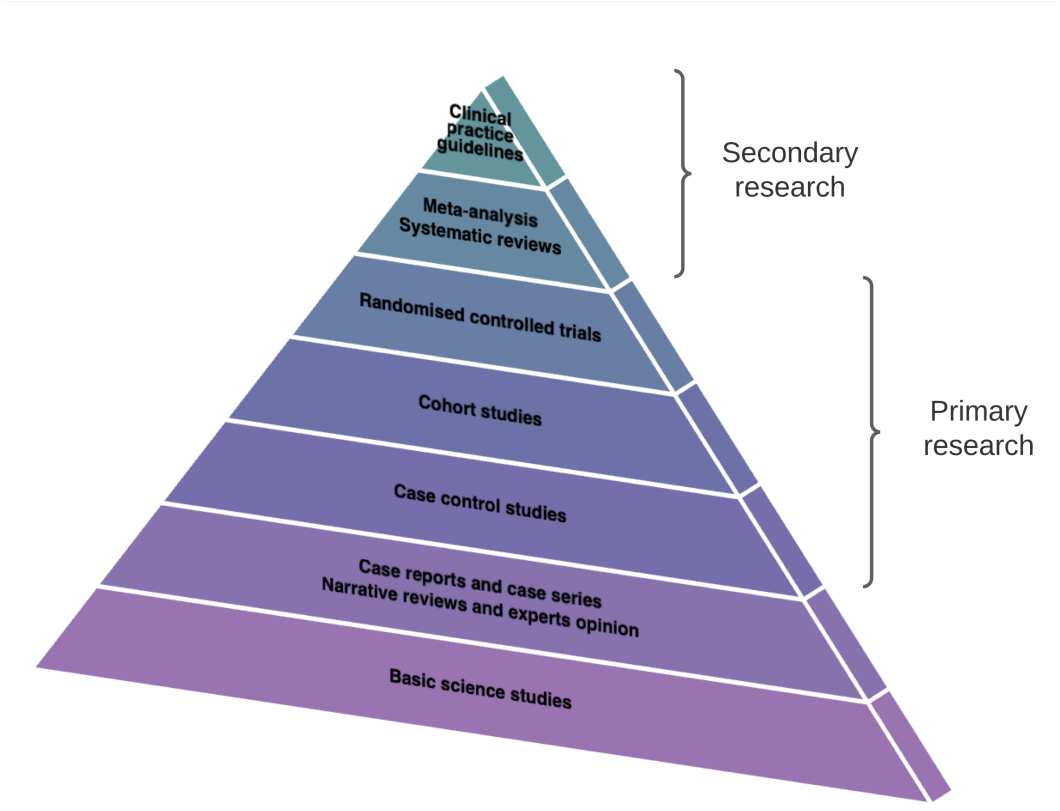


Figure 1.2: Pyramid of evidence. Adapted from Murad et al. [78]

Systematic reviews lie above randomised controlled trials because these are designed to summarise the findings obtained by multiple randomised controlled trials addressing the same clinical question. Furthermore, systematic reviews provide the opportunity to produce a

quantitative synthesis of the available data by means of *meta-analysis*, which pools and analyses gathered data, thus benefiting from the law of large numbers to increase the validity of findings.[80]

However, systematic reviews and meta-analyses are not the only methodologies available for summarising evidence. Systematic reviews themselves can also be grouped, appraised, and synthesised to obtain a synopsis of systematic reviews, or *synopsis of syntheses*, which provides a comprehensive summary in relation to a focused clinical question. As in isolated systematic reviews, synopses of syntheses allow for quality appraisal, data extraction, and meta-analysis,[81] usually accompanied by a brief commentary. These, however, do not tend to be broadly disseminated and are ordinarily found in evidence-based journals or specialised archives such as the Centre for Reviews and Dissemination Database hosted at the University of York.[82]

Sitting at the top of the pyramid of evidence above synopses of synthesis is a further category, the *denominated summary of evidence*, which includes evidence-based textbooks and evidence-based clinical practice guidelines.[83]

1.4.2 Role of Clinical Practice Guidelines in Modern Healthcare

Clinical practice guidelines document evidence-based recommendations intended to standardise and optimise patient care, while also considering benefits and costs within the overarching healthcare system.[84] These documents aim to close the gap between the actual care delivered and the best care possible as indicated by the available evidence gathered to date. Minimising this gap is achieved by promoting interventions having proven benefit, while discouraging ones deemed ineffective.[85]

Clinical practice guidelines have gained popularity across all areas of medicine within the context of wider access to healthcare by previously underserved groups, population ageing, emergence of new therapeutic alternatives, and rising costs of health services.[86] Thus, clinical practice guidelines have become an important resource for clinicians, academics,

policy makers, payers, educators, and patients alike, as all these groups benefit from addressing variations in service delivery usually associated with under- or over-utilised capacity.[87] By 2011, there were over 3,700 guidelines from 39 countries in the *Guidelines International Network Database*[88].

Also discussed are the role clinical practice guidelines can play in shifting attention towards previously overlooked conditions, spurring the creation of new services in order to comply with new guidelines.[86] As publicly available documents, these can play a significant role in patient education and involvement in their own care. Along with the inclusion of lay summaries, having patient representatives participate in the development of clinical guidelines is not uncommon.[89] Depending on the overarching healthcare system, guidelines can also play a role in determining private insurance coverage and public reimbursement for healthcare providers.

Among their multiple benefits, guidelines also provide a standard for conducting audits to ascertain the quality of care delivered, thus promoting continuous improvement in healthcare. They can also provide useful data to measure performance, improve efficiency, and achieve accreditation.[90] Lastly, clinical practice guidelines can highlight gaps to be addressed in future research.

However, these potential benefits can become potential detriments should a clinical practice guideline proves to be unsound. Over the years, several concerns have been raised regarding the quality of some guidelines, [91,92] highlighting how flawed recommendations can lead to inefficiency, loss of public trust, and, most importantly, avoidable patient harm.[93] In order to ensure that the recommendations included in a guideline reflect the best available evidence, a rigorous and transparent process should be followed for evaluating the literature, appraising the evidence, and reaching clinically meaningful conclusions.[94] Thus, guideline appraisal instruments are tools that offer a framework to evaluate the quality of existing statements and guide the development of future high-quality guidelines.[95]

1.4.3 Evolution of Open Fracture Clinical Guidelines in the United Kingdom

The current state of clinical practice guidelines for open lower limb fractures in the UK is the result of three decades of collaboration beginning with a combined meeting of the British Orthopaedic Association (BOA) and the British Association of Plastic Surgeons (BAPS) in 1991. At that time, the importance of cooperation between plastic and orthopaedic surgeons in managing this type of complex injury was recognised. The report produced as a consequence of this meeting was published in 1993; its purpose was to increase awareness of and offer advice on the joint management of open fractures.[96]

Following this effort, a BOA/BAPS work group was established to evaluate the impact of this report. It was recognised that the proposed optimal management of open lower limb fractures was far from being common practice in the UK, with most out-of-hours trauma operating being undertaken primarily by unsupervised junior surgeons. These findings led to the publication of a second updated and extended report in 1997.[97] This included, for the first time, sections on injury recognition, communication, and joint care; timing of fixation and soft tissue reconstruction; pre-operative management; first orthopaedic procedure (debridement); safe incisions and fasciotomy; and common methods for soft tissue reconstruction. The recommendations included were based on both existing literature and the expert opinions of the five orthopaedic and three plastic surgeons who developed the document.

Although these reports were able to raise awareness of best practices in lower extremity trauma, their publication did not immediately lead to a change in the standard of care delivered. A survey of orthopaedic surgeons published at that time showed that only 57% of the respondents were aware of the BOA/BAPS guidance, that less than 29% of orthopaedic consultants consulted a plastic surgeon pre-operatively about an open fracture, and that only 43% involved plastic surgeons at all.[98] A retrospective audit conducted in a large teaching hospital that included 66 patients treated for open fractures between 2001 and 2003 revealed

an average transfer delay of 7.8 days from presentation to assessment in a specialist centre. Following admission, 50% of the operations were performed by trainees, and plastic surgeons were involved in only 62% of these cases.[99] With only 25% of acute hospitals having plastic surgery departments at that time and the majority of open fractures presenting to district hospitals, further change was required to address geographical constraints and avoid unnecessary out-of-hours operations performed by inexperienced surgeons.[73]

A report titled *Trauma, Who Cares?* published in 2007 by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) based on information obtained from the Trauma Audit Research Network (TARN) highlighted several deficiencies in the management not only of open fractures but also of major trauma. According to it, 60% of patients received substandard care due primarily to cases being treated in district general hospitals, with high-volume trauma centres being a positive outlier of good practice. The report consequently recommended regional planning for the effective delivery of trauma services centralised in major trauma centres (MTCs).[100] This ultimately led to the reorganisation of regional trauma networks, with 27 designated MTCs in England that began operation as such between 2010 and 2012.[101]

During the planning phase that led to the implementation of trauma networks, BOA and the then re-named British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS, previously BAPS) published *Standards for the Management of Open Fractures of the Lower Limb.*[102] This presented standards of care that, according to the authors, every patient with open fractures should receive and also highlighted the importance of developing specialist services with multidisciplinary capabilities. It also mandated that patients with open fractures should not be transferred to hospitals lacking the necessary capabilities so as to avoid unnecessary delays in definitive treatment. It also redefined the ideal timing of wound debridement from 6 to 24 hours and recommended that this be done by an experienced surgeon during working hours.

According to several centres, the introduction of these standards led to a substantial improvement in open lower limb fracture care in the UK.[103–106] International units that have adopted similar guidelines as a standard of care have reported similar results.[107,108] Some of the recommendations made by BAPRAS and BOA in 2009 were later revisited by NICE in 2016 in a section within its complex fracture guideline dedicated to open injuries.[71] BAPRAS and BOA updated their standards in 2020, expanding these to cover several areas not addressed in their 2009 standards.[39]

1.5 Differing Management of Open Fractures in High-Income Versus Middle- and Low-Income Countries

Despite the advancements in open fracture care discussed above, its management and outcomes exhibit significant variability in different settings according to current reports. Pouramin et al. (2020) analysed the recorded time to hospital admission for a subgroup of patients included in the International Orthopaedic Multicenter Study (INORMUS). For 5,256 open fractures occurring in low- and middle-income countries, the median time to hospital admission was five hours, with 71.9% presenting after the recommended window of two hours.[109] Only 45.3% of these patients utilised ambulances to reach a healthcare facility, while 41% used a private vehicle and 10.4% public transport.

To the best of my knowledge, only one previous publication has compared the management and outcomes of lower limb trauma in high- versus middle- and low-income economies, as defined by the World Bank. Boriani et al. (2017) conducted a multicentric, prospective cohort study of patients with open fractures exhibiting severe soft tissue compromise.[107] Two participating units located in the UK and Pakistan adhered to an orthoplastic approach based on the BOA/BAPRAS 2009 standards of care, while the third unit located in Italy had no access to plastic surgery. Patients in the orthoplastic group achieved statistically significant shorter times to wound healing, durations of hospital stay, times to bone union, and times to full weight-bearing. Patients treated in the UK and Pakistan

also reported significantly superior functional recovery measured with respect to the Enneking score and a lower bone infection rate than the group in Italy. Although these results support the importance of multidisciplinary collaboration, the pooling of patients from the UK and Pakistan impedes further comparisons based on socio-economic factors.

Even though Boriani et al. (2017) presented a breakdown of demographic information and of the modalities of soft tissue closure, they failed to do so for functional and recovery outcomes. Given that the orthoplastic group included 88 patients treated in the UK and just 22 treated in Pakistan, the overall results were likely skewed towards the UK practice.[107]

1.6 Thesis Rationale, Aim, and Objectives

1.6.1 Rationale and Aim

In this chapter, I showed trauma to be a major source of morbidity and mortality on a global scale[1] and trauma's resulting burden, both physical and financial, to be relatively higher in low- and middle-income countries than in high-income ones.[2,8] Moreover, in the former, resource constraints and lack of infrastructure significantly increase the challenge of providing access and delivery of emergency healthcare services.[17]

Although trauma can vary greatly in terms of severity and can be either isolated or in the context of polytrauma, the focus of my doctoral research was restricted to the management and outcomes of open long bone extremity fractures. The relevance of this type of injury is associated with its limb-threatening potential and also its potential for life-changing consequences, [31] long-term physical disability, and profound psycho-social repercussions.[30]

As described above, the current management of open fractures has been the result of centuries of evolution.[55,57] The emergence of the role of military surgeon followed by the advent of antibiotics in the 20th century significantly reduced the morbidity and mortality associated with open fractures. [61,62] Further, close collaboration between orthopaedic and plastic surgeons has significantly improved the outcomes of patients with this type of injury.[68]

An orthoplastic approach advocates timely and multidisciplinary care in specialised centres having the requisite resources.[73] To the best of my knowledge, no previous reports have discussed the management and outcomes associated with this type of injury at a global level, including resource-constraint settings.

In the UK, current clinical guidelines for open lower limb fractures offer guidance not only to clinicians in both pre-hospital and hospital settings but also to the overarching healthcare system; these guidelines relate to the resources and capacity needed to treat this type of injury in a timely fashion applying orthoplastic principles. In the UK, this type of injury is treated in major trauma centres according to clinical practice guidelines developed by BAPRAS, BOA, and NICE.[39,71,102] Moreover, TARN employs an ongoing audit process both locally and nationally to assure compliance with guideline recommendations.[110]

Given the successful precedent set by the UK, I chose as the overall aim of my doctoral research to optimise the uptake of evidence to improve management and outcomes for patients sustaining open lower limb fractures**.** To achieve this, I identified four specific objectives, which **Table 1.3** summarises and which I discuss in detail below.

Table 1.3: Aim and objectives of my doctoral thesis research

Aim of thesis	*Optimise the uptake of evidence to improve the management and outcomes for patients with lower limb open fractures*
Objective 1	Investigate the management and outcomes of patients treated for open lower limb injuries internationally.
Objective 2	Determine the current availability and quality of international clinical guidelines for management of lower limb fractures, including trends in these guidelines over time.
Objective 3	Investigate the attitudes toward, barriers to, and facilitators of implementation of clinical guidelines to improve management of open lower limb fractures
Objective 4	Develop a framework for the development and implementation of open lower limb fracture guidelines internationally.

1.6.2 **Objective 1:** Investigate the Management and Outcomes of Patients Treated for Open Lower Limb Injuries Internationally

Although previous multi-centre studies have compared open lower limb fracture outcomes in units based in low- and middle-income nations versus ones based in high-income nations,[107] to the best of my knowledge, no previous reports have looked at the care patients receive for these injuries on a global level. Given that the aim of my doctoral research was to optimise the uptake of evidence to improve the management and outcomes of patients sustaining open lower limb fractures, my first step to achieve this was understanding how these injuries are currently treated globally. Additionally, as I previously highlighted, the impact of open lower limb fractures is not restricted to physical health.[50] Rather, the long-lasting detriment to QOL following this type of injury has only recently been investigated[48,49] and only for patients treated in English-speaking, high-income countries.[51,52]

Considering these gaps, I identified investigating the management and outcomes of patients with open lower limb injuries internationally, including its impact on QOL, as the first objective of my research. I achieved this objective by conducting an extensive survey of outcomes using retrospective and prospective data-collection strategies, which Chapter 2 presents in detail.

1.6.3 **Objective 2:** Determine the Current Availability and Quality of International Clinical Guidelines for the Management of Lower Limb Fractures, Including Trends in These Guidelines over Time

As presented previously, clinical practice guidelines play a fundamental role in modern healthcare.[93] Sitting at the top of the hierarchical Pyramid of Evidence, these reports summarise and are based on the relevant evidence for a condition while presenting tangible recommendations to improve patient care.[78] The purpose of these documents is to not only aid clinicians in their practice but also highlight systemic changes to be addressed by managers

and healthcare leaders so as to assure that these recommendations can be successfully followed.[86]

The care of open lower limb fractures involves coordinated and multidisciplinary care within systems having the capacity to provide interventions in a timely manner.[35,73,105] In the UK, the development of guidelines to treat open fractures and their implementation by major trauma centres to effectively deliver these standards has been a decades-long process. However, their evolution remains unclear at an international level, as has the number of nations other than the UK that have developed similar guidelines.

Given my aim to optimise the uptake of evidence related to treatment of open lower limb fractures, I deemed it necessary to determine the current availability and quality of international clinical guidelines for the management of open lower extremity fracture and trends over time. I addressed the research question associated with this objective by conducting a systematic scoping review to identify all available clinical practice guidelines for treatment of lower limb open fractures and followed with an in-depth comparison, which is discussed in Chapter 3 of my thesis.

1.6.4 **Objective 3:** Investigate the Attitudes towards, Barriers to, and Facilitators of the Implementation of Clinical Guidelines to Improve Management of Patients with Open Lower Limb Fractures

Once established the number and quality of available clinical guidelines pertinent to treatment of open lower extremity fractures and the potential benefits of their implementation, I considered it necessary to further explore the reasons why some countries have not been able to develop such guidelines, a previously unaddressed issue, either locally or on a global scale. Therefore, investigating the attitudes toward, barriers to, and facilitators of implementation of clinical guidelines for this condition became the third objective of my thesis.

Due to the exploratory nature of this research objective, I adopted qualitative methodology for its approach. The Limitations to the Implementation of Open Trauma Guidelines (LINEAGE) project was based on data obtained by interviewing 12 senior clinicians in six different countries that do not have formal recommendations for managing treatment of open fractures. Chapter 4 includes the analysis and themes developed during the course of this research study.

1.6.5 **Objective 4:** Develop a Framework for the Development and Implementation of Open Lower Limb Fracture Guidelines Internationally

The final objective of my doctorate was to formulate an aid to optimise the uptake of evidence for managing treatment of open fractures, thereby addressing the goal of my dissertation research. To accomplish this, I developed and am proposing a framework for development and implementation of clinical guidelines for open lower limb fracture treatment.

To ascertain the framework's relevance and practicality, I obtained feedback from clinicians working in settings that would potentially benefit from my proposal. To achieve this, I conducted a Delphi study to refine and validate it, incorporating the insight of an international sample of experts with an interest in open lower limb fractures. The results of this study comprises the fifth chapter of my thesis.

1.7 Conclusions

In this background chapter, I provided a narrative review encompassing the relevance of trauma in general and of open fractures in particular. In it, I described the contemporary concepts that guide managing treatment of these injuries and also current challenges in standardising the care of these patients on a global scale. This not only highlighted the relevance of research dedicated to open lower limb fracture but also allowed me to present the

gaps in the literature related to this topic and my intention to expand our understating of how we can achieve better outcomes.

At the end of this background chapter, I formally stated the primary goal of my research along with the four specific research objectives while also providing an overview of my thesis structure. As each one of the study objectives is treated individually in the following chapters along with the research I conducted relevant to each and the relevant methodology, I introduced these objectives briefly in Chapter 1.

Chapter 2 International Survey of Outcomes for Patients Sustaining Open Fractures: The INTELLECT and QUINTET Studies

Given that the overall goal of my thesis research was to optimise the uptake of evidence to improve management and outcomes for patients presenting open lower limb fractures, I viewed the first step to achieving this goal as understanding the current standard of care provided for these patients on a global scale. As discussed in the previous chapter, the published literature contains few reports regarding management and outcomes for patients with open lower limb fractures comparing international practice. The objective of this chapter is to discuss my efforts to address this gap by conducting an extensive, worldwide survey of patient outcomes given this type of injury, as this would provide a starting point for potential improvement.

This first "results" chapter therefore presents the findings of the International Lower Limb Collaborative (INTELLECT) study, a retrospective, multi-centric, international audit of open fractures' treatments of which I was the lead researcher. Following this is a summary of the INTELLECT-COVID study, a quickly conducted survey of the management and outcomes of this injury conducted during the first wave of the COVID-19 pandemic; the research network developed for INTELLECT facilitated this subsequent study. The current chapter concludes with a discussion of the prospective Quality of Life after Open Extremity Trauma (QUINTET) study, which had the same objective as the INTELLECT and INTELLECT-COVID studies but approached it from a different perspective. Unlike these, the QUINTET study was designed to prospectively capture clinical and patient-reported outcomes so as to measure the impact on QOL of an open fracture; it addressed some of the limitations of the INTELLECT and INTELLECT-COVID studies.

The papers cited in this chapter that I authored were peer reviewed and accepted for publication prior to submission of my thesis. The INTELLECT study[111] was published in the

British Journal of Surgery in 2022, while the INTELLECT-COVID[112] and QUINTET[113] studies were published in the *Journal of Plastic Reconstructive and Aesthetic Surgery* in 2020 and 2024, respectively.

2.1 INTELLECT Study: Introduction

Despite advances made in recent decades, trauma remains a major cause of mortality and disability worldwide.[4] According to the WHO, the burdens associated with this type of injury (in particular, inequalities in timely access to emergency services and specialist care for complex injuries) remain higher in developing nations than in developed ones.[17] In the previous chapter, I emphasised the devastation that open lower extremity injuries cause. For patients, they are life-changing events from both physical[34] and mental health perspectives[49] and are also detrimental to healthcare services from a socio-economic standpoint.[114]

Even though prospective and retrospective studies of the outcomes of open fractures have been published in the literature, these have primarily been single-centre studies or multi-centric within a specific country. To my knowledge, only one article exists comparing the difference in management of lower limb trauma treatment in high- and middle-income settings—Boriani et al.,[107] which reported on a prospective cohort of patients treated in the UK, Italy, and Pakistan. To the best of my knowledge, no other studies have investigated variability in care provided in different healthcare settings from a global perspective or the impact that evidence-based healthcare has on the management of patients with open lower limb fractures.[107] A better understanding of any potential disparities across national borders would be a first step in addressing these from a global and sustainable perspective.

Its impact on mental health and QOL has received considerably less attention than the physical consequences of an open lower limb fracture.[49,115] Few studies have described patient experience after these injuries, and those few have been sited primarily in high-income countries such as the UK,[116] the USA,[51] and Australia.[117] According to results of the WOLFF randomised controlled trial, immediately post injury, UK patients sustaining open lower limb

fractures scored their self-reported QOL at levels equivalent to death.[50] Furthermore, a recent systematic review concluded that patient experience, according to patient-reported outcomes, remains unknown in low- and middle-income countries.[52] Extrapolating patient-reported outcomes obtained in high-income countries is not only unfair but most likely inaccurate, as patient preferences and concerns may vary greatly from those of inhabitants of non-high-income countries.

As previously stated, the objective of this chapter is to investigate the outcomes of patients with open lower limb injuries internationally. To achieve this, I conducted a large, collaborative, international audit of patients with open lower limb fractures as part of the INTELLECT study. This allowed me to research global trends and disparities in the management and outcomes for patients with open lower limb fractures and analyse the impact of timely interventions, guideline-directed care, and World Bank income country-classification for patients with open tibial fractures.

2.2 INTELLECT Study: Methodology

Preliminary work for the INTELLECT study commenced in April 2019, following my enrolment as a probationary research student. In order to collect large amounts of international data on open lower limb fractures, I collaborated with the Reconstructive Surgery Trials Network (RSTN).

The RSTN is a research organisation founded by BAPRAS and the British Society for Surgery of the Hand (BSSH) in close collaboration with the Royal College of Surgeons. It pioneered the use of collaborative research strategies, providing early-career researchers with a platform on which to conduct large-scale multi-centric projects at low cost. To gather clinical data, it relies on volunteers, who are later acknowledged in any resulting publications.[118] Taking advantage of this model, I designed the INTELLECT study as a retrospective audit, allowing for rapid collection of large amounts of de-identified clinical

data while minimising research costs. In May 2019, I presented a proposal detailing the project to the RSTN, which peer reviewed its protocol and agreed to support it.

The INTELLECT protocol complied with the requirements established in the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) statement.[119] The study plan classified INTELLECT as an international, multi-centre, retrospective and collaborative audit coordinated by myself with the support of my supervisors. RSTN's support included granting access to its REDCap platform[120] hosted by the Kennedy Institute and listing INTELLECT on its webpage and in its newsletters. It also provided RSTN member contact details in centres that were potential participants in the study. Before commencing the study, I registered INTELLECT in the Open Science Framework[121] and posted it on the RSTN website.

2.2.1 Network Setup and Data Gathering

Orthopaedic, trauma, and plastic surgery clinicians working in centres that treat open lower extremity fractures were invited to participate in INTELLECT through RSTN, BAPRAS, and the International Confederation of Plastic Surgery Societies (ICOPLAST) channels. As this was considered an audit per NHS Health Research Authority guidance, no research ethics committee (REC) approval was sought for centres in the UK.[122] However, each participating centre in England registered the project with their local audit and quality improvement departments, and centres located in Scotland, Wales, and Northern Ireland followed a similar procedures in accordance with their respective devolved regulations.

For international collaborating centres, research ethics approval was obtained in compliance with local or national directives where necessary before study commencement. For each participating hospital, a lead senior clinician was identified and designated; this individual assumed responsibility for obtaining audit or ethical board approval and provided general oversight of the project locally. All collaborators were informed of the INTELLECT

project's dissemination intentions, including scientific presentations, publications, and also my DPhil thesis.

I instructed each lead senior clinician to set up a team of investigators to be tasked with retrieving data for patients treated with open lower extremity injuries between 1 January 2017 and 31 December 2018 in each of their respective hospitals. Given that data gathering was scheduled to begin early in 2020, this collection timeframe was chosen so as to allow all eligible cases to have at least two years of potential follow-up prior to data input. I pre-defined a list of inclusion and exclusion criteria, establishing a clear case definition while excluding cases whose definitive treatment occurred in a centre different from the participating centre for any reason (see **Table 2.1**).

Table 2.1: INTELLECT inclusion and exclusion criteria

Inclusion	**Exclusion**
Patients admitted following an open lower limb fracture. Admitted between 1st January 2017 and 31st December 2018. Any age.	Patients assessed at the participating centre but whose definitive treatment was performed at a different unit. Open forefoot and isolated open patella fractures.

Within the RSTN-maintained REDCap platform, I programmed a bespoke data-gathering instrument for the INTELLECT project. This instrument allowed participating investigators to input demographic and clinical information obtained from their respective medical records. These data included time to operative intervention, surgical team involvement, method of fixation and soft tissue reconstruction, acute and chronic complications, length of follow-up time, and time to full weight bearing and return to work. Primary outcomes were soft tissue infection, deep infection, non-union, and amputation, whereas secondary outcomes were median time to discharge and deep venous thrombosis cases. Definitions for all primary outcomes were provided and included in the data-gathering instrument (Appendix 1: INTELLECT Data-Gathering Instrument).

Data collection was undertaken following the General Data Protection Regulation (GDPR). All cases were de-identified and securely stored on the REDCap platform server hosted at the Kennedy Institute, both during and after the course of the study. Each case was given an individual case identification number to facilitate future data validation. I instructed investigators not to upload any information that could identify the patient, i.e., name, hospital number, or health system number. No data transfer occurred between institutions or across national borders, as data entries were created in the REDCap platform by users logging in from the UK or overseas.

2.2.2 Data Validation and Statistical Analysis

For quality assurance, lead senior clinicians in each collaborating centre were tasked with the cross-examination and validation of 2% of their cases. Depending on the number of collected entries in their respective units, I provided them with a random selection of case identification numbers and asked them to retrieve those cases in REDCap and verify their accuracy. Once data validation was completed, I proceeded to lock the database, thereby restricting further changes to the uploaded information. I then downloaded the complete de-identified dataset from REDCap and saved it to a Microsoft OneDrive server account provided by the University of Oxford as an encrypted and password-protected Microsoft Excel Spreadsheet (Microsoft Corporation. Washington, USA). Missing data were quantified for each variable as well as for the whole study cohort, and records having missing values were not considered for further analysis. Date of birth information was used to calculate age at time of injury and then erased from the spreadsheet to further preserve patient anonymity.

I performed a descriptive statistical analysis using the IBM SPSS Statistics package (IBM. New York, USA), including calculation of proportions and measures of central tendency and interquartile ranges, depending on whether the study variables were continuous or categorical. Except for age at presentation, for which the mean was calculated, I used the median for the remaining continuous variables, as it is less sensitive to potential outliers.

For the inferential statistical analysis and in agreement with my supervisors, I collaborated with a medical statistician to conduct the quantitative analyses for this project. As my role was to direct the analysis, my active involvement in this area consisted of formulating the study hypotheses and identifying the statistical tests to be conducted on the INTELLECT data. The medical statistician concurred with my analytic plan and conducted the statistical tests using the Stata statistical software (Statacorp. Texas, USA).

First, the Shapiro-Wilk test was run to assess the normality of the data collected. In this test, the null hypothesis is that the population is normally distributed. If the *p*-value obtained is below the pre-established alpha, or significance level, then the null hypothesis is rejected, assuming that the population is not normally distributed.

As I did not expect the data to be normally distributed, I planned to conduct nonparametric tests, including Pearson's chi-square and the Kruskal-Wallis tests. Even though parametric tests can be used with large nonparametric samples, I nonetheless elected to use nonparametric tests because these methods require fewer assumptions about the data and are less likely to reject the null hypothesis when the null hypothesis is true, the probability of which is termed type I error.

Pearson's chi-square is applied to categorical variables to estimate whether any observed differences between studied groups could have been due to chance. For this test, obtaining a *p*-value less than alpha, set at .05 for this study, indicates rejection of the null hypothesis, i.e., no difference between groups, and indicates a statistically significant difference between groups not likely attributable to random effects.

On the other hand, the Kruskal-Wallis test is a nonparametric method for analysing continuous variables by comparing the medians of two or more groups. In this case, the null hypothesis is that the population medians are equal. As with Pearson's chi-square, a *p*-value less than alpha also indicates rejection of the null hypothesis, indicating a statistically significant difference not attributable to chance. The Bonferroni correction was used for a

post hoc analysis requiring comparison of multiple groups. This adjusts the *p*-values, as the risk of a type I error increases with multiple statistical tests.

Given the importance of early intervention in the care of patients with open lower limb fractures, I incorporated investigation of the effects of delaying definitive wound closure on the incidence of infective complications as part of INTELLECT. For this purpose, I performed multivariate analyses using binary logistic regression models to assess the relationship between time to wound closure and the presence of wound infection, deep tissue infection and non-union. A model was formulated with each primary outcome acting as the dependent variable, and time to soft tissue closure was the independent variable.

Designed by our medical statistician collaborator, the models compensated for the effects of such confounding variables as patient age, mechanism of injury, and country where patients were treated. To compare categorical variables, the length of time from injury to definitive soft tissue closure was converted into an ordinal categorical variable having the following values: within 72 hours, 3-7 days, 8-14 days, 15-28 days or >28 days post-injury. The odds ratios (*OR*) for the resulting interactions between independent and dependent variables were calculated, including their *p*-values. Confidence intervals were set at 95%, and, as with the nonparametric analysis, alpha was set at 5%.

2.3 INTELLECT Study: Results

The INTELLECT network of investigators expanded to a total of sixty-two collaborating centres based in sixteen different countries (Appendix 2: List of INTELLECT Participating Centres and Collaborators). As previously mentioned, a senior lead clinician was appointed for each unit, and this individual liaised with me and supervised the data collection, acting as guarantor for the information retrieved from their hospital. During the course of the data-collection process for INTELLECT, a total of 2,712 cases were uploaded to our REDCap database, with a median of 17 cases (range 4-85) per unit per year. Of these, 18 were excluded as these were duplicate entries, were empty records, or concerned patients treated beyond the

timeframe defined in the INTELLECT study protocol. This resulted in a total of 2,694 cases of open lower extremity fractures included in the analysis. Of these, 272 (10%) were femur open fractures; in 2,131 (79%), the tibia/fibula was affected; and the remaining 291 (11%) were hindfoot injuries. Among all eligible cases, I calculated a total of 2.7% missing values across the complete dataset.

For the cases uploaded, the mean age at presentation was 44.5 years, with age ranging from 2 to 100 years. Of these, 104 cases (3.9%) involved patients under 16 years of age. In line with most reports on open factures, male individuals were more affected than females, with 71% of the sample for this project comprised of men. The median follow-up time for the cases included in the INTELLECT study was 11 months, with this time ranging from no follow-up to a maximum of 47 months post-injury.

Across the dataset, the most common mechanism of injury was road traffic accidents (53%), followed by low energy (19%) and high-energy falls (11%), as described in detail in **Table 2.2**. Significant gender differences were found, with low-energy falls significantly associated with female patients, and road traffic accidents, sports injuries, interpersonal violence, and work-related injuries significantly associated with males.

The median time to the first recorded intervention, i.e., the administration of prophylactic antibiotics, was two hours. Three-fourths of all patients were transferred directly by pre-hospital services to a specialist centre that provided definitive treatment, and 80% of all cases underwent surgical debridement within 24 hours of the time of injury.

In 82% of the cases, primary debridement was performed by the orthopaedic team, either as a sole specialty (68%) or as a joint procedure with plastic surgery (14%). Median time to definitive skeletal fixation was two days and, for the 42% of cases which required soft tissue reconstruction, the median time to wound closure was seven days. The reported median time to hospital discharge was 15 days for the whole cohort.

Table 2.2: Differences in mechanism of injury for male and female patients

Mechanism of injury	*Male*	*Female*	*p-value*	*Total*
Road traffic accident	58.2%	39.0%	<0.001	52.6%
Low-energy fall	10.6%	37.9%	<0.001	18.7%
High-energy fall	10.9%	11.1%	0.920	11.0%
Sports injury	4.9%	8.0%	0.002	5.8%
Work-related injury	5.7%	1.4%	<0.001	4.4%
Interpersonal violence	7.3%	1.4%	<0.001	5.5%
Other	2.4%	1.2%	0.050	2.0%

Among all cases included for analysis, 16.3% developed superficial wound infections that resolved with antimicrobial therapy and without surgical intervention. The median time to development of superficial infection was 34 days following the injury. Deep wound infection including bone, which required lavage, exchange of metalwork, or further debridement, was reported in 10.3% of the cases, with a median time of 63 days to diagnosis. Non-union that required further surgical intervention or was radiologically reported one year post-injury was documented for 10.9% of the studied cohort. In contrast to the 7.6% deep infection rate in patients that did not develop a non-union, 34% of cases that had a non-union had previously developed a deep tissue infection. Secondary amputation was required in 5.8% of the cases and 1.3% had a deep venous thrombosis documented during their treatment (**Table 2.3**).

Open fractures affecting patients younger than 18 years of age represented a small proportion of the INTELLECT dataset, with 163 cases recorded. Median age for this subgroup was 13 years (*range* 2-17), with 63 patients (39%) under the age of 12 at the time of injury. Males were also the majority of cases in this subgroup, with road traffic accidents causing (71%) of all injuries, followed by high-energy falls (28%) and low-energy falls (1%). Open fractures of the tibia and fibula represented 80% of the paediatric cases, with the remaining 20% split equally between open hindfoot fractures and open femoral fractures. Only 6% of patients reported comorbidity, with asthma accounting for 40% of these cases.

For the paediatric subgroup, 61 cases (38%) required soft tissue reconstruction following fracture fixation. However, following initial debridement, only one-third of these cases were classified as Gustilo IIIB or IIIC fractures. None of these patients developed deep venous thrombosis during treatment. Wound infection was reported in 12.3%, deep infection in 4.9%, and non-union in 6.7% of patients in this subgroup. Three patients, all involved in road traffic accidents and all aged 12 years or more, required amputation. Two were performed within 12 hours of injury, with the remaining requiring this one month post-injury.

Table 2.3: Descriptive information obtained from INTELLECT database

	Total: 2694	Femur fractures: 272 (10%)	Tibia/fibula fractures: 2131 (79%)	Hindfoot fractures: 291 (11%)
Demographics				
Mean age n=2670	44.5 years (SD: 20.4)	37.9 years (SD: 17.9)	45.5 years (SD: 20.8)	43.5 years (SD: 19.1)
Male:Female n=2690	71:29	79:21	69:31	72:28
Mechanism of injury n=2656	Road traffic accident: 53% / Low-energy fall: 19% / High-energy fall: 11% / Sports-related: 6% / Work-related: 4% / Interpersonal violence 5% / Other: 2%	Road traffic accident: 70% / Low-energy fall: 9% / High-energy fall: 4% / Sports-related: 1% / Work-related: 2% / Interpersonal violence: 12% / Other: 2%	Road traffic accident: 52% / Low-energy fall: 11% / High-energy fall: 21% / Sports-related: 4% / Work-related: 6% / Interpersonal violence: 5% / Other: 1%	Road traffic accident: 37% / Low-energy fall: 13% / High-energy fall: 17% / Sports-related: 12% / Work-related: 8% / Interpersonal violence 5% / Other: 8%
Fracture classification (Gustilo-Anderson) n=2593	I: 16% / II: 31% / III A: 20%, B: 28%, C: 5%	I: 16% / II: 38% / III A: 31%, B: 9%, C: 6%	I: 15% / II: 29% / III A: 19%, B: 32%, C: 5%	I: 21% / II: 38% / III A: 15%, B: 21%, C: 5%
Number of cases per country n=2694	UK: 1045 / Spain: 396 / Chile: 322 / Netherlands: 227 / Mexico: 113 / Italy: 98 / Austria: 78 / Australia: 70 / India: 60 / Taiwan: 59 / Argentina: 50 / Sweden: 45 / Sudan: 43 / Czechia: 37 / South Korea: 31 / Egypt: 20	UK: 73 / Spain: 51 / Chile: 35 / Netherlands: 30 / Mexico: 14 / Italy: 18 / Austria: 5 / Australia: 2 / India: 6 / Taiwan: 14 / Argentina: 2 / Sweden: 6 / Sudan: 7 / Czechia: 9 / South Korea: 0 / Egypt: 0	UK: 918 / Spain: 288 / Chile: 216 / Netherlands: 180 / Mexico: 86 / Italy: 74 / Austria: 60 / Australia: 53 / India: 54 / Taiwan: 38 / Argentina: 48 / Sweden: 24 / Sudan: 29 / Czechia: 25 / South Korea: 23 / Egypt: 15	UK: 54 / Spain: 57 / Chile: 71 / Netherlands: 27 / Mexico: 13 / Italy: 6 / Austria: 13 / Australia: 15 / India: 0 / Taiwan: 7 / Argentina: 0 / Sweden: 15 / Sudan: 7 / Czechia: 3 / South Korea: 8 / Egypt: 5
Comorbidities n=2447	None: 65% / Hypertension: 16% / Diabetes: 8% / Ischaemic heart disease: 4% / Asthma: 4% / COPD: 3% / Peripheral vascular disease: 1%	None: 73% / Hypertension: 9% / Diabetes: 7% / Ischaemic heart disease: 4% / Asthma: 2% / COPD: 2% / Peripheral vascular disease: 1%	None: 63% / Hypertension: 17% / Diabetes: 9% / Ischaemic heart disease: 4% / Asthma: 4% / COPD: 3% / Peripheral vascular disease: 2%	None: 70% / Hypertension: 15% / Diabetes: 6% / Ischaemic heart disease: 2% / Asthma: 5% / COPD: 3% / Peripheral vascular disease: 1%
Smoking n=2666	Yes: 24% / No: 42% / Unknown: 34%	Yes: 26% / No: 32% / Unknown: 42%	Yes: 23% / No: 43% / Unknown: 34%	Yes: 25% / No: 43% / Unknown: 32%

Treatment and outcomes	Total: 2694	Femur fractures: 272 (10%)	Tibia/fibula fractures: 2131 (79%)	Hindfoot fractures: 291 (11%)
Median time to antibiotics n=2303	2 hours (IQR: 4)	2 hours (IQR: 3)	2 hours (IQR: 4)	2 hours (IQR: 4)
Direct transfer to specialist centre n=2670	75%	83%	73%	78%
Wound debridement within 24 hours n=2580	80.2% / Median time to debridement: 10 hours (IQR: 16)	86.3% / Median time to debridement: 6.5 hours (IQR: 12)	79.6% / Median time to debridement: 10 hours (IQR: 16)	79% / Median time to debridement: 8 hours (IQR: 16)
Specialties involved in primary debridement n=2694	Orthopaedic surgeons: 68% / Plastic surgeons: 11% / Orthopaedic and plastic surgeons: 14% / Trauma surgeons: 7%	Orthopaedic surgeons: 80% / Plastic surgeons: 4% / Orthopaedic and plastic surgeons: 5% / Trauma surgeons: 10%	Orthopaedic surgeons: 65% / Plastic surgeons: 12% / Orthopaedic and plastic surgeons: 16% / Trauma surgeons: 7%	Orthopaedic surgeons: 79% / Plastic surgeons: 6% / Orthopaedic and plastic surgeons: 11% / Trauma surgeons: 4%
Seniority of surgeon leading debridement n=2619	Consultant level: 80% / Non-consultant level: 20%	Consultant level: 84% / Non-consultant level: 16%	Consultant level: 80% / Non-consultant level: 20%	Consultant level: 81% / Non-consultant level: 19%
Median time to definitive skeletal fixation n=2670	2 days (IQR: 8)	4 days (IQR: 8)	2 days (IQR: 8)	1 days (IQR: 1)
Primary mode of definitive skeletal fixation n=2670	Casting: 4% / Uni-biplanar external fixator: 7% / Frame external fixator: 12% / Plate and screws: 33% / Intramedullary nail: 36% / Kirschner wires: 4% / Other: 4%	Casting: 1% / Uni-biplanar external fixator: 2% / Frame external fixator: 5% / Plate and screws: 29% / Intramedullary nail: 58% / Kirschner wires: 1% / Other: 4%	Casting: 3% / Uni-biplanar external fixator: 7% / Frame external fixator: 14% / Plate and screws: 33% / Intramedullary nail: 38% / Kirschner wires: 2% / Other: 3%	Casting: 14% / Uni-biplanar external fixator: 6% / Frame external fixator: 4% / Plate and screws: 38% / Intramedullary nail: 2% / Kirschner wires: 27% / Other: 9%
Soft tissue reconstruction required n=2672	41%	18%	44%	41%
Modality of soft tissue closure n=1109	Conventional dressings: 6% / Negative pressure wound therapy: 5% / Skin grafting only: 21% / Local flaps: 9% / Perforator flaps: 16% / Free flaps: 43%	Conventional dressings: 8% / Negative pressure wound therapy: 6% / Skin grafting only: 56% / Local flaps: 4% / Perforator flaps: 11% / Free flaps: 15%	Conventional dressings: 6% / Negative pressure wound therapy: 4% / Skin grafting only: 20% / Local flaps: 10% / Perforator flaps: 17% / Free flaps: 43%	Conventional dressings: 9% / Negative pressure wound therapy: 11% / Skin grafting only: 19% / Local flaps: 3% / Perforator flaps: 3% / Free flaps: 55%
Median time to soft tissue closure n=1061	7 days (IQR: 16)	12 days (IQR: 18)	6 days (IQR: 14)	16 days (IQR: 24)
Flap survival rates n=748	Local and regional flaps (n=268): Total flap failure 3% / Partial flap failure: 9% / Total flap survival: 88%.	Local and regional flaps (n=7): Total flap failure 14% / Partial flap failure: 0% / Total flap survival: 86%.	Local and regional flaps (n=255): Total flap failure 3% / Partial flap failure: 9% / Total flap survival: 88%.	Local and regional flaps (n=6): Total flap failure 0% / Partial flap failure: 0% / Total flap survival: 100%.

	Total: 2694 Free flaps (n=480): Total flap failure 6% / Partial flap failure: 6% / Total flap survival: 87%.	Femur fractures: 272 (10%) Free flaps (n=7): Total flap failure 0% / Partial flap failure: 29% / Total flap survival: 71%.	Tibia/fibula fractures: 2131 (79%) Free flaps (n=408): Total flap failure 7% / Partial flap failure: 5% / Total flap survival: 88%.	Hindfoot fractures: 291 (11%) Free flaps (n=65): Total flap failure 2% / Partial flap failure: 9% / Total flap survival: 89%.
Deep venous thrombosis cases n=2694	35 (1.3%)	4 (1.5%)	27 (1.3%)	4 (1.4%)
Wound infection n=2649	16.3 % / Median time to wound infection: 34 days (IQR: 67)	12.5 % / Median time to wound infection: 15 days (IQR: 36)	16.7 % / Median time to wound infection: 39 days (IQR: 74) (SD+/- 133 days)	16.9 % / Median time to wound infection: 17 days (IQR: 29)
Deep wound infection n=2655	10.3 % / Median time to deep infection: 63 days (IQR: 157)	9.4 % / Median time to deep infection: 52 days (IQR: 143)	10.7 % / Median time to deep infection: 69 days (IQR: 157)	8.6 % / Median time to deep infection: 32 days (IQR: 48)
Non-union n=2594	10.9%	14.7%	11.7%	2.1%
Amputation n=2624	Immediate: 2.1% / Early: 2.7% / Late: 1%	Immediate: 1.9% / Early: 0.8% / Late: 0.8%	Immediate: 1.4% / Early: 2.3% / Late: 1.1%	Immediate: 7% / Early: 7.4% / Late: 0%
Median time to discharge n=2641	15 days (IQR: 23)	16 days (IQR: 25)	15 days (IQR: 22)	14 days (IQR: 26)
Median follow-up time n=2448	11 months (IQR: 16)	13 months (IQR: 17)	11 months (IQR: 16)	10 months (IQR: 17)

SD: Standard deviation / IQR: Interquartile range

2.3.1 Open Tibial Fractures

Among the 2,131 patients included in the INTELLECT study who sustained open tibial fractures, intramedullary nailing was the most commonly used method for definitive skeletal fixation (38%), followed by open reduction and internal fixation with plates and screws (33%). For this specific subgroup (43%), median time for definitive skeletal fixation was two days. Soft tissue reconstruction was required for 918 cases with a median time to wound closure of six days for those who required reconstruction. This was achieved by means of free tissue transfer for 408 patients and local-regional flaps for 255 fractures. Partial and total flap failure were 5% and 7% for free flaps, respectively, and 9% and 3% for regional flaps. Skin grafting was the reconstructive modality for 186 injuries, and, in 92 cases, the wounds were dressed until healed by secondary intention.

The planned multivariate logistic regression adjusting for age, mechanism of injury, and country income group revealed that patients sustaining either a Gustilo IIIB or IIIC fracture had a statistically higher likelihood of developing a wound infection (*OR*=1.44, *p*=0.047) and so requiring a secondary amputation (*OR*=2.39, *p*=0.027). However, no significant statistical association between Gustilo groups was found with respect to deep infection or non-union rates. In addition, there was no statistically significant association between time to antibiotics, time to debridement, or time to definitive fixation and soft tissue infection, deep infection, non-union, and amputation. However, male patients had a higher likelihood of developing superficial wound infection (*OR*=1.5, *p*=0.038), deep infection (*OR*=1.68, p=0.035), non-union (*OR*=1.96, *p*=0.016), and amputation (*OR*=8.02, *p*=0.004) than did females.

A delay in achieving soft tissue closure beyond 72 hours post-injury was associated with a higher likelihood of soft tissue infection, deep infection, non-union, or amputation. For each additional day that soft tissue closure, treated as a continuous variable, was delayed, the likelihood of developing a soft tissue infection increased by 1% (*OR*=1.01, *p*<0.0001) and

that of a deep wound infection increased by 2% (*OR*=1.02, *p*<0.0001). Joint treatment by orthopaedic or trauma surgeons along with plastic surgeons from debridement onwards was identified as a protective factor with respect to secondary amputation (*OR*=0.41, *p*=0.008). See **Table 2.4**.

Table 2.4: Results of multivariate logistic regression for days to wound closure

Days to soft tissue cover	Wound infection		Deep tissue infection		Non-union		Amputation	
	OR	*p*-value	*OR*	*p* value	*OR*	*p*-value	*OR*	*p*-value
0-3 days	1.00	-	1	-	1	-	1	-
4-7 days	1.02	0.92	2.61*	0.001	2.78*	<0.001	2.49*	0.0120
8-14 days	0.85	0.56	4.09*	<0.001	2.26*	0.007	6.48*	0.001
15-28 days	1.20	0.32	1.99*	0.047	0.84	0.650	11.75*	<0.001
> 28 days	3.07*	<0.001	7.40*	<0.001	1.52	0.190	5.34*	0.006

For the paediatric subgroup of open tibial fractures, patients younger than 5 years of age were more likely to develop soft tissue infection (*OR* 5.19, *p*=0.082) and deep infection (*OR* 16.89, *p*=0.005) than patients between 5 and 18 years. All patients with a reported non-union in this subset were aged 12 or older (range 13-17 years).

2.3.2 International Comparison and the Impact of Clinical Guidelines

Twenty-two units in the UK and the Netherlands had national guidelines in place[71,102,123] during the study period, accounting for 1,098 open tibial fracture cases. Both countries are considered high-income economies per the World Bank Country and Lending Groups. Thirty centres in other high-income countries were not following national guidelines for open lower extremity fractures during the same period, including Australia, Austria, Chile, Czechia, Italy, South Korea, Spain, Sweden, and Taiwan, which, combined, contributed a total of 801 patients to the study. The remaining ten contributing centres were based in the low- and middle-income economies of Argentina, Egypt, India, Mexico, and Sudan, which together added 232 individuals to the study cohort and none of which have clinical guidelines for this type of injury.

As shown in **Table 2.5**, comparison of these groups yielded statistically significant differences in age, gender distribution, time to antibiotics, debridement, skeletal fixation, and soft tissue cover. The proportion of injuries that required soft tissue reconstruction and that had been previously classified as Gustilo IIIB and IIIC was 69%. However, in high-income countries with guidelines, this proportion was 76%; in high-income countries with no guidelines, it was 58%; and in low- and middle-income countries, it was 63%. Statistically significant differences were also found in wound infection, deep infection rates, and median follow-up time, but not in non-union and amputation rates.

Table 2.5: Comparison of treatment management and outcomes following open tibia/fibula fractures in high-income countries with and without national guidelines and of middle- and low-income countries

Tibial open fractures (n=2,131)	*High-income countries with guidelines (n=1,098)*	*High-income countries with no guidelines (n=801)*	*Middle and low-income countries with no guidelines (n=232)*	*p-value*
Proportion of Gustilo IIIB-IIIC (n=2113)	45.3%	26.2%	35.5%	0.0001
Mean age (n=2113)	48.1 (SD:±22.1)	45.2 (SD:±18.5)	34.1 (SD:±17.3)	0.0001
Gender (M:F) (n=2127)	63:37	74:26	80:20	0.0001
Median time to antibiotics (n=1823)	2 hours (IQR: 3)	2 hours (IQR: 3)	5 hours (IQR: 8)	0.0001
Median time to debridement (n=2044)	14 hours (IQR: 16)	6 hours (IQR: 11)	11 hours (IQR: 17)	0.0001
Median time to fixation (n=2044)	2 days (IQR: 6)	3 days (IQR: 12)	5 days (IQR: 12)	0.0001
Median time to soft tissue cover (when required) (n=2044)	4 days (IQR: 7)	12 days (IQR: 23)	8 days (IQR: 35)	0.0001
Multidisciplinary debridement (n=2131)	24.4%	7.0%	6.9%	<0.0001
Consultant-led debridement (n=2073)	77.4%	90.7%	56.9%	<0.0001
Wound infection (n=2095)	17.7%	14.2%	20.3%	0.040
Deep infection (n=2100)	8.8%	11.6%	15.9%	0.003
Non-union (n=2051)	11.3%	12.5%	11.0%	0.688
Amputation (n=2079)	5.2%	5.1%	1.7%	0.374
Median follow-up (n=1931)	10 months (IQR: 14)	14 months (IQR: 18)	9 months (IQR: 14)	0.0001

A multivariate analysis adjusting for country income groups showed that being treated in a setting with national guidelines in place was protective with respect to developing deep tissue infection (*OR* = 0.66, 95% CI [0.443, 0.982], *p* = 0.04) or non-union (*OR* = 0.66, 95% CI [0.438, 0.986], *p* = 0.043), with 34% lower likelihood for developing either of these with the guidelines in place (Appendix 3: Multivariate Logistic Regressions for Deep Infection and Non-Union)

2.4 INTELLECT Study: Discussion

For the INTELLECT study, I collected data for 2,694 cases of open lower extremity fractures involving 62 units from 16 different countries and across six continents. In agreement with previous reports in the literature,[19,124] the INTELLECT data demonstrated an epidemiological trend in terms of gender disparity: male individuals represent a higher proportion of road traffic accidents and work-, sports-, and violence-associated injuries, whereas fragility fractures are more common among female patients. In the context of an ageing population within high-income countries,[125] females may still be underrepresented in the available body of evidence, and considerations should be made when applying the existing evidence in treating patients with fragility fractures.[126]

For the 2,131 included open tibial fractures in the INTELLECT data, the reported proportion of Gustilo IIIB and IIIC fractures was 45.3% in high-income nations with clinical guidelines, 26.2% in high-income nations with no guidelines, and 35.5% in middle- and low-income nations. One of the main features of this classification system is the difference between Gustilo I, II, and IIIA fractures, which do not require soft tissue reconstruction, and Gustilo IIIB fractures, which do require it. Although moderate inter-observer reliability has been previously reported for the Gustilo-Anderson classification,[127] it was surprising to find that 31% of the open tibial fractures in the INTELLECT cohort that eventually required soft tissue reconstruction were originally categorised as Gustilo I, II, and IIIA fractures. Given that this proportion was higher for cases treated in countries with no clinical practice guidelines,

we hypothesised that guidelines play a role in standardising the approach for wound debridement and classification of the resulting defects.

The discrepancy between the Gustilo classification and the proportion of cases needing reconstruction was double for patients younger than 18 years of age. In this subgroup, only one-third of cases that ultimately required reconstruction were graded as Gustilo IIIB or IIIC, possibly due to a more conservative use of debridement in this patient population.

The multivariate analysis included in this chapter showed how longer times to wound closure were associated with an increase in the likelihood of developing wound infection and deep tissue infection. I also found that a multidisciplinary approach involving orthopaedic and plastic surgeons was associated with a lower likelihood of requiring an amputation. On their own, a delay in administering prophylactic antibiotics or performing surgical debridement was not associated with poorer outcomes. However, these two variables in the INTELLECT cohort had a higher proportion of missing values than others.

Patients treated in the Netherlands and the UK, high-income countries with established clinical guidelines for open lower limb fractures, had statistically significantly shorter times to receipt of prophylactic antibiotics, surgical debridement, skeletal fixation, and soft tissue reconstruction and a greater likelihood of treatment by a multidisciplinary team including both orthopaedic and plastic surgeons. This phenomenon, i.e., being treated in high-income countries having guidelines, was also associated with better patient outcomes, as, according to the multivariate analysis, being treated in this type of setting was found to reduce a patient's chances of developing deep tissue infection and non-union by 34%.

However, these logistic regression analyses should be appraised carefully. Their associated p-values and confidence of intervals were close to the line of no significance and no effect, respectively. This was the case despite the large number of cases included in the modelling process. These results contribute to reducing the uncertainty regarding the relationship between clinical guidelines and patient outcomes for patients sustaining open

lower limb fractures, not eliminating it altogether. Weighing the effect benefits of a series of complex interventions, meant to be delivered in a country-specific health system remains challenging, due to the multiple confounding factors involved. Prospective collection of service delivery data and patients outcomes in settings with and without clinical guidelines would further assist in elucidating this matter.

Surgeons managing open fractures often find it challenging to gain access to emergency operating capacity and to the resources necessary to treat this type of complex injury. Although having dedicated operating time to treating patients with open extremity trauma would be ideal,[105,128] this is not always possible due to service and financial considerations.[129] Adherence to national guidelines allows the setting of uniform standards of care and service provisions that are founded on evidence-based recommendations. Such guidelines thus not only aid clinicians in the treatment decision-making process but can also play a significant role in enabling healthcare systems to provide the necessary support to ensure that recommendations are met as well as providing governmental health departments with a clear set of outcomes they can monitor.

The findings I obtained from the INTELLECT project support and contribute to previous research in open lower limb fractures. Several studies have investigated the role of prophylactic antibiotics, early debridement, skeletal stabilisation, and soft tissue closure in preventing long-term sequalae following an open extremity fracture. The Lower Extremity Assessment Project (LEAP), a prospective, multi-centre study that included 569 patients with severe leg injuries in the United States, compared outcomes of amputation and reconstruction. Of those patients who preserved their extremities, 10.9% developed a non-union while 9.1% of those who underwent amputation had non-healed wounds two years post-injury.[34] A systematic review published in 2008 and comprised of 28 studies that included patients with Gustilo IIIB and IIIC fractures reported non-union and amputation rates of 15.5% and 7.3%,

respectively.[31] Of all eligible studies for this review, only two were published by units based in middle-income countries, with the remaining reports from high-income nations.

INTELLECT was the first international collaborative study of its kind, accessing large amounts of data on open lower extremity fractures originating from a variety of international centres. To the best of my knowledge, INTELLECT was the largest study on open lower limb fractures ever conducted at its time of publication, obtaining cross-sectional descriptions of how these injuries are managed across the world. Furthermore, the collaborative ethos behind the INTELLECT network permitted a rapid-response study to be conducted in order to determine the effect that the first wave of the COVID-19 pandemic had on lower extremity trauma services in early 2020. A detailed report for the INTELLECT-COVID study is presented later in this chapter.[112]

The risk of bias is inherent in a retrospective study. Although I defined the outcomes of interest before commencing data collection, the quality of the information uploaded nonetheless relied on adequate patient record documentation, thus introducing the risk of information bias. In order to decrease the risk of detection bias for the proposed outcomes, a source of information bias, I provided a clear set of outcomes definitions in the data-gathering instrument given to the local investigators to follow. Moreover, centres from 16 different countries participated in this project, each with its own unique healthcare system and economic circumstances; each centre may not have been representative of its country's national practice, thus introducing possible selection bias.

I would have not been able to gather the amount of information that I did to conduct INTELLECT without employing a collaborative model for decentralised data collection. However, this approach required establishing a chain of accountability for the data obtained, relying on one senior clinician in each centre who acted as data guarantor. Not only were these clinicians responsible for data collection in accordance with local and national governance protocols but they also participated in data validation after the dataset was

complete. Inclusion of a large number of cases, as previously noted among the largest available in the literature, partially mitigated the risks of bias associated with a retrospective study design.

Considering the unique characteristics of the INTELLECT study, it is challenging to compare the results obtained with those from previous publications. Underrepresentation of studies conducted in less economically developed settings poses the risk of skewing the body of evidence towards trends and practices reported in relatively higher income nations. This caveat also applies when comparing the results obtained in INTELLECT with those obtained decades ago and so failing to capture the growing number of fragility fractures primarily affecting elderly female patients.

In the retrospective cohort presented in this chapter, patients treated in middle- and low-income settings were younger and experienced a statistically significant delay in accessing treatment, which was rarely delivered by multidisciplinary teams. This situation was associated with the relatively higher rates of wound infection and deep tissue infection observed for this subgroup. The lower amputation rates for patients treated in the low- and middle-income countries in our series, although not statistically significant, could imply an approach focussed on limb preservation in those contexts. Given that the lifetime cost of limb prosthesis triples the cost of limb-salvaging treatment, there may be a tendency towards the latter in resource-constrained healthcare settings.[130] Moreover, societal considerations with regards to limb loss may have also played a role in the lower amputation rate.

Previous studies have shown the impact of time to receipt of antibiotics and to debridement on infection rates for open fractures, but our data failed to confirm this association. Again, however, these data points proved challenging to obtain in the context of INTELLECT; while the date of an intervention was most likely included in a patient's record, the exact time of the day on a given date that these occurred may not have been reliably documented. Similarly, this project was not able to measure patient-reported and functional

outcomes or even such recovery milestones as time to full weight bearing or return to previous life roles due to discrepancies in recording of outcomes across participating units.

Following the conclusion of INTELLECT, it became clear, that, in order to successfully investigate the management and outcomes of open lower limb fracture treatment, the next step was conducting an international, multi-centre, prospective study. This would provide the opportunity for more reliable data collection while enabling exploration of less investigated aspects of open fracture management, such as impact on mental health and QOL, which INTELLECT was unable to cover. This need justified the design and execution of the QUINTET study, which is discussed later in this chapter.

2.5 INTELLECT-COVID Study

2.5.1 INTELLECT-COVID Study: Introduction

The INTELLECT-COVID study was not part of the initial plan for INTELLECT but was a fast-response study conducted during the first wave of the COVID-19 pandemic. While data gathering for INTELLECT was underway in early 2020, the world was hit by an unprecedented disruptor: the relentless propagation of the SARS-CoV-2 virus.[131,132] In a matter of months, most countries saw their healthcare services overwhelmed by patients suffering the respiratory decompensation associated to the emerging COVID-19 infection.[133]

Response to the COVID-19 pandemic involved a rapid redeployment of resources and staff that directly impacted elective care services[134] and so also affected access to and delivery of emergency procedures such as those needed to treat open fractures.[135] Early during the pandemic, concerns were raised about uncertain perioperative risk for surgical patients whose care could not be postponed.

These concerns remained largely unanswered until the first observational studies related to them were published. In May 2020, the CovidSurg Collaborative, an international network of surgeons and anaesthetists interested in researching the impact of COVID on surgical patients and services, reported in *The Lancet* the perioperative mortality and

pulmonary complications of 1,128 patients who had surgery during the first wave of the COVID-19 pandemic. Based on this sample, the authors estimated a 30-day post-operative mortality of 23.8% for surgical patients who had contracted the SARS-CoV-2 infection during the study period.[136]

This alarming emerging evidence led to the adaptation of established care pathways to both mitigate perioperative risks, thereby minimising inpatient stay, and reduce the burden on the overstretched healthcare system. Published in March 2020, a report led by the British Orthopaedic Association contained expert recommendations for the treatment of limb-threatening injuries during the pandemic.[137] In regard to open fractures, the authors recommended possibly deviating from current UK guidelines by avoiding complex procedures and also reducing the threshold for early amputations. During the first wave of the pandemic, I capitalised on the INTELLECT network to investigate the treatment provided for patients with open fractures during the pandemic and the incidence of COVID-19 and its complications for these individuals.

2.5.2 INTELLECT-COVID Study: Methodology

I designed the INTELLECT-COVID as an additional survey of outcomes at a moment in time in which the world faced unprecedented uncertainty due to the COVID-19 pandemic. With this study, I aimed to capture the management and outcomes of patient treatment for open fractures during the first wave of the pandemic while measuring the incidence of SARS-CoV-2 and its related complications, including death.

Following a similar collaborative approach as with the main INTELLECT study, I designed an international, multi-centric, retrospective study compliant with STROBE. I defined the main inclusion criteria to include patients with open lower extremity fractures who were admitted to a participating unit between the 1st of January 2020 and the 31st of May 2020 for definitive management. Choice of this window allowed the study to focus on

patients being treated during the first wave of the COVID-19 pandemic. I excluded isolated open patella fractures and forefoot open fractures.

The INTELLECT-COVID study was also supported by the RSTN, which had developed a portfolio of COVID-related studies to assess COVID's impact on plastic and hand surgery services. I invited the pre-existing network of INTELLECT collaborators to participate in this new study and published a protocol for the INTELLECT-COVD study as an open access document on the RSTN-COVID initiative website.[138]

Before the new study began data collection, each collaborating centre obtained approval from its clinical audit department or independent board review, as per its respective local governance and research ethics frameworks. Using the RSTN-supported REDCap platform, I programmed a new data-gathering instrument separate from that used for INTELLECT so as to capture patient demographic information, injury characteristics, management, and perioperative outcomes along with COVID-19 status and COVID-19-related complications (

Appendix 4: RSTN COVID–INTELLECT Data-Gathering Instrument).

Following the same data-management procedures as for INTELLECT, in compliance with GDPR, the resulting database containing de-identified information was exported to an encrypted and password-protected Microsoft Excel spreadsheet. This file was stored under a Microsoft OneDrive server account provided by the University of Oxford. As the aim of this study was to capture a snapshot of the disruption caused by the pandemic, I did not consider an inferential statistical analysis to be required and so performed a descriptive statistical analysis using SPSS Statistics software. This analysis included proportions and measures of central tendency; here, as previously discussed for the INTELLECT study earlier in this chapter, I preferred using the median rather than the mean as it tends to be less sensitive to outlier values.

2.5.3 INTELLECT-COVID Study: Results

Data collection for the INTELLECT-COVID study gathered information regarding the admission and management of 212 patients from 15 centres across the UK, Chile, Sudan, Spain, the Netherlands, Taiwan, South Korea, Mexico, and Italy (Appendix 5: List of RSTN COVID–INTELLECT Participating Centres and Collaborators). Under columns for the four countries that provided 80% of the recorded cases, **Table 2.6** summarises the demographic data, injury characteristics, treatment received, and inpatient recovery of the whole sample of patients.

Despite the pandemic and the emerging guidance advocating for a modification of stablished treatment pathways, I found that all participating centres treated patients according to their usual standards with minimal deviation from pre-existing protocols. Most patients (76%) were transferred immediately to a specialist centre by pre-hospital services, allowing for expedited care. The majority underwent surgical wound debridement within the first 24 hours (73%) post injury, and the median time to definitive skeletal fixation was two days. Seventy-six patients (36%) required soft tissue reconstruction, with a median time to closure

of 10 days for these individuals. Among this group of patients, local and perforator flaps were used in 20 patients and free flaps in 29.

Limb preservation at discharge was achieved in 94.4% of the cases, with 12 patients (5.6%) requiring immediate or early amputation. Serious complications included three total (6%) and five partial flap failures (10%), 10 cases of acute wound infection (5%), two hematomas that required evacuation (1%), and two deep venous thrombosis cases (1%). Three patients in the flap failure group required further reconstruction: two were managed with a subsequent local flap, and one was resolved with a second free flap. Only seven patients (3.3%) had their follow-up appointments delayed or adapted to telephone consultations in order to reduce their chances of contracting COVID-19 during outpatient visits.

Of all the patients included in the INTELLECT-COVID study, four died, two as a result of their injuries and two due to hospital-acquired pneumonias in the context of pre-existing COPD. None of these patients tested positive for SARS-CoV-2 infection. No individuals with a previous COVID-19 diagnosis were admitted, and only one patient tested positive for SARS-CoV-2 infection as an inpatient (0.5%), on both a polymerase chain reaction (PCR) and with suggestive imaging on computed tomography (CT) scans. This patient made a full recovery without the need of respiratory support.

Table 2.6: Data for cases included in the INTELLECT-COVID study

	Total (n=212)	***UK (n=79)***	***Chile (n=42)***	***Sudan (n=29)***	***Spain (n=21)***
Demographics					
Mean age	46 years (range: 6-98)	47 years	38 years	35 years	52 years
Male : Female	74:26	70:30	83:17	93:7	62:38
Location of fracture	Femur: 15% / Tibia-fibula: 69% / Foot: 16%	Femur: 10% / Tibia-fibula: 77% / Foot: 13%	Femur: 45% / Tibia-fibula: 31% / Foot: 24%	Femur: 0% / Tibia-fibula: 85% / Foot: 15%	Femur: 10% / Tibia-fibula: 76% / Foot: 14%
Mechanism of injury	Road traffic accident: 54% / Low-energy fall: 19% / High-energy fall: 12% / Work-related: 11% / Other: 4%	Road traffic accident: 39% / Low-energy fall: 35% / High-energy fall: 18% / Work-related: 5% / Other: 3%	Road traffic accident: 64% / Low-energy fall: 0% / High-energy fall: 6% / Work-related: 25% / Other: 5%	Road traffic accident: 80% / Low-energy fall: 4% / High-energy fall: 0% / Work-related: 4% / Other: 12%	Road traffic accident: 38% / Low-energy fall: 33% / High-energy fall: 24% / Work-related: 5% / Other: 0%
Fracture classification (Gustilo-Anderson)	I: 20% / II: 37% / III A: 17%, B: 21%, C: 5%	I: 19% / II: 27% / III A: 13%, B: 38%, C: 3%	I: 18% / II: 66% / III A: 16%, B: 0%, C: 0%	I: 22% / II: 39% / III A: 14%, B: 22%, C: 3%	I: 24% / II: 37% / III A: 24%, B: 5%, C: 10%
Treatment and outcomes					
Direct transfer to specialist centre	76%	80%	76%	62%	86%
Wound debridement within 24 hours	77% / Median time to debridement: 11 hours	72.2% / Median time to debridement: 20 hours	93% / Median time to debridement: 5 hours	66% / Median time to debridement: 10 hours	86% / Median time to debridement: 9 hours
Specialties involved in primary debridement	Orthopaedic surgeons: 64% / Plastic surgeons: 24.2% / Orthopaedic and plastic surgeons: 6.6% / Trauma surgeons: 5.2%	Orthopaedic surgeons: 34% / Plastic surgeons: 53% / Orthopaedic and plastic surgeons: 13% / Trauma surgeons: 0%	Orthopaedic surgeons: 95% / Plastic surgeons: 5% / Orthopaedic and plastic surgeons: 0% / Trauma surgeons: 0%	Orthopaedic surgeons: 86% / Plastic surgeons: 14% / Orthopaedic and plastic surgeons: 0% / Trauma surgeons: 0%	Orthopaedic surgeons: 95% / Plastic surgeons: 5% / Orthopaedic and plastic surgeons: 0% / Trauma surgeons: 0%
Median time to definitive skeletal fixation	2 days	1 day	1 day	4 days	5 days
Primary mode of definitive skeletal fixation	Casting: 5% / Uni-biplanar external fixator: 5% / Frame external fixator: 17% / Plate and screws: 32% / Intramedullary nail: 29% / Kirschner wires: 4% / Other: 8%	Casting: 8% / Uni-biplanar external fixator: 3% / Frame external fixator: 19% / Plate and screws: 23% / Intramedullary nail: 39% / Kirschner wires: 3% / Other: 5%	Casting: 0% / Uni-biplanar external fixator: 3% / Frame external fixator: 0% / Plate and screws: 52% / Intramedullary nail: 26% / Kirschner wires: 0% / Other: 19%	Casting: 10% / Uni-biplanar external fixator: 0% / Frame external fixator: 48% / Plate and screws: 14% / Intramedullary nail: 14% / Kirschner wires: 14% / Other: 0%	Casting: 5% / Uni-biplanar external fixator: 24% / Frame external fixator: 24% / Plate and screws: 24% / Intramedullary nail: 5% / Kirschner wires: 5% / Other: 13%
Soft tissue reconstruction required	36%	51%	19%	21%	19%

	Total (n=212)	***UK (n=79)***	***Chile (n=42)***	***Sudan (n=29)***	***Spain (n=21)***
Median time to soft tissue closure	10 days	4 days	29 days	37 days	35 days
Modality of soft tissue closure (Total n=76)	Conventional dressings: 3% / Negative pressure wound therapy: 5% / Skin grafting: 16% / Local flaps: 10% / Perforator flaps: 22% / Free flaps: 44%	Conventional dressings: 3% / Negative pressure wound therapy: 8% / Skin grafting: 13% / Local flaps: 11% / Perforator flaps: 21% / Free flaps: 45%	Conventional dressings: 0% / Negative pressure wound therapy: 0% / Skin grafting: 25% / Local flaps: 13% / Perforator flaps: 13% / Free flaps: 50%	Conventional dressings: 20% / Negative pressure wound therapy: 0% / Skin grafting: 40% / Local flaps: 20% / Perforator flaps: 20% / Free flaps: 0%	Conventional dressings: 0% / Negative pressure wound therapy: 0% / Skin grafting: 0% / Local flaps: 33% / Perforator flaps: 66% / Free flaps: 0%
Flap survival rates	Local and perforator flaps (n=20): Total flap failure 5% / Partial flap failure: 10% / Total flap survival: 85%. Free flaps (n=29): Total flap failure 6.8% / Partial flap failure: 6.8% / Total flap survival: 86.2%.				
Unexpected return to theatre in first 30 days	8%	9%	0%	10%	5%
Amputation	Immediate: 1.4% / Early: 4.3%	Immediate: 1.2% / Early: 2.5%	Immediate: 0% / Early: 4.7%	Immediate: 3.4% / Early: 3.4%	Immediate: 0% / Early: 0%
Median hospital stay	13 days	14 days	10 days	6 days	11 days

Patients diagnosed with COVID pre-admission: 0
Patients diagnosed with COVID during admission: 1 (0.47%)
Missing data 0.83%

2.5.4 INTELLECT-COVID Study: Discussion

Four years following the irruption of the COVID-19 pandemic, its impact on global health is yet to be fully determined.[139] With 5.4 million COVID-related deaths and 14.83 million excess deaths attributed to the pandemic, the wider repercussions the outbreak has had for patients that had their treatment management modified and/or postponed because of the pandemic are still unknown.[140] As previously stated, the purpose of this study was to address the uncertainty faced during the pandemic regarding the management of patients admitted with open lower limb fractures. The results of the INTELLECT-COVID study demonstrated that the services of centres comprising the study sample across eight countries were sufficiently resilient to adhere to their usual pre-COVID standards of care.[39]

As previously discussed earlier in this chapter, prior to the publication of the main INTELLECT study, few previous publications had addressed the management of patients with open fractures from an international perspective.[107] When compared with the results of the INTELLECT-COVID study, pre-pandemic reports from the United States[141] and the UK[50,142] reported comparable rates of amputation and soft tissue reconstruction outcomes.

Even though the aims and methodology of the INTELLECT and INTELLECT–COVID were similar, although in two very different contexts, there were important differences. The number of participating centres was considerably smaller for the INTELLECT–COVID sample as well as the number of countries from which the data originated. Also, the median follow-up for the INTELLECT study was 11 months, whereas for the INTELLECT-COVID study, we focused on events that occurred during acute admission and the first 30 days following admission. Despite these disparities, I found that the immediate and early amputation rates for the INTELLECT and INTELLECT-COVID studies were 4.8% and 5.7%, respectively. While the median time to skeletal fixation was equivalent for both studies, for patients in the INTELLECT-COVID cohort that required soft tissue reconstruction, this was achieved in 10 days compared with 7 days for the INTELLECT

group. The proportion of patients that had free flaps in the INTELLECT sample was 43%, very similar to the 44% that I found for the INTELLECT-COVID patients. The total local and regional flap success rates were 85% and 86% for INTELLECT and INTELLECT–COVID, respectively, with the total free flap success rate being 87% and 86.2%, respectively, again very similar overall.

The INTELLECT-COVID study had several limitations including its retrospective design, geographic variability, and a follow-up limited to a 30-day post-injury period. Furthermore, as with INTELLECT, the participating centres that engaged with this study may not have accurately reflected the standard of care in their respective countries. However, I chose to pursue a collaborative research approach as I had with INTELLECT, in order to achieve a rapid and global response during the rapidly evolving COVID-19 pandemic.

The results of the INTELLECT-COVID study demonstrated that the incidence of perioperative COVID-19 was very low, with only one patient contracting infection as an inpatient (0.47%). Moreover, this individual did not require respiratory support and recovered uneventfully, a finding not dissimilar to the low incidence of COVID-19 in emergency admissions later reported for other specialties.[143]

Guidelines for clinicians dealing with emergencies were welcomed at a time of great uncertainty about the impact of COVID-19 on patients, staff, and the overall functioning of health services.[144] These recommendations were based on well-intentioned expert opinion and preliminary evidence obtained during the first stages of the pandemic. However, once the results of this study were disseminated, I advocated for critical appraisal of the guidance emerging during the pandemic in the light of an evolving epidemiological situation, based on the same evidence-based principles as the previously formulated open lower limb fracture guidelines. At the time, maintaining standard surgical SARS-CoV-2 precautions also seemed reasonable, including screening patients with unknown COVID-19 status upon admission and routine use of personal protective equipment. Nevertheless, as I clearly reported, the results of

the INTELLECT-COVID study supported adherence to pre-pandemic evidence-based guidance for open lower limb fractures.

2.6 QUINTET Study: Introduction

Following the succesful conclusion of the INTELLECT study, it became clear that a project of its kind had weaknesses worth addressing in order to achieve the objective to which this chapter is dedicated. Even though I was able to collect vast amounts of data for INTELLECT, this was retrospective data obtained from patient medical records and, therefore, could only be as reliable as the clinical documentation, which was not standardised across participating centres. Furthermore, INTELLECT was not capable of capturing any patient-reported outcomes that could reflect the impact on QOL and mental health associated with open fractures.[49,115] The QUINTET study was my response to these limitations; in this study, I took advantage of the lessons learned from the INTELLECT studies and of the collaborative network set up for INTELLECT.

The primary goal of the QUINTET study was to prospectively characterise the QOL following open lower limb fractures in an international sample of patients. This was not only aligned with the objective of the work described in this chapter by providing a different perspective on the intended large survey of outcomes, but also supported by a recent research prioritisation exercise undertaken by BAPRAS, which ranked "*Outcome assessments (all areas especially psychosocial)*" second in importance for their specialty.[145]

I considered that in the same way that INTELLECT was able to detect inequalities in the management and clinical outcomes following open fractures from an international perspective, QUINTET would achieve the same, but from a mental health and QOL perspective. Better understanding how patients cope after this type of injury, along with protective and risk factors, would be key in the development of succesful interventions to help patients during their recovery. Furthermore, considering the successful application of a

collaborative research model for INTELLECT, QUINTET was the natural next step towards large-scale, international, collaborative clinical trials on lower extremity reconstruction.

2.7 QUINTET Study: Methodology

I planned the QUINTET study as a STROBE-compliant, international, multi-centric, prospective study with the goal to investigate the impact of lower extremity open fractures on the QOL of patients sustaining such injuries. This study was funded by a major research grant provided by AO UK&I (Appendix 6: AO UK&I Major Grant Notification) and was sponsored by the University of Oxford Clinical Trials Research & Governance (CTRG) unit for Integrated Research Application System (IRAS ID 295778) submission. Following this application, the QUINTET study received approval from the East of England – Cambridge South – Research Ethics Committee and Health Research Authority on the 19th October 2021 (REC reference 21/EE/0197) (Appendix 7: East of England – Cambridge South Research Ethics Committee Approval, Appendix 8: NHS Health Research Authority Approval). The approved study protocol was published in the International Standard Randomized Controlled Trial Number registry (ISRCTN31179727)[146].

In order to achieve the QUINTET study's primary objective, I employed four assessments of QOL using validated patient-reported outcome measures: pre-injury and acute post-injury evaluations completed during the patients' acute admission and two further assessments at three and 12 months post-injury (**Table 2.7**). A secondary objective for this study was the prospective collection of management and clinical outcomes for the recruited patients.

Table 2.7: Objectives, outcomes and assessment timepoints for the QUINTET study

Objectives	Outcome Measures	Timepoints of evaluation of outcome measures
Primary Objective	- 5-Dimension EuroQol (EQ-5D-3L) [147] - Short Form 12 (SF-12) [148]	- Acute admission - 3 months - 12 months
Secondary Objectives	- Time to debridement - Time to fixation - Time to soft tissue closure - Postoperative superficial infection - Postoperative deep infection - Postoperative non-union - Revision procedures or re-exploration required	Throughout the follow-up period (12 months from enrolment, per participant)

Following the obtention of research ethics approval in the UK, I sent the final version of the QUINTET protocol to prospective collaborators in Austria, Chile, the Netherlands, New Zealand, Spain, South Africa, and Sudan. All had either taken part in the INTELLECT study or had expressed an interest in future collaboration. While facing clinical pressures due to the COVID pandemic at the time, three international units were able to secure local approval: Hospital del Tabajador in Chile, Hospital Universitario de Canarias in Spain, and Ribat University Hospital in Sudan. From the UK, I received the support of the National Institute for Health and Care Research (NIHR) Clinical Research Network, which supported the involvement of five major trauma centres in QUINTET: St Georges Hospital and St Mary's Hospital in London, Royal Victoria Infirmary in Newcastle, Hull Royal Infirmary in Hull, and University Hospital in Coventry.

2.7.1 Eligibility and Recruitment

Patients 18 years or more years of age presenting at one of the participating centres with a long open lower limb fracture were considered eligible for participation. Patients that required transfer to a nonparticipating centre for definitive management or that were not able

to commit to the necessary follow-up were excluded (**Table 2.8**). I instructed local investigators to screen daily trauma admissions to identify potentially eligible patients so that they could be approached with the relevant study information and invited to participate (Appendix 9: QUINTET Study Participant Information Sheet).

Recruitment of participants began on 1 June 2022 and was scheduled to be completed by 31 December 2022. Following NIHR approval, this recruitment window was later extended to the 31st of March 2023 to optimise the sample size.

Table 2.8: Eligibility criteria for the QUINTET study

Inclusion	Exclusion
• Patients ≥ 18 years of age with a long bone open lower limb fracture • Willing and able to provide informed consent	• Patients whose definitive treatment did not take place in a participating centre. • Patients not able to commit to follow up • Patients with more than one long bone open fracture or polytrauma

When designing this study, I was conscious of the fact that recruitment would be occurring at a moment in which patients would feel themselves to be particularly vulnerable. For this reason, eligible individuals were given a minimum of 24 hours to reflect on their choice to participate, and they were able to communicate an answer until the end of their inpatient stay. This allowed them adequate time to consider the information they had been given and pose questions to the investigators or other independent parties prior to deciding to participate. Informed consent was obtained as part of this process (Appendix 10: QUINTET Study Consent Form).

2.7.2 Data Collection and Outcomes Measures

Local investigators were tasked with prospectively collecting injury, treatment, and outcome information from recruited participants. As with INTELLECT, I designed a REDCap data-gathering sheet to facilitate prospective data collection (Appendix 11:

QUINTET Data-Gathering Instrument) with the pre-defined list of definitions for the outcomes of interest shown in **Table 2.9**.

Table 2.9: List of outcomes definitions used for the QUINTET study

Superficial infection	Redness and swelling, with or without discharge, that was treated with antibiotics. If surgery was performed, no evidence of infection was found deep to muscle fascia
Deep infection	Infections below muscle fascia, including bone, that require surgical exploration for lavage, removal of metalwork and/or further bone debridement
Non-union	Lack of union requiring unplanned surgical intervention after definitive wound closure or incomplete radiographic healing at 1 year
Amputation	immediate if it is in the first 24 hours, acute if it is performed within 3 months after the injury and late if it is performed after than that.

Two validated QOL patient-reported questionnaires were used for the QUINTET study: the EQ-5D-3L and Short Form 12 (SF-12). The former measures five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[147] For each domain the respondent was asked to self-rate, choosing one of three options for each of the assessed domains: *no problems*, *some problems*, or *a lot of problems*. The EQ-5D-3L instrument also includes a visual analogue scale (VAS) QOL assessment with which participants can rate their sense of wellbeing on a scale ranging from 0 to 100. The SF-12 differs, as it involves a twelve-item questionnaire instead. This was developed as a shorter version of the original Short Form Health Survey 36.[148] Using the scoring algorithm provided, the SF-12 supplies two summary measures: Physical Component Summary (PCS) and Mental Component Summary (MCS). I chose these instruments because both had been widely used and hence validated in multiple settings and had been previously mentioned in the literature for assessing QOL after open fractures. Both instruments can be summarised using numeric scores, thus allowing comparison of repeated measurements over a period of time.

For each recruited patient, a baseline assessment of QOL was conducted using the EQ-5D-3L and SF-12 during their emergency admission following an open lower extremity

fracture. This assessment involved completing the questionnaires with the patient's recollection of pre-injury QOL (T0) and a second measurement with the immediate post-injury status at the moment of enrolment (T1). Following discharge, at three months (T2) and 12 months (T3) post-injury, patients were re-assessed using the same set of instruments. As per the approved protocol, local investigators were given the alternative of doing these post-discharge assessments either face to face during routine follow-up appointments or over the phone following a pre-defined script (Appendix 12: QUINTET Study Telephone Follow-Up Script).

Participants were informed that they could withdraw from the study at any time. I also instructed local investigators to reassure patients that, if they decided to discontinue their participation, they would receive the same standard of care treatment.

2.7.3 Data Management and Statistical Analysis

Following the same GDPR-compliance procedures used for the INTELLECT study, clinician and patient-reported data were collected and stored securely in a REDCap database hosted at The Kennedy Institute of Rheumatology. Each participant was assigned a unique trial-specific number to allow local teams to identify patients while data collection was ongoing. No study data other than the signed consent form and participant contact details were stored locally. Paper forms for data collection were permitted, although investigators were to destroy these immediately after uploading the information into REDCap.

Following completion of data collection, the database was locked, and the de-identified data were exported as a password-protected, encrypted Excel spreadsheet stored on the secure University of Oxford OneDrive server. Identifiable information such as date of birth was used to calculate participant age at the time of injury and then deleted to de-identify the data.

In in compliance with the STROBE guidelines, I designed a statistical analysis plan prior to data collection, using the advice of the medical statistician that had conducted the

analysis for INTELLECT.[119] Using SPSS software, I undertook a descriptive statistical analysis that included demographic data, injury characteristics, and the treatment provided the patients. This included calculation of measures of central tendency and proportions, depending on whether these data were continuous or categorical, respectively. Missing data points were documented but not analysed, so that these could be included in the report to achieve transparency.

Inferential statistical analysis commenced with the Shapiro-Wilk test to assess distribution normality of the results obtained. For this, I also selected a significance level of 5% for rejection of the null hypothesis. I then used the Pearson's chi-square test to assess whether observed differences in categorical variables were explainable by chance. Since the reliability of Pearson's chi-square decreases when the test is applied to small samples, I substituted Fisher's exact test for Pearson's chi-square for groups having five or fewer cases. As its name indicates, Fisher's exact test yields the exact significance of a deviation from expected value, making it a reliable test for small sample sizes. For comparison of continuous variables by group, I employed the Kruskal-Wallis test, a nonparametric alterative to a one-way ANOVA, based on the rationale previously presented in the INTELLECT study's discussion.

For assessing significant changes in the sequential QOL measures obtained during the course of the study, I conducted either a repeated measures analysis of variance (rANOVA) or a Friedman one-way repeated measure analysis of variance by rank, depending on whether the variable's data appeared to be normally distributed or not.

As with other ANOVA analyses, rANOVA compares means of two or more groups. In theory, an ANOVA segments the variability in data into systemic variability, that due to group differences, and random variability, which is not dependent on group. It yields an *F*-statistic or *F*-ratio. If there is no difference across the groups of interest, i.e., the null hypothesis is true, the value of the *F*-statistic is greater than the significance level. For an

rANOVA, the categorical independent variable is the within-subject factor, while the dependent continuous variable is the repeated measurement of interest. Five assumptions are required to conduct this test: the dependent variable is continuous; the independent, categorical variable denotes membership in at least two otherwise comparable groups; there should be no significant outliers; the dependent variable's distribution is approximately normally distributed; and the intra-group variances and their combinations must be equal.

The Friedman test is the nonparametric alternative to rANOVA. It is preferred if the data are not normally distributed or when any of the necessary assumptions required for running an ANOVA is absent. The Friedman test ranks the repeated measures and compares the ranking instead of the actual measured values and their means.

For repeated assessments of non-continuous variables, such as that obtained from the five domains included in the EQ-5D-3L, percentages were calculated as per the user guide for this instrument. Even though the Cochrane Q test has been suggested for comparing repeated measurement of categorical variables, I opted to avoid this analysis, as it would involve transforming the EQ-5D-3L five-domain assessment into a dichotomous variable and thereby losing information contained within the data.

2.8 QUINTET Study: Results

2.8.1 QUINTET Dataset Overview

The prospective data collection exercise for the QUINTET study involved a network of investigators based in eight participating centres located in four countries: the UK, Spain, Chile, and Sudan (Appendix 13: List of QUINTET Participating Centres and Collaborators). As with INTELLECT, one senior lead clinician was selected in each of these units and was responsible for the local running of the study in coordination with me. A total of 92 patients admitted with open lower limb fractures were successfully enrolled in the study after obtaining their informed consent, with a median of 13 cases per unit. Of these, 87 were open

tibial fractures, and the remaining five were open femur fractures. UK hospitals contributed the majority of these, 72 individuals in total (78.2%).

With males representing 60.9% of all recruited participants, mean age at presentation was 53.6 years of age (range 21-92), 47 years for males and 64 years for females. **Figure 2.1**.below shows this gender-dependant difference in age at presentation. Even though all patients completed their quality-of-life assessment upon recruitment and none indicated they were withdrawing from the study, only 66 (71.7%) and 68 (73.9%) completed their three-month and twelve-month assessments, respectively. Among the patients who did not participate in further data collection, three died following discharge and not as a direct consequence of their injuries.

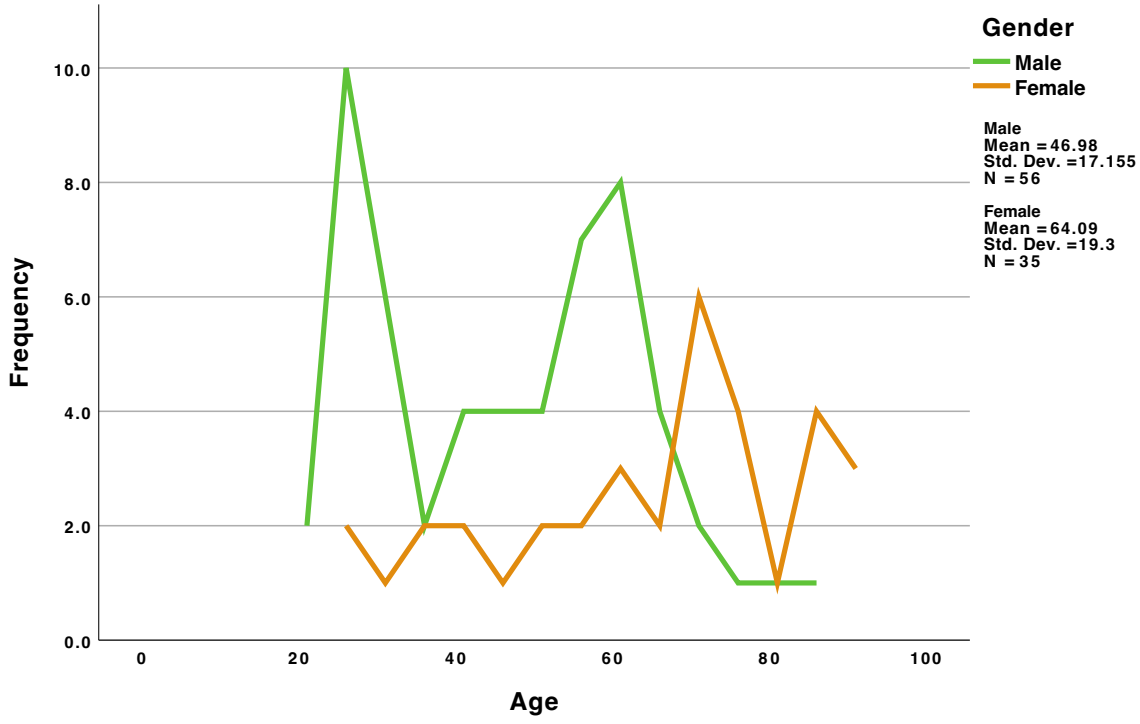


Figure 2.1: Linear histogram comparing age for male and female participants

According to the data obtained from the QUINTET study, the most common mechanism for injury was low-energy falls (41.1%), which were followed by road traffic accidents (28.9%) and then by high-energy falls (14.4%). A gender comparison using

Pearson's chi-square, and Fisher's exact test when appropriate, exhibited a statistically significant association of males with road traffic accidents as the mechanism of injury with females significantly associated with low-energy falls (**Table 2.10**).

Table 2.10: Differences in mechanism of injury for male and female patients

Mechanism of injury	**Male**	**Female**	***p*-value**	**Total**
Road traffic accident	38.2%* [40]	14.3%* [38]	0.015	28.9% [40]
High-energy fall	14.5% [54]	14.3% [48]	0.973	14.4% [51]
Low-energy fall	23.6%* [61]	68.6%* [73]	<0.001	41.1% [69]
Work-related	12.7%^ [49]	0%^	0.040^	7.8% [49]
Interpersonal violence	1.8% [24]	0%	0.422	1.1% [24]
Sports-related	5.5% [26]	0%	0.279^	3.3% [26]
Other	3.6%^ [44]	2.9%^ [69]	0.841	3.3% [52]

Mean age presented for each subgroup in square brackets [ ]
* Pearson's chi-square test / ^ Fisher's exact test

Table 2.11 provides a summary of the demographic information, treatment management, and outcomes for the recruited cohort. The median recorded time to administration of prophylactic antibiotics was two hours. For all recruited cases, 71.4% were transferred directly by ambulance to the unit for definitive treatment. The median time to wound debridement was 20 hours, with 69.6% of participants having this in the first 24 hours post-injury. Orthopaedic surgeons performed debridement solely in 44.8% of the cases and jointly with plastic surgeons in 52.9% of the fractures. The reported median time to definitive osteosynthesis was two days, and the median time to soft tissue reconstruction for the 27 cases (29.3%) cases that required it was three days. Lastly, the median time to discharge from the acute hospital setting was 11.5 days.

Table 2.11: Demographic and clinical data of QUINTET study patients

Demographics	*Femur fractures: 5 (5.4%)*	*Tibia/fibula fractures: 87 (94.6%)*
Mean age n= 91	53 years (SD: 20)	54 years (SD: 20)
Male : Female n=92	80:20	60:40
Mechanism of injury n=90	Road traffic accident: 40% / Low-energy fall: 0% / High-energy fall: 40% / Sports-related: 0% / Work-related: 20% / Interpersonal violence: 0% / Other: 0%	Road traffic accident: 28.2% / Low-energy fall: 43.5% / High-energy fall: 12.9% / Sports-related: 3.5% / Work-related: 7.1% / Interpersonal violence: 1.2% / Other: 3.5%
Gustilo-Anderson classification n=88	I: 20% / II: 40% / III A: 40%, B: 0%, C: 0%	I: 14.5% / II: 26.5% / III A: 22.9%, B: 34.9%, C: 1.2%
Number of cases per country n=92	UK: 1 / Spain: 3 / Chile: 0 / Sudan: 1	UK: 71 / Spain: 10 / Chile: 5 / Sudan: 1
Comorbidities n=92	None: 40% / Hypertension: 20% / Diabetes: 0% / Ischaemic heart disease: 0% / Asthma: 0% / COPD: 0% / Peripheral vascular disease: 0%	None: 48.2% / Hypertension: 16.5% / Diabetes: 11.8% / Ischaemic heart disease: 2.4% / Asthma: 10.6% / COPD: 5.9% / Peripheral vascular disease: 3.5%
Smoking n=85	Yes: 0% / No: 100%	Yes: 23.8% / No: 76.3%
Treatment and outcomes		
Median time to antibiotics n=80	1 hours (IQR: 12)	2 hours (IQR: 6)
Direct transfer to specialist centre n=91	80%	70.6%
Wound debridement within 24 hours n=83	80% / Median time to debridement: 20hours (IQR: 12)	68.2% / Median time to debridement: 20 hours (IQR: 21)
Specialties involved in primary debridement n=87	Orthopaedic surgeons: 100%	Orthopaedic surgeons: 41.5% / Plastic surgeons: 2.4% / Orthopaedic and plastic surgeons: 56.1%
Median time to definitive skeletal fixation n=79	1 days (IQR: 3)	2 days (IQR: 5)
Primary mode of definitive skeletal fixation n=92	Uni-biplanar external fixator: 20% / Frame external fixator: 5% / Plate and screws: 20% / Intramedullary nail: 60%	Casting: 1.2% / Uni-biplanar external fixator: 3.5% / Frame external fixator: 4.7% / Plate and screws: 21.2% / Intramedullary nail: 43.5% / Kirschner wires: 1.2% / Other: 9.4%
Soft tissue reconstruction required n=7	0%	33.8%
Modality of soft tissue closure n=24		Conventional dressings: 16.7% / Negative pressure wound therapy: 4.2% / Skin grafting only: 8.3% / Local flaps: 8.3% / Perforator flaps: 12.5% / Free flaps: 50%
Median time to soft tissue closure n=24		3 days (IQR: 7)
Flap survival rates n=17		Local and regional flaps (n=5): Total flap failure 0% / Total flap survival: 100%. Free flaps (n=12): Total flap failure 16.7% / Total flap survival: 83.3%.
Wound infection n=72	20 % / Median time to wound infection: 6 days	11.9 % / Median time to wound infection: 59 days (IQR: 188)
Deep wound infection n=72	20 % / Median time to deep infection: 6 days	6% / Median time to deep infection: 29 days (IQR: 90)
Non-union n=68	0%	3.2%
Amputation n=69	Immediate: 0% / Early: 20% / Late: 0%	Immediate: 0% / Early: 3.1% / Late 0%
Median time to discharge n=66	15 days (IQR: 12)	10 days (IQR: 13)
Median time to full weight bearing n=65	61 days (IQR193	52 days (IQR 97)

SD: Standard deviation / IQR: Interquartile range.

In terms of complications, wound infection was reported for nine patients (9.7%) and deep tissue infection for five cases (5.4%). Three patients in this cohort (4.3%) required a secondary amputation, and one patient being diagnosed with deep venous thrombosis.

2.8.2 Quality of Life Analysis

Following the instructions provided for the SF-12 and EU-5D-3L instruments, patient scores were tabulated for further analysis. SF-12 outcomes were processed using the QualityMetric Pro CoRE Scoring Software (QualityMetric, Rhode Island, United States) to obtain the PCS and MCS for each encounter. The data derived from the application of the EU-5D-3L was organised according to the recommendations provided in the EuroQol EQ-5D-3L User Guide.[149]

Table 2.12 displays the results obtained from the repeated application of the EQ-5D-3L instrument for the study period with each individual domain for this tool separated: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. When asked about their QOL prior to injury, most participants reported *no problems*. However, most reported a dramatic reduction in QOL following the open fracture, with a substantial increase in participants' reporting *some* or *a lot of problems* in the assessed domains. The repeat assessments at three- and twelve-month intervals showed significant improvement, although, in most cases, these did not reach pre-injury levels by the end of the study. This was particularly true for the mobility and usual activities and pain/discomfort domain assessments, and less so for that for the self-care and anxiety/depression domain.

Table 2.12: EQ-5D-3L results for the QUINTET study

EQ-5D-3L dimension		***Pre-injury***	***Post-injury***	***3-months***	***12-months***
Mobility	No problems	66 (72.5%)	0	11 (16.9%)	26 (38.2%)
	Some problems	25 (27.5%)	38 (41.3%)	52 (80.0%)	42 (61.8%)
	A lot of problems	-	54 (58.7%)	2 (3.1%)	-
Looking after myself	No problems	79 (86.8%)	5 (5.5%)	37 (56.9%)	50 (73.5%)
	Some problems	12 (13.2%)	48 (52.7%)	25 (38.5%)	16 (23.5%)
	A lot of problems	-	38 (41.8%)	3 (4.6%)	2 (2.9%)
Doing usual activities	No problems	75 (83.3%)	2 (2.2%)	11 (16.9%)	31 (45.6%)
	Some problems	12 (13.3%)	15 (16.7%)	35 (53.8%)	28 (41.2%)
	A lot of problems	3 (3.3%)	73 (81.1%)	19 (29.2%)	9 (13.2%)
Having pain or discomfort	No problems	69 (75.8%)	8 (8.8%)	18 (27.7%)	23 (33.8%)
	Some problems	17 (18.7%)	61 (67.0%)	42 (64.6%)	43 (63.2%)
	A lot of problems	5 (5.5%)	22 (24.2%)	5 (7.7%)	2 (2.9%)
Feeling worried, sad or unhappy	No problems	68 (74.7%)	35 (38.5%)	43 (66.2%)	45 (66.2%)
	Some problems	19 (20.9%)	41 (45.1%)	17 (26.2%)	19 (27.9%)
	A lot of problems	2 (2.9%)	15 (16.5%)	5 (7.7%)	4 (5.9%)

The continuous results obtained for EQ-5D-3L VAS and the SF-12 MCS and PCS were analysed using the Shapiro-Wilk, which indicated that only the pre-injury results for these instruments were normally distributed ($p < 0.0001$). However, this was not the case for the later measures. Therefore, and as per our analysis plan, I employed the Friedman test to compare the repeated assessments and **Table 2.13** displays my results, which indicated a statistically significant change over time for the repeated assessments of EQ-5D-3L VAS, SF-12 MCS, and SF-12 PCS over the course of the study.

Table 2.13: Comparison of continuous variables obtained from the SF-12 and EQ-5D-3L repeated assessments

	Pre-injury	*Post-injury*	*3-months*	*12-months*	*p-value*
SF-12 PCS (mean)	50.9 (SD: 10.3)	27.5 (SD: 5.5)	38.3 (SD: 8)	45.1 (SD: 10.7)	0.0297
SF-12 MCS (mean)	52.7 (SD 9.3)	41.4 (SD: 12.3)	48.9 (SD: 11.5)	51.1 (SD: 11.4)	< 0.001
EQ-5D-3L VAS (mean)	79 (SD: 20)	45 (SD: 22)	65 (SD: 21)	71 (SD: 21)	< 0.001

The box-plots included in **Figure 2.2** display the initial drop in QOL scores along with gradual, partial recovery over the course of twelve months. Repeated assessments for SF-12 MCS and the EQ-5D-3L VAS yielded a $p < 0.001$. The *p*-value for SF-12 PCS was less

significant, although still below the significance threshold ($p = 0.0297$). When the analysis was run separately for males and females, significance levels were maintained for both genders for EQ-5D-3L VAS and SF-12 MCS, but, for SF-12 PCS, men showed a statistically significant difference ($p = 0.0451$) while women did not ($p = 0.0591$).

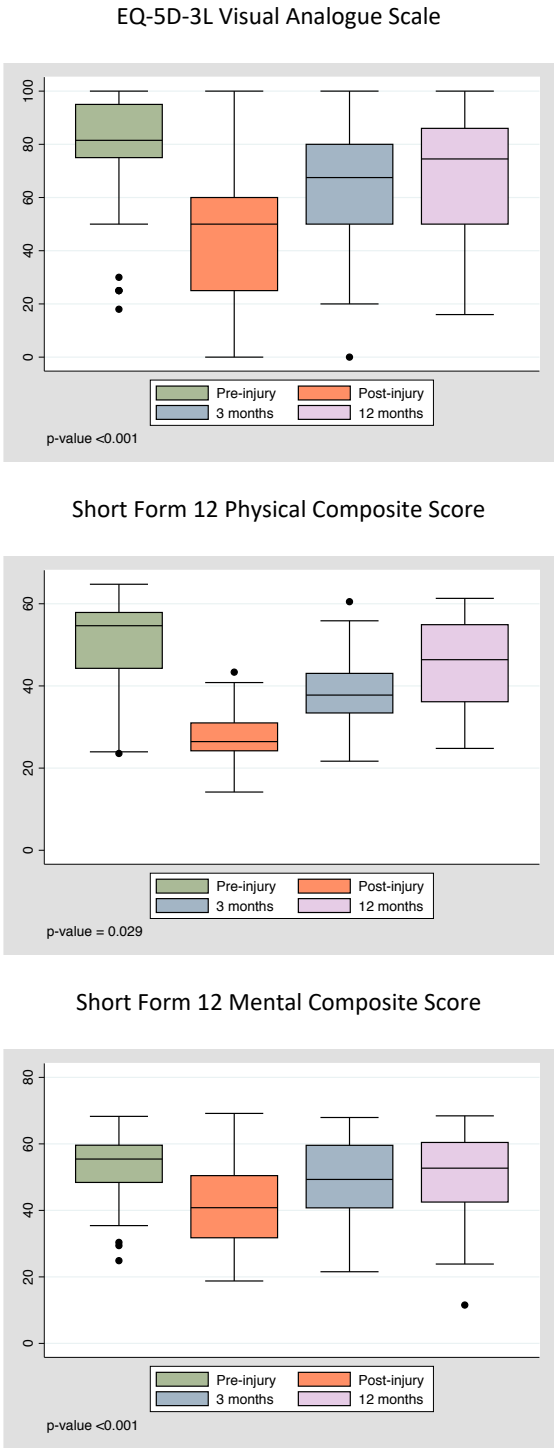


Figure 2.2: Box-plots for EQ-5D-3L and Short Form-12 Physical and Mental Composite repeated assessments

When comparing results for participants in the UK with their counterparts treated in Spain and Chile, the former presented consistently lower QOL scores throughout the study. This difference was not statistically significant in terms of pre-injury status for SF-12 PCS and MCS. However, UK scores were significantly lower for PCS at twelve months post-injury, and MCS three months and twelve months following an open lower limb fracture. EQ-5D-3L VAS scores were significantly lower for UK participants for all assessments (**Table 2.14**).

Table 2.14: Comparison of median SF-12 PCS, SF-12 MCS and EQ-5D-3L VAS scores for UK participants and participants treated in Spain and Chile

		UK (n=71)	**Spain + Chile (n=15)**	***p*-value**
SF-12 PCS	Pre-injury	54.6 (IQR 14.6)	54.8 (IQR 8.2)	0.580
	Post-injury	26.6 (IQR 6.8)	25.5 (IQR 5.1)	0.201
	3-months	36.9 (IQR 10.6)	39.7 (IQR 7.6)	0.332
	12-months	44.6 (IQR 19.1)	54.8 (IQR 10.6)	0.024*
SF-12 MCS	Pre-injury	53.5 (IQR 10.9)	56.8 (IQR 10.8)	0.097
	Post-injury	37.0 (IQR 16.2)	50.5 (IQR 13.6)	0.001*
	3-months	46.9 (IQR 18.4)	54.91 (IQR 17.0)	0.035*
	12-months	50.5 (IQR 18.0)	60.2 (IQR 12.8)	0.054
EQ-5D-3L VAS	Pre-injury	80.0 (IQR 23.0)	90.0 (IQR 15.0)	0.036*
	Post-injury	44.0 (IQR 30.0)	55.0 (IQR 19.0)	0.023*
	3-months	65.0 (IQR 27.0)	80.0 (IQR 20.0)	0.036*
	12-months	70.0 (IQR 35.0)	90.0 (IQR 25.0)	< 0.001*

2.9 QUINTET Study: Discussion

The QUINTET study, which constitutes the third and final research project discussed in this chapter, began following the successful conclusion of the INTELLECT and INTELLECT-COVID studies. QUINTET aimed to address limitations encountered with INTELLECT due primarily to its retrospective design and lack of inclusion of patient-reported outcomes. QUINTET was, therefore, designed as an international, prospective study whose goal was investigating patient QOL after sustaining an open lower limb fracture.

With the assistance of local investigators based in the eight participating units, QUINTET was able to recruit 92 patients and maintain a response rate of over 70% for the intended three- and twelve-month assessments. The repeated, patient-reported QOL measures obtained reflected the significant detriment that patients experienced following open lower limb fracture. Although scores reported via the EQ-5D-3L and SF-12 instruments did improve over time, they did not reach pre-injury levels at twelve months post-injury. However, The Friedman test used to evaluate the variation repeated QOL measures cannot be used to compare two individual sets of QOL measures obtained at specific times during the study period. On the contrary, it provides an overall assessment for all repeated measures. For this reason, I was not able to statistically evaluate the change in quality of life between participants' pre-injury self-reported QOL with their status after 12 months. Therefore, it remains unanswered if the observed residual detriment in QOL after one year is significant or not.

The QUINTET results showed a similar trend when compared to those of the WOLLF trial,[50] with QOL scores not reaching their pre-injury baseline after one year. However, QUINTET's results showed a less dramatic decline in the assessed parameters, especially immediately after an open fracture, possibly due to differences in patient selection, as the WOLLF trial recruited only patients having severe open fractures. Furthermore, WOLLF focused on measuring differences between two study arms and not necessarily analysing repeated QOL assessments over time.

While the repeated EQ-5D-3L VAS and SF-12 MCS measurements revealed a statistically significant change in QOL for both males and females, this was not the case for the female PCS scores measured by the SF-12 instrument. While this could be explained by the study's relatively small sample size, this could also be related to the finding that females were older and so reported a lower self-reported physical QOL baseline. Additionally, females presented a significant association with low-energy mechanisms of injury. Although

these interpretations may serve for future hypothesis generation, the clinical relevance of this observed gender difference remains unanswered. The p-values obtained when comparing PCS scores for male and female were both close to the pre-established threshold for significance, challenging their interpretation. As previous authors have highlighted, there is a difference between statistical significance and clinical significance, as these two are not always associated with one another.[150] While qualitative research has been conducted to explore patient experience following this type of injury,[48,49,116] to the best of my knowledge, no previous study has analysed potential gender differences on patient physical or psychological rehabilitation following an open fracture.

While INTELLECT demonstrated that a collective, international, retrospective audit was a viable means for retrieving large amounts of data for patients with open fractures, QUINTET was designed as a smaller study taking advantage of prospective data collection. Although I sought to include a significant international component in QUINTET to avoid skewing its results towards UK practice, this proved challenging. Despite reaching out to overseas centres that had successfully contributed to INTELLECT, securing engagement for QUINTET was difficult.

Whereas the retrospective clinical records review required for INTELLECT was a relatively low-effort enterprise, securing ethical approval followed by prospective data collection proved more demanding for my partners abroad. In the UK, support from the NIHR Clinical Research Network in participating major trauma centres facilitated study logistics, leading to successful recruitment and retention in these settings. Despite this limitation, we found patients treated in the UK reported lower QOL compared to those treated in Chile and Spain, although this difference could be explained by the relatively smaller sample size of the latter group. Additionally, although higher recruitment numbers were expected for both Chile and Sudan, social unrest and military conflict, respectively, inevitably affected these during QUINTET's recruitment phase.

The literature contains multiple reasons for recruitment failure, which has been identified as one of the main factors behind discontinuation of clinical trials in general.[151] Briel et al. (2021) explored this issue by conducting interviews with an international sample of trial stakeholders. Among the reasons identified, the most commonly reported were overoptimistic recruitment estimates, lack of engagement of recruiters, lack of recruiter competence/training, insufficient funding, and high burden for trial participants.[152] Identifying exactly which of these, if any, was the driver for QUINTET's limited recruitment in the Chilean and Sudanese centres. Given the crucial role that the support provided by the NIHR Clinical Research Network played in QUINTET's successful UK recruitment, I conjecture that affiliating with similar organisations overseas could be an effective strategy to optimise international recruitment. This would enable engagement of local investigators, while providing on-site training and support that we were not able to deliver as part of QUINTET.

Despite its limitations, the QUINTET study's results highlight the differences in patient-reported QOL from a gender and international perspective. However, the quantitative methods used were unable to facilitate further analysis of the complexity underlying the experience of sustaining and receiving treatment for an open fracture. The use of a qualitative, gender-sensitive, research approach may provide further answers to the questions QUINTET has raised. Prioritisation of research in this direction would contribute to the holistic management of the raising number of fragility fractures affecting primarily females,[153–155] while assisting in the effective standardisation of open extremity care internationally.[156]

2.10 Conclusions

The QUINTET study provides closure to this chapter, which, along the INTELLECT and INTELLECT-COVID studies, shared the goal of investigating current treatment management and outcomes of patients with open lower limb injuries on an international basis. While INTELLECT was able to gather large amounts of data using a collaborative and

retrospective strategy, QUINTET focused on a smaller, international cohort of patients, thus allowing for collection of patient-reported outcomes following an open fracture.

The studies presented in this chapter contribute to the understanding of how open lower limb fractures are managed on a global scale by means of a large survey of patient outcomes. I deemed this to be the first necessary step to achieve the main goal of my doctoral research: optimising the uptake of evidence to improve the treatment management and outcomes of patients with lower limb open fractures. Thus, both INTELLECT and QUINTET provide a baseline for future advances, while identifying gaps in knowledge worth addressing, especially those related to subgroups that may have received less attention in the open fracture literature.

Like no previous study, INTELLECT illustrated wide variability in the care provided and outcomes obtained for open lower limb fractures internationally. Unsurprisingly, patients treated in low- and middle-income countries experienced delays in their treatment, which was associated with higher infective complication rates. However, even among high-income countries, significant differences were seen. INTELLECT thus demonstrated the positive association of clinical practice guidelines with improved outcomes for open lower limb fractures. Study results showed that patients treated in contexts that included such recommendations received therapeutic interventions sooner and presented fewer infective complications.

At this stage of my doctoral research, I hypothesised that clinical practice guidelines could not only standardise the management of patients with open lower limb fractures but could also act as a vector for introducing evidence-based practice. Until the publication of INTELLECT, no previous studies had inquired into the role of clinical practice guidelines for lower limb fractures at an international level. However, the number of countries that had developed such documents remained unknown, including their scope, methodology, and

recommendations. The chapter which follows revisits this research question and discusses my approach to addressing this gap in the literature.

Chapter 3 Scoping Review and Quality Comparison of Open Lower Extremity Fractures Clinical Guidelines

The large survey of outcomes presented in the previous chapter provided an overview of the current treatment management of open fractures internationally along with its associated patient outcomes, thus establishing a baseline for future improvement while allowing comparison of practices across countries with and without clinical guidelines. However, the question remained as to whether having clinical guidelines for this type of injury is the norm across international borders or the exception. Given the potential impact that clinical guidelines could have in optimising the uptake of evidence and patient outcomes, I sought to address this question, and the research presented in this chapter summarises my efforts to do so.

In this chapter, I present two research projects to which the chapter's two sections are dedicated. The first consists of a systematic scoping review conducted to identify all clinical guidelines for open lower limb fractures discussed in the literature. As this review includes an in-depth analysis of existing guidelines, the second part of the chapter utilises the results of this review.

As were those for INTELLECT and INTELLECT-COVID, the reports and findings for these projects were also published prior to the completion of my DPhil dissertation, the systematic scoping review in the *European Journal of Orthopaedic Surgery and Traumatology*[157] (2022) and a brief guideline comparison of only the UK and the Netherlands, which the *Journal of Plastic, Reconstructive and Aesthetic Surgery* accepted for publication in 2021.[156,158]

3.1 Background

The primary aim of developing a clinical practice guideline is to improve quality of care by providing clinicians with cost-effective, evidence-based recommendations.[93] Their

development usually involves a collaborative effort commonly orchestrated by governmental bodies and scientific societies having the capacity, resources, and reputation to support this type of endeavour. Guidelines promote standardisation of practice for clinical conditions that might otherwise be managed in heterogeneous ways not necessarily following best practice as indicated by the most recent evidence.[86] Furthermore, guidelines can provide a benchmark for quality control and continuous audit of and improvement in best practices.

The large survey of outcomes presented in the previous chapter (as part of the INTELLECT[111] and QUINTET[113] studies) demonstrated the severe impact of open lower limb fractures on patients' lives, including permanent loss of function and a significant decrease in QOL. As my introduction made clear, BAPRAS and BOA were amongst the first surgical societies to recognise the importance of joint care for open tibial fractures. Initial work done almost three decades ago resulted in the publication of two collaborative reports in 1993 and 1997[97] promoting collaboration between orthopaedic and plastic surgeons in management of open fractures, along with a series of expert recommendations. Produced jointly by BAPRAS and BOA, publication of the Standards for the Management of Open Fractures of the Lower Limb followed in 2009;[102] the NICE guidelines for the management of fractures, including open ones, in 2016;[71] and the latest iteration of the BAPRAS and BOA Standards for the Management of Open Fractures in 2020.[39]

The Dutch guideline for management of complex lower limb fractures was published in 2017 following a series of independent systematic reviews and applying the GRADE evidence-based recommendation system.[123] Although the committee responsible for this document considered publishing an adaptation of the British BAPRAS/BOA Standards, it instead developed a completely new set of guidelines for the Netherlands, a decision due primarily to the strict methodology required by the Dutch Federation of Medical Specialties for approval of a multidisciplinary guideline.[159]

As a result of these initiatives, management of open fractures in the UK and the Netherlands is now largely guideline driven, mandating the direct transfer of patients to specialist centres capable of providing multidisciplinary interventions.[73,107] This allows the timely involvement of orthopaedic and plastic surgeons, microbiologists, radiologists, and physiotherapists with an interest in major trauma, to achieve early skeletal stabilisation and soft tissue coverage of the fracture site. This multidisciplinary setting facilitates patient management in accordance with current guidelines for open lower limb fractures, including pre-defined timescales for critical interventions, ensuring that patients receive an evidence-based and cost-effective package of care, while reducing disparities within the healthcare system.[103,160]

The INTELLECT study demonstrated that patients treated in settings with open lower limb fracture guidelines presented lower rates of infective complications. Patients treated in the UK and the Netherlands received a better standard of care and achieved better outcomes than patients treated in high-income countries that did not have clinical guidelines in place. These findings reaffirmed the need to determine the availability and quality of international clinical guidelines for the management of this condition, and quality of development and reporting trends over time.

3.2 Scoping Systematic Review of Clinical Guidelines for Open Lower Limb Fractures

3.2.1 Systematic Scoping Review: Methodology

Systematic reviews are an approach to evidence synthesis that uses "explicit, systematic methods that are selected with a view to minimising bias, thus providing more reliable findings from which conclusions can be drawn and decisions made."[161] To ensure that the conclusions accurately reflect available primary research findings, these reviews follow a structured and pre-defined protocol.

Although a systematic review methodology can be adapted to address a variety of primary study designs,[162] such as those whose focus is efficacy or diagnosis, traditional systematic reviews usually requires a well-defined research question. However, this is not always possible, especially if the investigator's interest lies in the characteristics and concepts needed to provide an overview of the available evidence[163] rather than answering a specific query. For such projects, systematic scoping reviews have been proposed as an alternative methodology[164] as they provide a more flexible alternative approach to traditional systematic reviews.

Due to the exploratory nature of the objective this chapter concerns, I concluded that the best approach was to conduct a systematic scoping review.[165] I therefore designed a protocol for this study, which followed the methodological steps proposed by Mak and Thomas (2022)[166] and complied with the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Scoping Reviews (PRISMA-ScR).[167,168] Similar to the STROBE statement presented in the previous chapter, PRISMA Sc-R is also part of the EQUATOR network and provides best practice guidance to minimise bias and increase reproducibility when conducting and reporting results of this type of study.

In the protocol for this study, whose purpose was to identify all clinical guidelines for open lower limb fractures published to date, I established clear inclusion and exclusion criteria (**Table 3.1**) and screening and data management strategies. National lower extremity open fractures clinical guidelines or publications that referred or cited a clinical guideline were eligible for inclusion, whereas narrative and systematic reviews on the management of open fractures and personal or institutional recommendations were excluded.

Table 3.1: Inclusion and exclusion criteria for systematic scoping review

Inclusion	**Exclusion**
- National or regional clinical guidelines on the management of open extremity fractures. - Publications referencing national or regional clinical guidelines	- Local or single-institution guidelines - Narrative or systematic reviews on the management of open fractures

I worked with a senior librarian affiliated with the Bodleian Library to design the systematic search strategy for this review. I avoided filters or limitations in terms of language or publication date to maximise capture of all guidelines available in the literature and employed the following search terms: “open fracture,” “compound fracture,” “guideline,” “consensus,” “recommendation,” and “standards.” The full search strategy is available in Appendix 14: Search Strategy for Open Fracture Guidelines Systematic Scoping Review. Both the Excerpta Medica Database (EMBASE) and the Medical Literature Analysis and Retrieval System Online (MEDLINE) databases were searched on 10 February 2021, and abstracts and conference proceedings were included.

I used Mendeley Desktop (Elsevier. London, UK) to manage the retrieved entries, identify and eliminate duplicate articles. Blinded and in parallel with a second assessor, I then employed Rayyan QCRI software[169] (Qatar Computing Research Institute, Qatar) to screen the resulting titles and abstracts in order to identify potentially eligible studies. Following was a full text and reference review that, with the support of my principal supervisor, resolved any discrepancies. I then designed a data-gathering instrument that I later used, again in parallel with and independent from a second investigator, to identify and retrieve bibliographical information for all the identified national clinical practice guidelines for open lower limb fractures.

When this project was conducted, the PROSPERO international prospective register for systematic reviews[170] did not accept scoping systematic reviews for registration. Therefore, I prospectively registered the protocol for this study in the Open Science Framework instead.

3.2.2 Systematic Scoping Review: Results

The utilised search strategy identified a total of 475 publications, 215 retrieved from MEDLINE and 260 from EMBASE. Using Mendeley Desktop, I identified 99 duplicate entries, which resulted in a list of 376 articles for further review. A total of 45 publications were

identified as presenting or referring to a national guideline for open fracture management after completing the title, abstract, and full-text review strategy. **Figure 3.1** shows the PRISMA flow-diagram summarising my screening process.

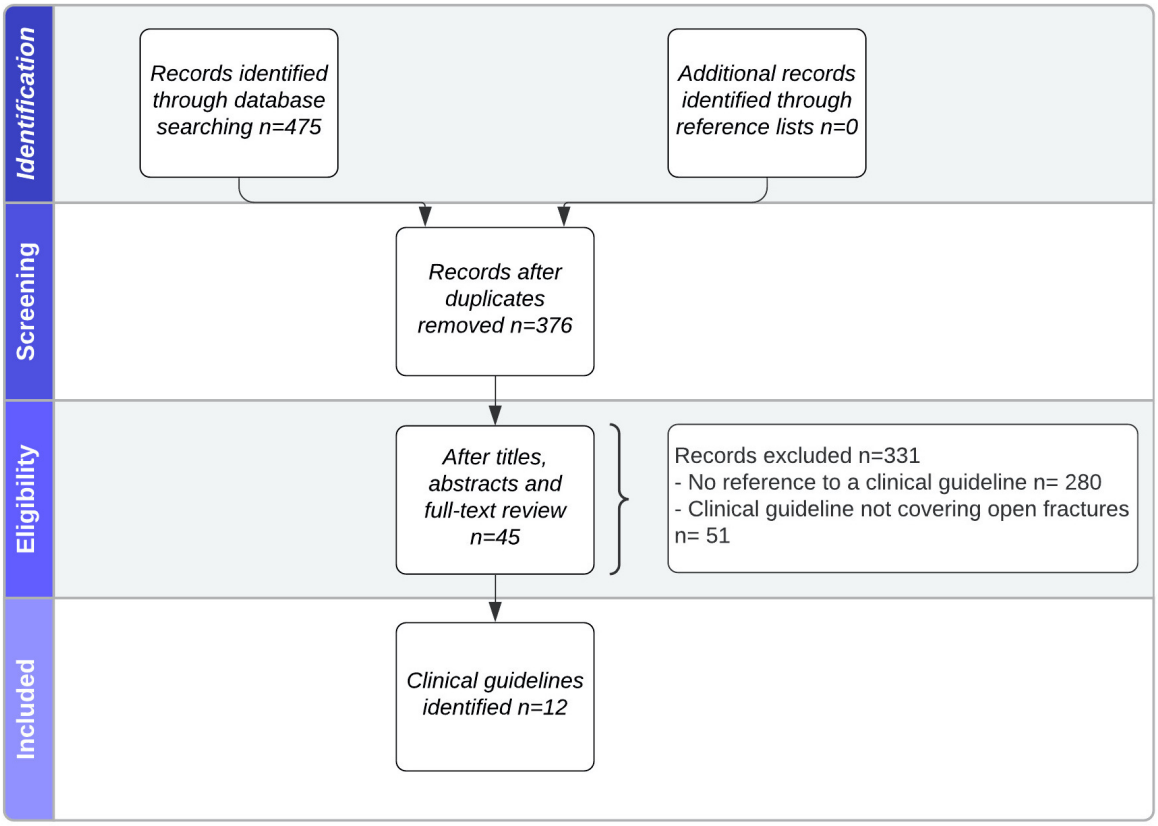


Figure 3.1: PRISMA Sc-R flow-diagram demonstrating the screening process for this review

The final list of eligible studies included forty-five manuscripts published from 1997 through the date the searches were conducted. Of these, 40 were in English, three in German, and two in Finnish. Only six were actual clinical practice guidelines for the management of open lower extremity fractures, while the remaining thirty-nine publications referred to at least one clinical practice guideline for this condition. As a result of this process, I identified twelve clinical practice guidelines for the treatment of open fractures. **Table 3.2** shows the resulting list of publications.

Table 3.2: List of identified clinical practice guidelines for open lower limb fractures

Title	Responsible Organisation	Country	Year
A report by the British Orthopaedic Association/British Association of Plastic Surgeons Working Party on The Management of Open Tibial Fractures[97]	BOA and BAPS	UK	1997
[Guidelines for the treatment of tibial fractures of adult patients][171]	Finnish Orthopaedic Association	Finland	2004
Prophylactic Antibiotic Use in Open Fractures: An Evidence-Based Guideline[172]	Surgical Infection Society	USA	2006
Standards for the Management of Open Fractures of the Lower Limb[102]	BOA and BAPRAS	UK	2009
Guidelines for the prevention of infections associated with combat-related injuries: 2011 update[173]	Infectious Diseases Society of America and the Surgical Infection Society	USA	2011
East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures[174]	Eastern Association for the Surgery of Trauma (EAST).	USA	2011
[Update on current care guidelines: treatment of tibial shaft fractures][175]	Finnish Orthopaedic Association	Finland	2011
Best Practices in the Management of Orthopaedic Trauma[176]	American College of Surgeons and Orthopaedic Trauma Association	USA	2015
Fractures (complex): assessment and management[71]	NICE	UK	2016
Open Fractures of the Lower Limb[123]	Federatie Medisch Specialisten	Netherlands	2017
Standards for the Management of Open Fractures[39]	BOA and BAPRAS	UK	2020
The Malawi Orthopaedic Association/AO Alliance guidelines and standards for open fracture management in Malawi[177]	Malawi Orthopaedic Association and AO Alliance	Malawi	2020

Two of these guidelines, one developed by the Surgical Infection Society and the other by the Eastern Association for the Surgery of Trauma (EAST), focused solely on recommendations for antibiotic prophylaxis following an open fracture.[172,174] A third guideline, published jointly by the Surgical Infection Society and the Infectious Diseases Society of America, focussed exclusively on management of combat-related injuries.[173]

The remaining nine publications provided a wide-ranging list of recommendations for management of open fractures. Of these, three were the result of the previously discussed partnership between BAPRAS and BOA and had been published in 1997,[97] 2009,[102] and 2020.[177] A further UK guideline identified, developed by NICE,[71] was published in 2016. The searches also identified the clinical practice guideline developed by the Dutch Federation of Medical Specialties disseminated in 2017.[123] Prior to commencing this study, I was already

aware of the UK and Dutch guidelines, as their impact had been investigated as part of the INTELLECT analysis.

The systematic scoping review also identified several guidelines of which I was not aware. The American College of Surgeons Trauma Quality Improvement Program had developed the *ACS TQIP Best Practices on the Management of Orthopaedic Trauma*[176] published in 2015. This report provides an overview of multiple trauma presentations, including open fractures. Due to its brief presentation, a limited number of open fracture recommendations concerning the following were included: antibiotic and tetanus prophylaxis, surgical debridement within 24 hours of admission, and soft tissue reconstruction within seven days when indicated. The Finnish Orthopaedic Association (FOA) published a clinical guideline for the management of open tibial fractures in 2004[171] that was later updated with a brief addendum in 2011.[175] This also presents a comprehensive overview and is structured similarly to UK and Netherlands guidelines. Additionally, I identified a national clinical guideline for Malawi published in 2020 that was the result of a collaboration between the Malawi Orthopaedic Association (MOA) and the AO alliance.[177] The authors of the Malawi guidelines state that they used the UK guidelines as a starting point, adapting it in a process involving a consensus reached by local experts. **Table 3.3** shows the table of contents for each guideline, thus providing an overview of the individual scope and comprehensiveness of each.

Table 3.3:Table of contents for each clinical practice guideline included in this study

BAAPS and BOA – UK, 1997[97]	Epidemiology of open fractures Injury recognition Communication Timing Pre-operative management The first orthopaedic procedure Safe incisions and fasciotomy Commonly used methods of soft tissue reconstruction
FOS – Finland, 2004[171]	Incidence and methods of treatment Definition and soft tissue injuries classification Choice of treatment setting First aid Assessment and diagnosis Principles for treating tibial fractures and treatment modality selection Intramedullary nailing Follow-up treatment Plate fixation Conservative treatment External fixation Treatment of severe open fractures Centralisation of specialist centres Treatment of tibial fractures in high-risk patients Complications Costs Evaluation criteria
SIS – USA, 2006[172]	Prophylactic antibiotics
Standards for the Management of Open Fractures of the Lower Limb – UK, 2009[102]	Specialist centres for complex open lower limb fractures Primary management in the emergency department Antibiotic prophylaxis Timing of wound excision in open fractures Guidelines for wound debridement (excision) Bone exposure, decontamination and preservation: debridement Degloving Classification of open fractures Temporary wound dressings Techniques for skeletal stabilization in open tibial fractures Timing of soft tissue reconstruction Type of soft tissue reconstruction Compartment syndrome Vascular injuries Open fractures of the foot and ankle When things go wrong with soft tissues When things go wrong with bone Guidelines for primary amputation Outcome measures Management of severe open fractures in children
Infectious Diseases Society of America and the Surgical Infection Society – USA, 2011[173]	Initial care in the field Prophylactic antibiotics Debridement and irrigation Surgical wound management Facility infection control and prevention
EAST – USA, 2011[174]	Antibiotic prophylaxis
FOA, 2011[175]	First aid Research Intramedullary nailing Plate fixation Plaster treatment Treatment of severe fractures Complications Non-union

ACS – USA, 2015[176]	Prophylactic antibiotics Open fractures Damage control orthopaedic surgery The mangled extremity Compartment syndrome
NICE – UK, 2016[71]	Initial management of open fractures before debridement Splinting long bone fractures of the leg in pre-hospital setting Destination for people with suspected fractures Vascular injury in hospital settings Compartment syndrome Whole-body CT of multiple injuries Management of open fractures before debridement Limb salvage in people with open fractures Debridement, staging of fixation and cover Documentation
Federation Medical Specialists – Netherlands, 2017[123]	Diagnosis and treatment of open limb fractures Debridement of open limb fractures Provisional treatment of soft tissue injury Internal fixation of open limb fractures Cancellous bone grafting open limb fracture Definitive treatment of soft tissue injuries Amputation of open limb fracture Postoperative antibiotics open limb fractures Exercise therapy after open limb fractures Organisation of care open limb fractures Patient communication
BAPRAS and BOA – UK, 2020[39]	Prehospital and Emergency Department Care, Including Prophylactic Antibiotics Timing of Wound Excision Wound Excision Degloving Injuries Temporary Wound Dressings Skeletal Stabilisation Timing of Soft Tissue Reconstruction Soft Tissue Reconstruction Bone Loss in Open Fractures Vascular Injuries Compartment Syndrome in the Lower Limb Amputation Infection Open Tibial Fractures in Children Open Fragility Fractures Outcome Measures Patient Experience of Open Fracture and Practical Psychological Support Rehabilitation After Severe Open Tibial Fractures Special Circumstances: Blast, Ballistics, and Mass Casualties Setting Up an Effective Orthoplastic Service
The Malawi Orthopaedic Association/AO Alliance – Malawi, 2020[177]	ATLS Prophylactic antibiotics Primary management in emergency department Timing of debridement Timing of soft tissue reconstruction Timing of skeletal stabilisation Amputation Documentation

Excluding the clinical practice guidelines that focused solely on antibiotic prophylaxis and combat-related injuries, the contents of the remaining guidelines presented considerable

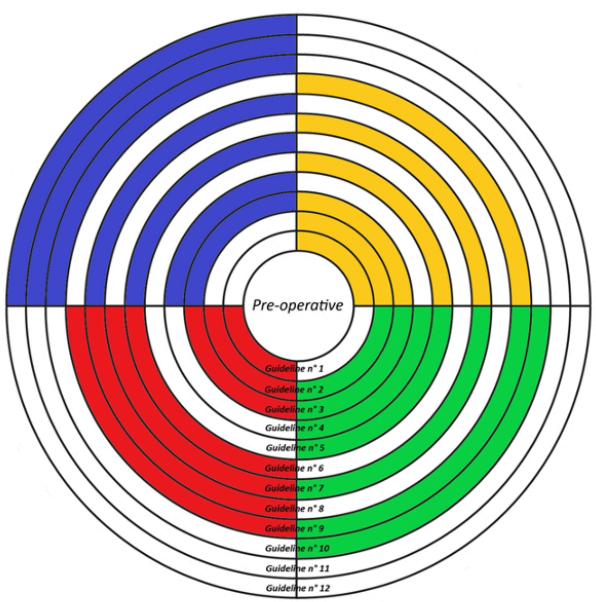
overlap. **Figure 3.2** illustrates these findings, showing the extent of overlap for preoperative, surgical, and post-operative recommendations for managing open extremity fractures.

3.2.3 Systematic Scoping Review: Discussion

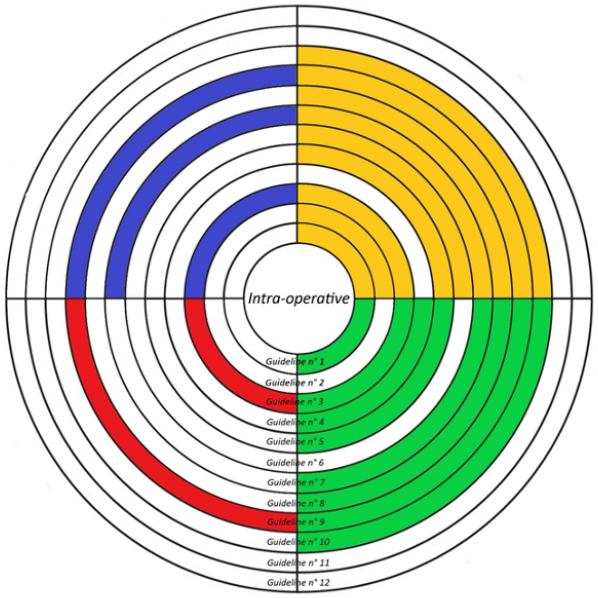
As previously established, the aim of this systematic scoping review was to identify all available clinical practice guidelines for lower limb open fractures. This was the necessary first step in achieving the objective of the research to which this chapter is dedicated: investigating the availability and quality of international clinical guidelines for management of this condition. I identified a total of 12 clinical practice guidelines for open lower extremity fractures, with only five countries worldwide having developed at least one: Finland,[171,175] Malawi,[178] the Netherlands,[123] UK,[39,71,97,102] and the United States.[172–174,176] These results demonstrated the limited availability of clinical practice guidelines for open lower limb fractures across the world.

Professional organisations in the United States developed four sets of clinical practice guidelines, two of which focus on antibiotic prophylaxis[172,174] and a third on combat-related injuries.[173] The fourth, published by the American College of Surgeons, provides an overview of management of open fractures in addition to a limited number of best practice recommendations. In contrast, the guidelines from the UK, the Netherlands, and Finland had many similarities in scope and contents. All aimed to provide a comprehensive set of evidence-based recommendations, including pre-hospital management, referral to a specialist centre, management in the emergency department, and timing and modalities for skeletal fixation and soft tissue closure.

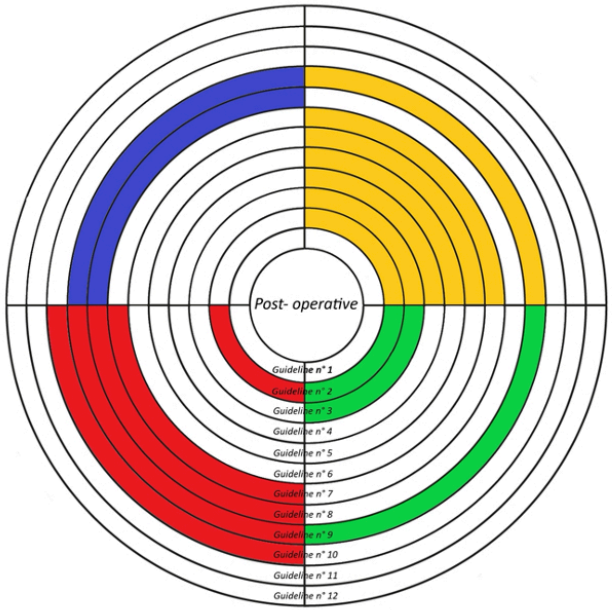
As mentioned previously in the chapter dedicated to the INTELLECT study, the Federation of Medical Specialties considered adapting the British recommendations. However, due to the Netherland's strict methodological requirements for approval of a multidisciplinary guideline, it developed its own guideline *de novo*.



Yellow: Epidemiology and general concepts / Green: Pre-hospital and emergency department management / Red: Diagnostic and management algorithms / Blue: Antibiotic prophylaxis



Yellow: Orthopaedic procedures / Green: Plastic surgery procedures / Red: Open fractures in children and special populations / Blue: Management of vascular injury



Yellow: Post-operative complications / Green: Associated costs / Red: Follow-up / Blue: rehabilitation

Figure 3.2: Table of contents for each clinical practice guideline identified in scoping review

Malawi's clinical practice guideline resulted from the collaboration of experts based in the UK, Switzerland, and Malawi using a consensus development conference approach involving orthopaedic surgeons and allied health professionals. Prior to their panel meeting, a list of questions to be addressed, the existing BAPRAS/BOA guidelines, recent systematic reviews, and primary research articles were circulated among the experts who had been invited to participate. At the panel meeting, after revising the consensus methodology and levels of evidence presentations to be used, the participants discussed the proposed recommendations and voted on these until a consensus was reached. The Malawi Orthopaedic Association then approved the contents of the resulting guideline during its annual general meeting in 2019

At the time I published my findings, mine was the first systematic scoping review to investigate published clinical guidelines for open fractures.[157] By following the PRISMA-ScR-guidelines[167,168] and conducting a broad systematic search with no limits or filters, I sought to capture all the guidelines published to date. Other clinical guidelines may have existed at that time but had not yet been indexed or referenced in MEDLINE- or EMBASE-indexed publications. An expanded search including additional databases and grey literature could address this limitation. However, given that clinical guidelines are to be widely disseminated, I expected all to either be indexed or else referenced in a MEDLINE- or EMBASE-indexed article.

As previously mentioned, clinical practice guidelines provide clinicians with recommendations based on the best available evidence at the time of their formulation.[93] This contributes to standardisation of the quality of care provided regardless of geographical location and patient financial situation and reduces disparity in a healthcare system. Although poor-quality guidelines have been identified, potentially leading clinicians towards ineffective and potentially harmful interventions,[179] specialised institutions such as NICE in the UK and

the Federation of Medical Specialties in the Netherlands have optimised the process involved in development of clinical guidelines so as to assure their quality.

The systematic search I conducted as part of this study identified only one clinical practice guideline for open fractures in a low- or middle-income country: Malawi. The development of robust, evidence-based national guidelines is resource and time consuming and so can prove prohibitive in resource-constrained settings. Malawi's experience provides an innovative approach to guideline development using a consensus-driven guideline-adaptation strategy that could be replicated in other countries. Given the considerable overlap in scope and content among existing guidelines, adaptation of these to a local culture, healthcare system, and the resources available that context could hypothetically be more cost effective than development of new guidelines from scratch. This approach would also stimulate international collaboration, further empowering organisations with global reach such as the AO Alliance.

Initially, I did not include a quality assessment for eligible guidelines identified in the systematic scoping review presented here. However, during the scoping study, the necessity for comparison of guidelines became increasingly evident, as this allowed identification of the strengths and weaknesses of existing guidelines. The first step in evaluating the potential for guideline adaptation consisted of better understanding the evolution of clinical guidelines as they crossed national borders. Assessing the quality of different nations' clinical guidelines thus consisted of an in-depth comparison of guidelines, which is presented below.

3.3 In-Depth Comparison of International Guidelines for Lower Limb Open Fractures

In the scoping review presented earlier, I reported the limited number of available national guidelines dedicated to management of open fractures. Only twelve documents were identified, of which eight provided a wide-ranging set of recommendations with considerable

overlap in terms of scope and content. As previously mentioned, the next step was assessing the availability and quality of these guidelines.

In Chapter 1 of this thesis, I detailed how poorly developed guidelines can potentially lead to ineffective or even deleterious recommendations, resulting in inefficiency, loss of resources, and even patient harm.[91,92] An example of this were the multiple "rapid" guidelines developed during the COVID-19 pandemic. A recently published quality appraisal of COVID-related guidelines by Florez et al. (2022), concluded that the majority of these were developed under pressure and took methodological shortcuts, resulting in insufficient quality and affecting overall trustworthiness.[180] Even the INTELLECT-COVID study, presented in the previous chapter, showed the limited impact that the BOA rapid guideline for open lower limb fractures had during the pandemic.[112]

Several approaches have been proposed to ascertain the quality of recommendations contained in clinical guidelines.[158] The *Appraisal of Guidelines for Research & Evaluation* (AGREE) instrument is a popular and widely used tool to assess methodological and reporting quality of clinical practice guidelines. Developed originally by an international team (AGREE Collaboration) and resulting in a 23-item tool published in 2003,[181] this instrument assesses six quality-related domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence, using a 4-point Likert scale. Later revised and updated in 2009, it was re-named the AGREE II[182] and employed a 7-point Likert score, allowing for greater granularity in eliciting information. According to its developers, a score of 1 indicates the absence of information for a domain, whereas a score of 7 indicates exceptional reporting quality.

Considering that the body of primary research is the same for all available open lower limb fracture guidelines, I hypothesised that recommendations following robust methodologies would ultimately present similar recommendations. If this could be proven to be the case, it

would then justify their adaptation as a time- and cost-saving alternative for places that do not have guidelines at present.

3.3.1 International Guideline Comparison: Methodology

The results of the systematic scoping review described above provided the starting point for this quality appraisal exercise. The included guidelines for this analysis were the 2009[102] and 2020[39] editions of the BAPRAS/BOA *Standards for the Management of Open Fractures*; the NICE 2016 *Assessment and Management of Complex Fractures*[71] guideline; The Dutch Federation of Medical Specialists (KIMS) 2017 open fractures of the lower limb guideline;[123] the FOA guideline for the management of open tibia fractures in adults published in 2004[171] and updated in 2011;[175] the 2015 *Best Practices in the Management of Orthopaedic Trauma* developed by the American College of Surgeons,[176] and the Malawi Orthopaedic Association/AO Alliance guideline and standards for the management of open fractures.[178]

I assessed each guideline included in the study using the AGREE II instrument for all domains in a blinded and parallel fashion with a second investigator. Consensus was achieved by means of an itemised discussion, with any disputes resolved by my principal supervisor. Subsequently, I calculated the overall score for each domain, summing individual items' scores and converting these to percentages according to the AGREE II User's Manual. In this framework, a score over 60% is considered good, between 30-60% moderate, and less than 30% poor.

Following this quality appraisal, I conducted a detailed comparison of the recommendations reported in each of the guidelines included for analysis. I defined clear inclusion and exclusion criteria to construct an inventory of recommendations related to open tibial fractures (**Table 3.4**). This was necessary given that some of the guideline sets included in this analysis also contained recommendations not necessarily related to open fracture

management. Within this inventory of relevant themes, I compared all recommendations and identified similarities, disparities, and gaps in the guidance provided.

Table 3.4: Inclusion and exclusion criteria for identifying open lower limb fracture recommendations.

Inclusion criteria	Exclusion criteria
- Clinical themes related to the management of open tibia fractures. - Non-clinical themes related to the improvement of systems involved in the management of open limb fractures	- Themes only applicable to closed fractures - Themes with no direct clinical application

3.3.2 International Guideline Comparison: Results

Table 3.5 shows the AGREE II scores obtained for each of the analysed guidelines. Although all guidelines scored above the *good* quality threshold for the "clarity of presentation" domain, other areas showed considerable differences. In terms of "editorial independence" and "rigour of development," most guidelines presented scores indicating *moderate* or *poor*, with the exception of the NICE 2016 and the Dutch 2017 guidelines. Both had the highest scores overall and were closely followed by the BAPRAS/BOA 2020 guideline. The latter scored below the *good* quality threshold for "rigour of development domain" (52%) because it did not include systematic review protocols and recommendation-selection methodology.

The FOA document published in 2011 is a two-page report that updates selected recommendations in the original 2004 version for the Finnish guideline. Given its brevity, I did not consider the 2011 publication as a guideline in its own right but rather a complement of its predecessor. For the BAPRAS/BOA guidelines, the 2009 and 2020 publications are clearly separate guidelines, with different tables of contents and extensions, although some of the same authors and editors participated in both editions. According to the scores, the 2020 guidelines consistently scored higher in all domains than did their 2009 counterpart.

A total of 25 different topics were considered across guidelines. After applying our previously defined inclusion and exclusion criteria, 20 topics were considered eligible for further analysis (**Table 3.6**), as they referred to management of open tibial fractures. The topic open fractures of the foot and ankle was excluded as it is covered in a separate guideline in the Netherlands. Other excluded topics were "pelvic fractures," "hip fractures," "pilon fractures," and "humeral fractures."

Of the 20 selected topics, five were covered across all seven guidelines. Overlapping topics were mostly related to the first week of management post-injury, including: management and assessment in the emergency department, antibiotic prophylaxis, timing of wound excision (debridement), and timing and modality of soft tissue reconstruction. Recommendations regarding the indication for early amputation were also covered in all the publications analysed. The management of such complications as deep infection and bone loss were included in only the BAPRAS/BOA and Finnish guidelines, and the management of compartment syndrome was included in all except the MOA/AO Alliance report.

The most comprehensive guideline was the 2020 BAPRAS/BOA one, which covered the aforementioned topics while also encompassing additional chapters on fragility open fractures, blast injuries and mass casualties, rehabilitation, psychological support, and setting up an orthoplastic centre. It was followed by the NICE and Dutch guidelines in terms of number of topics covered. On the other hand, the ACS and MOA/AO Alliance guidelines were considerably more concise. For example, the former did not (and still does not) provide recommendations relating to methods of fracture fixation.

Table 3.5: AGREEII results for the guidelines included in this analysis

	Scope and purpose	*Stakeholder involvement*	*Rigour of development*	*Clarity of presentation*	*Applicability*	*Editorial independence*
Finnish 2004	95%	57%	36%	66%	50%	21%
BAPRAS/BOA 2009	66%	27%	31%	95%	33%	25%
ACS 2015	33%	52%	20%	86%	57%	14%
NICE 2016	95%	90%	98%	90%	86%	100%
Dutch 2017	88%	88%	86%	77%	83%	66%
BAPRAS/BOA 2020	100%	90%	52%	100%	93%	78%
MOA/AO Alliance 2020	66%	62%	57%	95%	57%	36%

Table 3.6: List of open limb fracture themes covered across guidelines

	Finnish 2004	BAPRAS/BOA 2009	ACS 2015	NICE 2016	Dutch 2017	BAPRAS/BOA 2020	MOA/AO 2020
Prehospital management and transfer	+	-	-	+	+	+	-
Multidisciplinary approach	+	+		+	+	+	-
Management in Emergency Department	+	+	+	+	+	+	+
Antibiotic administration	+	+	+	+	+	+	+
Wound excision (debridement)	+	+	+	+	+	+	+
Temporary wound dressings	+	+	-	+	+	+	-
Skeletal stabilisation	+	+	-	+	+	+	+
Soft tissue reconstruction	+	+	+	+	+	+	+
Early amputation	+	+	+	+	+	+	+
Management of vascular injuries	-	+	-	+	+	+	-

	Finnish 2004	BAPRAS/BOA 2009	ACS 2015	NICE 2016	Dutch 2017	BAPRAS/BOA 2020	MOA/AO 2020
Compartment syndrome	+ **(2011 update)**	+	+	+	+	+	-
Degloving injuries	-	+	-	-	-	+	-
Management and avoidance of complications: flap failure, bone loss, deep infection	+	+	-	-	-	+	-
Rehabilitation and psychological support	+	-	+	+	+	+	-
Open fractures in children and older patients	-	+	-	+	-	+	-
Blast injuries and mass casualties	-	-	-	-	-	+	-
Patient centred approach and rehabilitation	-	-	-	+	+	+	-
Documentation	-	-	-	+	-	+	+
Classification of open fractures	+	+	-	+	+	+	-
Organisation of the orthoplastic team	+	+	-	+	+	+	-
Measuring outcomes in clinical practice	-	+	-	-	+	+	-

Next, I compared recommendations relating only to open tibial fractures. The British, Dutch, and Malawi guidelines made explicit reference to the Advanced Trauma Life Support (ATLS) principles, prioritising life-saving interventions in the context of polytrauma. This was not the case for the ACS or the FOA guidelines. All guidelines mentioned the importance of antibiotic prophylaxis, although the recommended timeframes varied. In the UK the BAPRAS/BOA 2009 guideline mentioned this should be administered within three hours of sustaining the injury. However, the NICE and BAPRAS/BOA 2020 guidelines modified this timeframe to within one hour of the open fracture, which agrees with the ACS and MOA/AO Alliance reports.

The Dutch and British guidelines advocated the management of all open tibial fractures in specialist centres with the capacity to deliver all complex interventions, independent of the severity of the open fracture. The Finnish and Malawian guidelines provided a different recommendation, advising that specialist centres should treat only severe open fractures, i.e., Gustilo-Anderson type IIIA or above.

Some recommendations evolved as new evidence emerged over time. Whereas the BAPRAS/BOA 2009, NICE, and Dutch guidelines recommended negative pressure therapy as a temporary dressing, although not as a substitute for definitive soft tissue cover, the BAPRAS/BOA 2020 and NICE guidelines amended this, publishing an evidence review update for negative pressure wound therapy for temporary closure of open fractures in 2022.[183] The reason for the change was the publication of the results stemming from the WOLLF and WHIST trials, which demonstrated the lack of added benefit of negative pressure therapy compared to conventional dressings.[50,142177]

Similarly, there have been changes in relation to the correct timing for wound excision and soft tissue coverage. The Finnish guideline disseminated in 2004 recommended that open fractures should be debrided as soon as possible and no later than six hours post-injury. The BAPRAS/BOA 2009 guideline, published five years later, instead recommended that wound

excision be performed within 24 hours, thus allowing this to be done in the next available scheduled list and so facilitating orthopaedic and plastic surgeon availability. Although the ACS guideline maintained this timeframe, this recommendation was further amended for all guidelines published from 2016 onwards. The NICE, Dutch, BAPRAS/BOA 2020 and MOA/AO Alliance guidelines recommend debridement of high-energy open fractures within 12-hours and low-energy ones within 24-hours.

In terms of achieving soft tissue cover, the tendency has been to accomplish this earlier. The FOA guideline comments on this, although it provides no clear timeframe. While the BAPRAS/BOA 2009, Dutch, and ACS guidelines recommend that this be done within seven days post-injury, the NICE, BAPRAS/BOA 2020 and MOA/OA Alliance publications recommended three days.

All guidelines discussed indications for early amputation, emphasising the importance of involving senior clinicians and of encouraging joint decision-making. The Finnish, Dutch, and BAPRAS/BOA guidelines also included recommendations on preferred amputation level, all advising a trans-tibial amputation when possible. For cases in which a trans-tibial amputation was not possible, the BAPRAS/BOA 2009 guideline recommended trans-femoral amputation. However, following the publication of a systematic review covering this subject in 2011, both the Dutch and the more recent BAPRAS/BOA 2020 guidelines both recommended through-knee amputation.[184]

3.3.3 International Guideline Comparison: Discussion

As previously discussed, the aim of clinical guidelines is to provide evidence-based recommendations to improve patient outcomes, while optimising resource utilisation and establishing norms for future audit and research.[86] However, for these recommendations to have a positive impact, the methodology behind their development must be sound and reproducible.[185] As previously mentioned, I hypothesised prior to conducting this project that organisations adhering to robust guideline development practices were likely to reach similar

recommendations; their conclusions would be inevitable if obtained from the same body of primary research.

The studies presented in this chapter demonstrated the considerable overlap in topics and recommendations across the guidelines for open lower limb fractures, particularly for acute, time-sensitive interventions such as administration of antibiotics, surgical wound debridement, definitive osteosynthesis, and definitive soft tissue coverage. All guidelines agreed about the importance of joint orthopaedic and plastic surgery management for severe open lower limb fractures.

Also, the in-depth analysis I pursued allowed me to identify how lower extremity fracture guidelines have evolved over time, especially for areas for which new evidence has emerged in recent years. In addition to the previously discussed use of topical negative pressure dressings, recommendations guiding timing of wound excision and definitive soft tissue reconstruction have also continued to evolve as a consequence of seeking standardisation of care and improved patient outcomes.

Among the guidelines included in my review, the FOA report was the oldest, having been published in 2004. This guideline recommends performing surgical debridement for an open fracture as soon as possible, preferably within six hours post-injury. At the time these guidelines were disseminated, the traditional "6-hour rule" was considered standard practice and had been for decades. The 6-hour rule likely originated from the pre-antibiotic era, when surgery was the only modality available to prevent infection.[186] Not until the first decade of the 21st century had sufficient evidence emerged challenging this perception; debriding patients within six hours was shown to not be associated with such clinical benefits as avoidance of deep infection and reducing non-union rates.[187–189] The BAPRAS/BOA 2009 guidelines addressed this controversy, moving explicitly away from the 6-hour rule to recommend wound excision within 24 hours post-injury. This particular guideline emphasised

the importance of performing the necessary debridement at a time when senior orthopaedic and plastic surgery input was readily available.

Recommendations regarding the ideal time for debriding an open fracture wound would continue to evolve as further evidence emerged.[190,191] In later years, NICE, BAPRAS/BOA2020, and MOA/AO Alliance guidelines would all agree on the recommendation of performing a wound excision within 12 hours for high-energy injuries and within 24 hours for low-energy injuries.

This ongoing evolution emphasises the importance of challenging unfounded clinical dogma along with periodic re-evaluation of evidence.[192] In this regard, NICE has estimated that clinical guidelines, in general, have an average lifespan of 60 months. After this period, they can be considered out of date.[193] Following this policy, NICE published an evidence update review update in 2022 for its 2016 complex fracture guideline.[183]

The AGREE II analysis showed how quality of clinical practice guidelines for open lower limb fractures has improved over time, with the tendency being towards higher scores in multiple domains. However, higher quality and a more robust methodology come at considerable expense. While, according to these associations, the production expense of the BAPRAS/BOA guidelines ranged from £17,252 and £20,000, the Dutch and NICE guidelines reportedly cost £60,608 and £311,434, respectively.

Although most recommendations had a reference to the relevant published articles, extracting how recommendations were reached for questions with insufficient evidence was not evident in the publications I studied. However, these were likely the consequence of expert recommendations within the writing groups dedicated to those questions, a phenomenon previously reported in the development of clinical guidelines for other conditions. A recent study on adaptation of the Pre-Hospital Trauma Life Support in Germany found that recommendations for areas with a paucity of evidence tended to be based on the preferences of the members of the respective working committees.[194]

Involving patient and public representatives in guideline development groups their perspectives and inclinations to be to incorporated in the formulation of clinical recommendations.[195] However, a standardised approach to effectively involve laypeople in the writing of clinical guidelines is lacking.[196] Recognising its importance, NICE has adopted an explicit patient and public involvement policy based on two key principles: (1) laypeople are to be given the opportunity to participate in the development of NICE guidelines, advice, and quality standards and (2) as an outcome of this contribution, the resulting guidance is expected to have a greater focus on the people affected by the proposed recommendations than would otherwise be the case.[197]

As demonstrated earlier in this chapter, having national guidelines on the management of open extremity trauma is not the norm worldwide. Personal communications with INTELLECT collaborators based in Italy and Spain revealed that, even though their countries had well-established health systems, they had as of yet been unable to develop their own national guidelines on open extremity trauma. Attempts to do so had been made, however. In 2016, the Italian orthopaedic (SIOT), plastic surgery (SICPRE), hand (SICM), and microsurgery (SIM) societies agreed to collaborate to produce upper and lower limb open fracture guidelines. At a meeting in January 2017 in Trieste, representatives agreed to use the BAPRAS/BOA 2009 publication as a starting point in a set of guidelines for Italy. Although literature reviews for each topic of interest were later conducted, the joint effort ground to a halt due to insufficient financial resources to cover the administrative costs of the process required by the Italian National Centre for Clinical Excellence, Quality, and Security.[198]

At the time these projects were conducted, Spain had no initiatives underway to develop open fracture guidelines. Management of these patients was variable across different units, which tended to follow local or regional protocols. Nevertheless, some moves toward standardisation had been made, such as participation of the Spanish Orthopaedic Surgery

Society (SECOT) in the development of an International Consensus on Musculoskeletal Infections,[199] which includes recommendations for management of open tibial fractures.

Given the large sums of money and other resources that have been expended in the development of some guidelines, the prospect of international collaboration for guideline adaptation is a cost- and time-saving alternative. This proposal was first disseminated in an article we published in the *Journal of Plastic, Reconstructive and Aesthetic Surgery*, which presents an extract of the comparison presented in this chapter focusing on the guidelines published in the UK and the Netherlands.[156] Along with our Dutch collaborators, we stated our support for effective guideline adaptation in settings that do not at present have guidelines. In the context of my doctoral thesis, I extend this postulate even further, demonstrating that the introduction and implementation of clinical guidelines could optimise the of evidence for management of open lower limb fractures.

Currently available robust guidelines could be used as a starting point for the development of affordable, locally applicable, culturally sensitive, up-to-date, national guidelines for countries lacking them at present. The development of the Malawi Orthopaedic Association/AO Alliance guidelines provides a practical precedent. As described above, this was the result of an expert consensus meeting in which representative committee members were asked to comment and vote on key recommendations contained in the BOA/BAPRAS 2009 guidelines. This approach to guideline development enabled incorporation of local views and provided the opportunity to address challenges related to local implementation. Following this, the finalised set of guidelines was voted on and approved in the 2019 Malawi Orthopaedic Association annual general meeting.[178] The resulting publication, which contains a smaller number of recommendations than the BOA/BAPRAS 2009 guidelines, represents an achievable, gradual change in national practice. This reasonable approach based on continuous progress over the past three decades has resulted in the standards currently provided in the UK. Considerable costs and time can be saved by stablishing effective collaborations across borders

to adapt existing guidelines, whilst also remaining sensitive to local needs and challenges. The examples provided by Italy and Spain illustrate the hurdles a country attempting the process alone will most likely face.

3.4 Conclusions

The objective of the research described in this chapter was to investigate the availability and quality of international clinical guidelines for management of open fractures and to delineate trends in guideline development over time. I achieved this objective by conducting two separate projects: a systematic scoping review to identify all available open lower limb fractures available in the literature and an in-depth quality comparison of these sets of guidelines using the AGREE II methodology.

The first conclusion discussed in this chapter is that clinical practice guidelines for management of lower limb fractures are uncommon, an exception on the global scale rather than the norm. I was only able to identify five countries that have developed at least one clinical practice guideline for open fractures to date. Although the INTELLECT study provided an overview of the management provided for patients treated in countries with no guidelines, the factors influencing clinicians and their conduct when treating patients in these settings remained unclear. At this point, it was also unclear what barriers and limitations impede the development of guidelines for managing open lower limb fractures in countries that do not yet have them.

While the INTELLECT study provided promising results regarding the potential positive impact of clinical guidelines on patient outcomes, the contents of this chapter demonstrated that most countries have yet to benefit from such recommendations. The guideline comparison presented also revealed the improvement in methodological quality in guideline development that has occurred over the years and the association of the resulting increasingly robust methodologies with an increasing overlap in guideline contents and recommendations. In other words, utilising adequate evidence-based procedures in guideline

development leads to adoption of similar recommendations, as these are based on the same bodies of primary research.

However, guideline adaptation presents the challenge of developing recommendations that are relevant and applicable to a specific local setting. Although it may be tempting to import a successful foreign guideline *verbatim*, failing to recognise epidemiological, cultural, and health system differences[109] may lead to no improvement in care or resulting outcomes.[200] The exercise of adaptation, on the other hand, may present a middle-ground alternative. Incorporating key domestic factors into existing guidelines could facilitate their effective implementation in settings that still have not benefited from such standardisation of care.[201] Even though the Malawian experience presents an exceptional example of adapting foreign open fracture guidelines for use in a very different setting, this approach may not be the only way this could have been achieved. Even though frameworks for adapting clinical guidelines have been described for other conditions, no comparable proposals have been reported in the open fracture literature.[202]

The next chapter presents my continued investigation into the role clinical guidelines can play in optimising management of open lower limb fractures and its result. This necessitated shifting my attention to the factors that have prevented the propagation of such evidence-based publications internationally.

Chapter 4 Limitations of the Implementation of Open Trauma Guidelines (LINEAGE) study

The work presented in the previous chapter revealed that guidelines for open lower limb fractures remain an exception rather than the norm at an international level. These publications not only offer an evidence-based resource to inform practice, but, based on the INTELLECT project's findings, being treated in a setting with guidelines is associated with improved patient outcomes. Given that the overarching aim of my dissertation research was to optimise the uptake of evidence to improve the treatment management and outcomes of patients sustaining open lower limb fractures, I defined as one of my thesis objectives the investigation of the attitudes, barriers, and limitations to developing and implementing clinical guidelines.

In this chapter, I present the Limitations to the Implementation of Open Trauma Guidelines (LINEAGE) study I conducted to address this objective and its findings. This qualitative research project laid the foundation for development of a theoretical framework to facilitate the successful introduction of clinical guidelines for open lower limb fractures in settings that do not yet have them. Chapter 5 discusses this framework in detail.

As was the case for the research presented in the previous chapters, that included in this chapter has also been published recently, prior to submission of my dissertation, and is featured in 2024's last issue of *Injury*.[203]

4.1 Background

Achieving standardised and cost-effective care while also improving service delivery and patient outcomes is the primary justification for development of clinical practice guidelines. Whilst the number of countries with guidelines has been steadily increasing since the late 1980s, assessing not only their quality but also the impact their implementation has on patient outcomes is needed.[92]

Three decades ago, Grimshaw and Russell published a systematic review detailing their investigation of the effect clinical guidelines had on medical practice.[204] The authors found that, in most cases, clinical guideline publication led to significant changes in care and patient outcomes. They highlighted the importance of rigorous evaluations to ascertain compliance with and continuous improvement in guidelines and discussed the importance of appropriate methods for developing, disseminating, and implementing clinical guidelines to achieve a positive change in practice.

However, they later identified several weaknesses in the process of guideline development that impeded their maximal use and the benefits derived from their use. Grimshaw and Russell summarised these as deficient quality and rigour during the development phase, lack of evidence in the available literature, inadequate translation of evidence into recommendations for practice, variability in interpretation of evidence, and feasibility of and difficulties with implementation.[205]

The AGREE methodology presented in the previous chapter was a collaborative effort to measure and advocate for robust methods in guideline formulation. However, twenty years after its publication, no consensus has yet been reached as to what constitutes a gold standard for clinical practice guideline development.[182] A recent scoping review by De Leo et al. (2023) found six scientific articles and five health-related organisational publications proposing different strategies to achieve this.[206] A qualitative analysis of these reports synthesised the most commonly used steps for guideline development *de novo*: planning and defining guideline scope; forming a multidisciplinary development panel; defining guideline purpose and target audience; reviewing the relevant literature and formulating clinical recommendations; consulting stakeholders and conducting peer reviews; presenting and publishing; disseminating and implementing; evaluating and revising when needed.

Guideline adaptation, on the other hand, provides an abbreviated and cost-saving alternative to the process presented above. Although I discussed the potential benefits of this

strategy in relation to treating open lower limb fracture guidelines previously, this approach is not new. In their 1997 article titled “Clinical Guidelines: Where Next?” Baker and Feder described the development of multiple guidelines on the same topic by different groups as a waste of resources and stressed the importance of quality appraisal prior to adaptation of existing recommendations.[207]

Since then, multiple strategies have been proposed to standardise the process of guideline adaptation.[208] In 2006, Fervers et al. published a literature review of available frameworks and procedures for this; they found eighteen published models and experiences among which eleven described adaptation of a guideline to a different culture or organisational setting.[209] The stages of adaptation common to all were search for existing guidelines, assessment of guideline quality, assessment of applicability and adaptation of recommendations to new setting, literature update adaptation of format, and implementation. Following this review was publication of the ADAPTE process, a collaboratively developed, validated process for reliable guideline adaptation, either as an alternative to *de novo* guideline development or as an initial step in implementation while preserving evidence-based principles (**Figure 4.1**).[210]

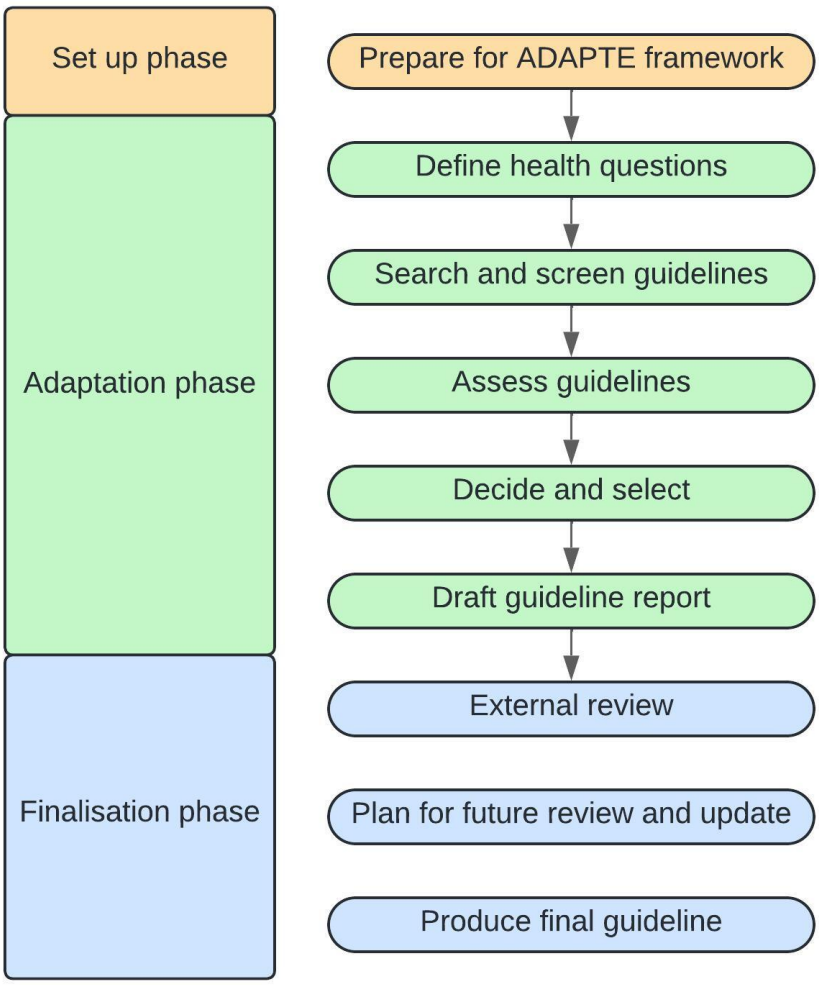


Figure 4.1: ADAPTE framework phases and tasks. Adapted from Fervers et al.[210]

More recently, Dizon et. al (2016) proposed a simplified approach, arguing that implementing a foreign guideline as local practice was achievable through three different pathways: adoption, contextualisation, or adaptation.[211] Adoption without modification of recommendations based on evidence having international external validity is viable provided the healthcare systems are similar. If this is not the case, the recommendations can still be considered; however, local context should be considered to achieve successful implementation. For topics lacking evidence to ensure external validity, adaptation of the relevant recommendations is preferable with local evidence of stakeholder input where possible. The Grading of Recommendations Assessment, Development and Evaluation (GRADE)–ADOLOPMENT framework extends this approach even further.[212] Where

evidence supporting an existing recommendation is not trustworthy, adoption, contextualisation, or adaptation should not be attempted, and development of *de novo* recommendations is required.

Despite these efforts to streamline guideline adaptation, limitations associated with adaptation have been identified. Although the main benefit of adaptation is assumed to be reductions in cost and time, limited evidence proving this to be the case in practice has been published.[213] Guidelines adapted using the ADAPTE method have reported project durations of eighteen months to three years[214,215] with little published evidence regarding resources consumed and project cost-effectiveness.

Guideline implementation entails a challenge in its own right, i.e., applying the final product to real-world scenarios. Publishing a clinical guideline does not automatically translate to clinicians changing their practice, improved outcomes, or predicted cost-savings.[216] The main barriers identified in guideline implementation are clinician related and include knowledge and attitude; guideline-related factors, including evidence base, plausibility, and presentation; and external factors, e.g., resource constraints, organisational factors, and social norms.[217]

I designed the LINEAGE study to address the issue of guideline development, adaptation, and implementation for open lower extremity fractures. Although previous experiences related to other clinical conditions have been published, no previous studies have investigated the attitudes, barriers, and facilitators related to introduction of clinical guidelines for open lower limb fractures.

4.2 LINEAGE Study: Methodology

4.2.1 Philosophical Foundations of Qualitative Research

The research presented in earlier chapters has been quantitative in nature. Before discussing the specific methodology utilised for the LINEAGE study, I present an overview

of the philosophical foundations of qualitative research and its differences from quantitative methods.

The aim of academic research, independent of the field of study, is to find the truth about a particular matter of interest. Consciously or not, researchers work within conceptual paradigms that agglomerate preferred philosophical assumptions regarding what is *the truth* and how it can best be known. These frameworks require the adoption of the ontological and epistemological positions needed to make sense of the research conducted and the conclusions drawn.[218]

Ontology refers to the philosophical branch dedicated to the nature of being and existence. It can also be described as the study of what *there is* and how things that exist relate to each other. Having addressed some of the most transcendental questions concerning human existence, ontology is a vast field that has been approached by philosophers with contrasting points of view.[219]

Realism, for example, considers reality to exist independent of the existence of an observer, their consciousness, or their beliefs.[220] This stance can be applied not only to entities in the physical world but also abstract concepts such as mathematics or morality, which, from this position, are perceived as existing, even in the absence of the mind. *Idealism*, the contrasting ontological position, lies at the opposite end of the philosophical spectrum,[221] arguing that reality and all that exists are ultimately a collection of ideas within our minds.

Epistemology is another philosophical body, different from but inherently related to ontology.[222] While ontology aims to define what *there is* and what is *the truth* about what exists, epistemology is concerned with studying how knowledge can be acquired about what exist.[223] *Empiricism*, closely aligned with realism, has been one of its most prolific currents. It proposes that knowledge can only be achieved by questioning reality with our senses and the obtention of empirical evidence.[224] Empiricists believe that this is a more reliable method of approaching the truth than through pure logical reason, thus preferring the use of experiments

to progress our understanding of the world. *Subjectivism*, on the other hand, rejects this position. Closer to ontological idealism, subjectivism argues that the only truth that exists is the one contained in our mental activity as a result of our individual perception and our interactions with others and our surroundings.[225]

This dialogue between ontological and epistemological positions results in the formulation of philosophical paradigms, the sets of conceptual assumptions that provide sense to the research conducted. *Positivism*, one such paradigm, is influenced by realism and empiricism. This philosophical stance assumes that reality exists independent of the observer and can be understood, identified, and measured by conducting research. It is therefore aligned with the hypothetico-deductive model, or the scientific method.[226] The paradigm positivism has dominated biomedical science for the last two centuries, focusing on the investigation of measurable variables through use of quantitative research methods.

The paradigm *interpretivism*, also called *anti-positivism*, arose as a response to positivism and highlights the limitations of the latter when trying to address questions related to human interactions in the social realm. Closer to idealism and subjectivism, it not only accepts that every individual experience is real and true but also that the investigator's background and beliefs inevitably contribute to shape the findings of the research being conducted.[227] The paradigm *constructivism* extends this concept even further, emphasising individuals' construction of their own notions of reality. According to constructivism, knowledge is co-constructed through the interaction of researcher and participants, as personal experience cannot be separated from perception of truth.[228]

Both interpretivism and constructivism provide the theoretical framework that supports the use of qualitative research methods. This approach differs substantially from positivism, providing a foundation for investigating matters that cannot be quantified or that which an attempt to quantify would result in a reductionist or inaccurate impression of the subject of interest.

4.2.2 LINEAGE Study: Outline of Methodology

Given that the LINEAGE study's goal was to investigate the perceived barriers, limitations, and facilitators for developing and implementing open fractures guidelines, I viewed a quantitative research approach as unsuitable. Adopting a positivist strategy would have forced me to reduce the research question to succinct, measurable elements and robbed me of the opportunity to broadly explore this issue. Therefore, I adopted a qualitative research strategy.

I embraced a constructivist stance for addressing the objective of this study. I chose this methodology accepting that my background, beliefs, and experience would inevitably play a role in my conduct of the project. I therefore envisioned an inductive process in which data obtained from senior clinicians in countries with no guidelines could be analysed. I chose a method that would allow me to identify common themes across the data in order to formulate a theoretical framework that could assist in the development or adaptation and implementation of clinical guidelines in settings that did not have one.

Prior to starting any research activities for this project, I prepared the protocol, participant information sheet, consent form, and scripts for the LINEAGE study. I then presented these to the University of Oxford Central University Research Ethics Committee. Following review, approval was granted (CUREC 1 / Ethics approval reference: R85977/RE001) (Appendix 15: LINEAGE Study University of Oxford CUREC Approval).

4.2.3 LINEAGE Study: Sampling Strategy, Data Collection, and Management

I used a purposive sampling strategy, intending to gather data from senior clinicians and leaders in the field of plastic and orthopaedic surgery. I chose these specialties because they are the most intensely involved in the care of open lower limb fractures in an acute clinical setting. Recruitment was achieved by contacting the national scientific societies for these specialties utilising official channels of communication and a pre-defined invitation to participate (Appendix 16: LINEAGE Study Recruitment Email Script). Orthopaedic and

plastic surgeons with extensive experience working in places with no clinical guidelines for lower limb fractures in place were considered eligible for recruitment.

I adopted this sampling strategy given the role that national scientific societies have historically played in the development of clinical guidelines, either leading the process or acting as consultants. Although other allied specialties and healthcare professionals are also routinely involved in management of this type of patient, orthopaedic and plastic surgeons usually lead in providing care. I assumed that clinicians of such seniority would also appreciate issues concerning other professional bodies, management, organisational structures, and health system factors. I considered that interviewing participants belonging to these groups was the most effective means of gathering high-quality data with the required depth to address the matter of interest.

I sought a sample size of ten to twelve participants based in five or six countries, ideally located in differing geographical regions. This sample size was selected based on reports that qualitative research saturation can be reached with a relatively small number of interviews, especially if homogeneous groups are being investigated.[229]

Once I had established communication electronically with prospective participants, I sent them a patient information sheet (Appendix 17: LINEAGE Study Participant Information Sheet), a consent form (Appendix 18: LINEAGE Study Consent Form), and an invitation to schedule a virtual interview. I provided a minimum of one week between the date these documents were sent and the arranged interview date to provide them adequate time to review these and ask questions. I used Microsoft Teams (Microsoft Corporation. Washington, USA) software to conduct these meetings.

For every participant, the session started by answering any outstanding questions about the study and, after all queries were resolved, obtaining a virtual informed consent from each participant. Only then, and only after clearly signposting this to participants, I began recording the conversation using a physical audio-recorder. Although video cameras were

used during the duration of the meeting to facilitate communication, video footage was not recorded. Participants were not provided with a list of questions beforehand but were reassured that the interviews would cover professional topics exclusively, with no personal, sensitive, embarrassing, or upsetting questions planned. I told them that they could withdraw from the interview and the study at any point, without providing a reason for doing so.

I conducted semi-structured interviews, allowing participants to elaborate on their views and minimising interruptions while ensuring we covered certain topics of interest. I used a pre-defined although flexible script as a guide, including questions and prompts to explore the current status of the care given patients with open fractures in their local settings, their views on the development and implementation of national guidelines for this type of injury, and their opinion on research for open lower limb fractures (Appendix 19: LINEAGE Study Semi-Structured Interview Script). This approach provided flexibility to explore other subjects that I had not considered prior to the interviews.

Audio recordings were downloaded from the physical recorder and stored on the University of Oxford OneDrive server. Transcription was *verbatim,* including all interactions, pauses, and fillers, using Sonix transcription software (Sonix Inc. California, USA). I checked the transcriptions by listening to the recordings, comparing these with the transcriptions, and making the necessary adjustments. Once the transcription was completed, the audio files were deleted. The transcriptions were stored as Microsoft Word documents (Microsoft Corporation. Washington, USA) on the same OneDrive server.

Any information that could identify a participant or a direct reference to a participant's country of origin was redacted from the transcript in the interest of preserving participant anonymity. Participants were told that no acknowledgement regarding their participation was planned nor would any direct reference to their country or affiliation be included.

4.2.4 Reflexive Thematic Analysis Method

To qualitatively investigate the data obtained as described above, I used the reflexive thematic analysis method, which allowed me to identify themes directly related to the research question from the data[230] and which recognises the researcher's active role in the generation of knowledge from a constructivist stance. [231] Braun and Clarke conceptualised reflexive thematic analysis so that it could be flexible and organic, with the outcome of the analysis being at the intersection of the data, the theoretical assumptions of the analysis, and the analytical resources of the researcher.[232]

This method involves a six-phase analytical process which I summarise.[233] Phase 1 involves familiarisation with the data by the researcher, which can be achieved by repeated reading of the data or being involved in its transcription, giving equal consideration to the breadth and depth of the dataset. This is followed by Phase 2, in which systematic coding takes place, yielding brief descriptive or interpretative labels for all meaningful sections of the dataset. By going back and forth in the dataset, codes can be refined, allowing identification of codes that may conduce to the generation of themes. Phase 3 begins when all relevant data have been coded, and the focus shifts towards codes that enrich each other and share meaning, leading to the development of preliminary themes from the data. The researcher plays an active role in this process by interpreting meaning and constructing a narrative for each theme. In Phase 4, all initial themes are reviewed and their contribution to answering the research question is assessed. This process leads to Phase 5, in which the refined themes are precisely defined, named, and presented in detail. Ideally, all themes should coalesce consistently and coherently, thus reflecting how the data address the research question. Finally, in Phase 6, the researcher produces a report, proposing the conclusions to be derived from the data analysis and detailing the analytic process that led to these.[231]

4.3 LINEAGE Study: Analysis and Results

Participants in the LINEAGE study were recruited from six countries, resulting in a total of twelve interviewees. Each of the countries represented are located in different global regions: Africa, East Asia, the Indian Subcontinent, Europe, North America, and South America (**Table 4.1**). As previously stated, I conducted all interviews. While some were effortless with the interviewees needing little prompting to expand on their views, others required active prompting on my part. Like myself, English was not the native language of all participants, presenting a potential language barrier. However, all were proficient in professional use of English, and I did not perceive a language barrier as posing difficulty in conducting the interviews. I was also directly involved in transcribing the audio recordings obtained from the interviews.

Table 4.1: Interviewee countries of professional practice

	Region	*World Bank Country and Lending Group*
Country A	South America	High-income
Country B	Europe	High-income
Country C	Africa	Lower middle-income
Country D	North America	High-income
Country E	East Asia	High-income
Country F	Indian Sub-continent	Lower middle-income

4.3.1 Reflexivity

Prior to commencing the reflexive thematic analysis for LINEAGE study, I engaged in a reflexivity exercise to document my research background, perspective regarding the research question, and pre-conceived ideas about the subject to be studied.

Professionally, I am a board-certified plastic surgeon and a doctoral student in evidence-based healthcare with a clinical and research interest in the management of open

fractures. I was trained in the UK, where guidelines play an important role in the management of this type of injury, although I have personally witnessed variations in its application at different hospitals in England.

As a result of my experience and the research presented earlier in this thesis, I believe in the value of guidelines as a useful resource in managing open fractures. In settings that have available resources, I have seen how guidelines facilitate multidisciplinary collaboration and stablish clear pathways for patients admitted with this type of injury, while also mitigating variability in the care provided. For settings with no guidelines in place, I believe that guidelines would provide an opportunity for evidence-based practice and service improvement.

I am conscious that I have a positive attitude towards guideline development and implementation that may have influenced the way I conducted the LINEAGE interviews and subsequent analysis. In order to address this, during the interviews, I consciously sought to allow interviewees to elaborate freely on their views, especially if they did not agree with mine. My aim was to obtain data of the required depth and breadth in order to be able to draw meaningful conclusions in my analysis. While analysing the data, I was careful to appreciate dissenting views, especially those of interviewees apathetic toward or with negative opinions of clinical guidelines, or pessimistic about their implementation.

My professional background provided an advantage, as it facilitated my understanding of technical aspects or examples presented by the interviewees. My counterparts were also aware of my background, cognisant that they were communicating with a peer and so not needing to establish a common ground before elaborating on a particular subject of interest.

At this stage, I also appreciated how the responses the interviewees provided reflected not only their experience, thoughts, and beliefs but also their workplace and sociocultural *milieu*. Although language was not perceived to be a direct barrier to conducting the interviews, I was mindful how use of language and the meaning it conveys varies across

regions and among native and non-native speakers. Considering the international nature of the participants, I accepted that their local practice may differ from the setting I was used to. This was especially the case with respect to their approach to balancing paternalism and autonomy regarding clinical decision-making, as the impact of these cross-cultural differences have previously been described in the literature.[234]

4.3.2 Familiarisation with Data

I familiarised myself with the data by actively listening while conducting the interviews, listening to the recordings of the interviews during their transcription, and re-reading the data prior to beginning coding. At this stage, I wrote notes containing my reflections about the process and my first impression of the data. In general terms and due to the semi-structure approach I chose, interview flow varied from one interviewee to the next. Although I gave interviewees time to expand on issues they considered relevant, I was nonetheless able to cover all pre-defined topics that I wanted to explore.

During the process of familiarising myself with the data, I noticed how the concept "variability of care" was discussed extensively by all interviewees. In countries with co-existing health systems, differences between private and public hospitals were highlighted. However, variability also arose in countries with a predominant, state-run health system, although in these cases the discussion around variability focused on differences between specific hospitals and regions. In middle- and low-income countries, resource constraints were cited as a major barrier to providing what interviewees considered should be standard care. In all studied settings, orthopaedic surgeons were the responsible specialty following hospital admission, and interaction with other specialties depended on local agreements or interpersonal relationships rather than on established pathways.

4.3.3 Systematic Coding and Identification of Themes

I uploaded all the interview transcriptions to the NVivo software package (Lumivero, Colorado, USA) and used this computer program to systematically code the entire dataset. Instead of using a predetermined list of codes, I developed each code by writing a sentence interpreting or summarising ideas or concepts as they were presented in the data.

Unless an exact concept was repeated during an interview, I refrained from reutilising or grouping codes at this stage. Instead, I opted for creating a new code instead, a practice that allowed me to be very descriptive at this stage of my analysis. When I had finished coding the complete dataset, I revisited all the generated codes and their descriptors, grouping and merging similar codes that referred to the same concept and synthetising their descriptor to very short sentences. This process led to the creation of 219 individual codes, with **Table 4.2** showing examples.

Table 4.2: Examples of initial codes created during the analysis

Initial codes	Data extracts
Concern that guideline may not capture individual circumstances	"But in [Country E], we don't have guidelines, because…but the other way, I think open fracture is, sometimes, it is case by case. This patient, for example lower limb, maybe has a single artery leg, maybe no artery leg." – Plastic surgeon, country E.
It is up to individual orthopaedic surgeon to involve plastic surgery or not	"Then orthopaedic surgeons, they will decide if they want to cooperate with plastic surgeons - if they decided, okay, I cannot handle this totally by myself, they will consent." – Orthopaedic surgeon, country F.
Limited access to external fixators	"After debridement, we lack the necessary facilities like external fixators. Many times, we just put a back slab, that is just a POP, and then take the patient to the ward. After the ward stay, the patients are advised to purchase external fixator." – Orthopaedic surgeon, country C.

As I went back and forth through the data checking and re-checking my coding, I was able to refine the preliminary set of codes. Using NVivo, I merged codes that reflected the

same underlying idea or concept. At the expense of granularity of initial code labels, I developed a succinct and refined list of codes using brief descriptors, and **Table 4.3** presents the definitive list of eighteen codes. I used NVivo to maintain a log of this process, a practice that allowed revisiting and reviewing my analysis as needed.

Table 4.3: Final list of codes following merging and refining initial codes

Barriers to guideline development	Nuances of guideline adaptation	Orthopaedic and plastic surgery relationships
Barriers to guideline enforcement	Health system heterogeneity	Pathways for orthopaedic and plastic surgery collaboration
Benefits of guidelines	Lack of evidence-based practice	Perceived variability of care
Centralisation of care	Role of leadership	Plastic surgery access limitations
Delays in care	Limitations to research enrolment	Resource constraints
Financial incentives	Absent auditing outcomes culture	Barriers to researching open fractures

Table 4.4 presents a practical example of refining and merging codes. In this case, four distinct, initial codes were appraised, each concerning data reflecting the difficulties involved in accessing plastic surgeons, and their expertise, for management of open fractures. Appreciating the similarity of the underlying ideas behind the extracts associated with each, I merged the four codes into a single code that encompassed the meaning of the four and labelled it “plastic surgery access limitations.”

Table 4.4: Plastic surgery access limitations - code refinement process merging initial codes

Refined code	Initial codes	Data extracts
Plastic surgery access limitations	Absence of plastics on call makes joint care difficult	"The plastic surgeon is not involved initially in the Emergency Department. Why? Because they are not present for on-calls, they have to be called in." – Plastic surgeon, Country B
	No access to plastic surgeons. Wounds dressed until plastic surgeon gets interested	"If the wound is extensive, many times you don't have plastic surgeons. So, you continue dressing the wound until a plastic surgeon avail themself and cover the wound." – Orthopaedic surgeon, Country C
	It takes effort to get plastic surgeon involved. Need of a critical mass to keep a plastic surgeon busy with open fractures	"It requires an effort for me to bring them. I think that the problem is that these injuries are not incredibly common. And there needs to be sort of a critical mass of these patients to keep a plastic surgeon busy just doing that type of thing. So that they can still make themselves available on somewhat short notice to do a fairly complex procedure." – Orthopaedic surgeon, Country D
	Limited number of certified plastic surgeons compared to orthopaedics	"A difficult situation where they depend on plastic surgeons to help them to do free flap. Again, those plastic surgeons are not adequately employed in all those hospitals, so that they can handle all those factors and handle the open fractures." – Orthopaedic surgeon, Country F

Once I had completed and was satisfied with the coding refinement process, I actively developed themes from the dataset, considering these to be "patterns of shared meaning organised around a central concept" as per Braun and Clarke.[235] To do so, I clustered codes that, although not having the same meaning, related to each other in broader patterns with coherent meaning. This process involved generating candidate themes, which I mapped, reviewed, and refined in subsequent iterations depending on how these themes synthesised the data. Discussions I had with my doctoral supervisors augmented this development.

Figure 4.2 shows an early version of a mind map that resulted from looking at and linking codes related to clinician, team, and systemic factors that play a role in managing a patient with an open fracture. At this stage of the analysis, I developed three initial themes that are discussed individually below.

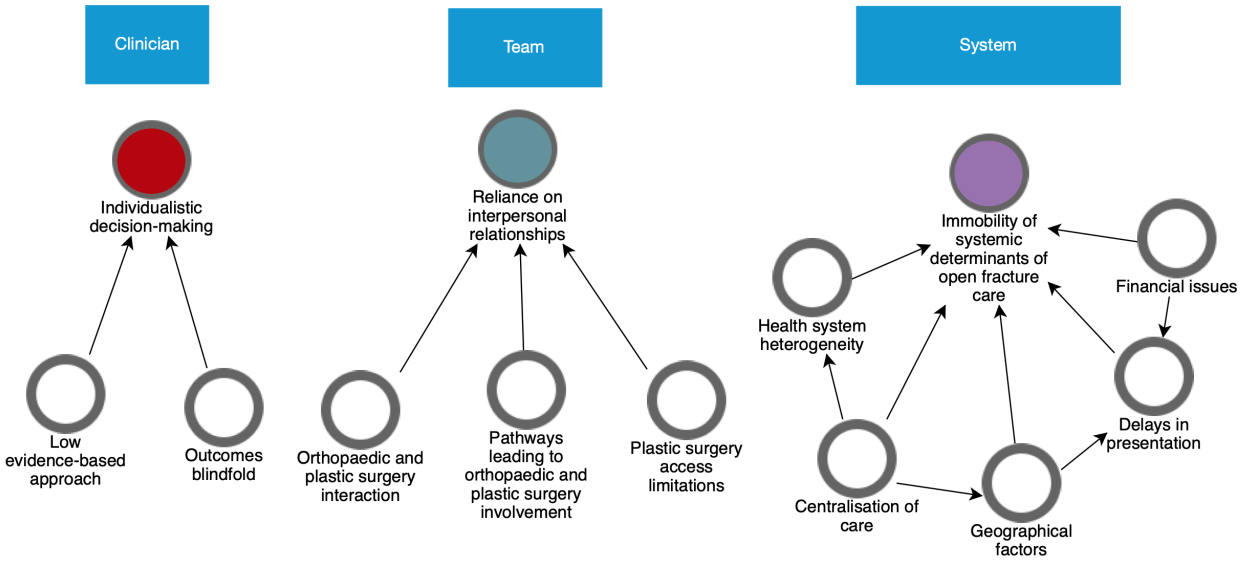


Figure 4.2: Provisional themes mind map that I used to further develop, refine review and name themes.

4.3.4 Theme 1: Individualistic Decision-Making

All interviewees commented on who bears primary responsibility for the care of patients presenting with lower limb open fractures and on the factors that play a role in

determining the interventions offered in each case within their respective countries. Absent standardised protocols, clinical decision-making is based on previous knowledge and experience, the interviewees reported:

> *There is no guideline for the management of open fractures. And it will all be dependent on the doctor's training. It is all based on what the surgeon knows, but there's no protocol yet. – Plastic Surgeon, Country C*

Reliance on individual expertise did not necessarily have a negative connotation among the interviewees; however, as the interviewee from Country F emphasised, this leads to variability in care:

> *We are relying on the individual expertise for treating open fractures. Patients have to wait until the expert comes and they decide what to do. The expert can decide on anything. They could even decide to wait and see. – Orthopaedic Surgeon, Country F*

The following data extract is an interviewee's answer when asked about use of guidelines for open fractures. The interviewee stated that a protocol did exist in their practice. However, and without need for further clarification, it soon became apparent that they were not referring to a formal document but rather to "a way of doing things" that was taught in undergraduate and post-graduate courses. This interviewee confirmed that, ultimately, whoever is on call when a patient is admitted determines that patient's treatment, which, in turn, is therefore whatever the admitting physician typically decides for his own patients. Most other interviewees made similar statements:

> *There is a standard management that we teach in medical school, that we teach our residents, and that we apply when patients turn up in the Emergency Department. However, ultimately depends on who is the orthopaedic surgeon on call that day. – Orthopaedic surgeon, Country A*

From these comments, I inferred that the knowledge and skills with which clinicians are equipped during their training are a major determinant of decision-making regarding open fractures. The interviewees commented on the value that attending continuing professional development courses have in keeping clinicians up to date but mentioned no other evidence-based resources. Furthermore, a study participant from Country B stated that, in their country,

clinicians do not know patient outcomes, a situation that occurs in the absence of an outcomes-based audit culture, and, as a consequence, practices are perpetuated:

> *There is no formal patient follow up that would allow measuring outcomes and tell if what we are doing is right. The British have a guideline and outcomes that back their use in terms of infection rates. In [Country B] there is no data, not in [Country B] or in many other places. Therefore, is impossible to discuss if we do things properly. – Orthopaedic surgeon, Country B*

These extracts show that, in the studied settings, clinicians currently rely on their previously acquired, internal resources to manage patients with complex injuries. Decisions depend on specific individuals, their training, and their preferences, and so, in the absence of an audit culture, practice remains unmeasured, unchallenged, and unchanged. I defined this *modus operandi*, i.e., the absence of conscious, evidence-based practice or of formal feedback mechanisms, as my first theme **"individualistic decision-making."**

4.3.5 Theme 2: Reliance on Multidisciplinary Interpersonal Relationships

According to the interviewees, orthopaedic surgery is the leading specialty most often providing care for patients admitted with an open fracture. However, they also recognised the role plastic surgery can play in providing complex interventions after such injuries, when necessary, to achieve wound closure. However, limited access to plastic surgeons was a common challenge, most interviewees reported. In resource-constrained settings, the number of accredited plastic surgeons is small, and they may not be present in all hospitals providing definitive treatment for open fractures. In high-income settings, such specialists may be available, but conflicting clinical commitments and lack of established collaboration pathways may impair their involvement; see **Table 4.4** for interview extracts addressing this issue. One interviewee commented on how this challenge worsens outcomes:

> *In the absence of plastic surgeons most patients end up with an external fixator, destined to undergo multiple washouts and VAC therapy for eternity. The use of VAC is maximised until granulation happens. – Orthopaedic surgeon, Country A*

On the other hand, a positive interaction between orthopaedic and plastic surgeons was seen as a key factor associated with better care. Absent formal collaboration pathways, interpersonal relationships can play a key role, either facilitating or compromising cooperation.

> *Have in mind that there is an important factor that is usually not accounted for: the interaction between plastic and orthopaedic services. If you have a good relationship, like I do, these teams can work well. If you don't, then it is a disaster. Patients are left lying somewhere and are not treated properly. That is why hospitals with clear leadership do better, as there is less dependence on interpersonal relationships. – Plastic surgeon, Country B*

While the previous extract confirms the consequences of poor inter-specialty relationships in patient management, it also introduces the positive role leadership plays. Throughout the interviews, leaders were presented as clinicians with the capacity to establish partnerships, address factors that impeded collaboration, and navigate the politics of multidisciplinary collaboration:

> *And I had a plastic surgery chair coming in who said—I want you to do exactly this. I want you to do lower limb. You don't need to pay the bills doing breast reconstruction—and then provided me kind of the bandwidth, but also the resources to build out an actual team. – Plastic surgeon, Country D*

Difficulties accessing plastic surgery input due to lack of formal referral pathways leave orthopaedic surgeons with few mechanisms with which to access the skillsets necessary to perform the complex interventions these patients require. As a consequence, functional orthoplastic teams **rely on multidisciplinary interpersonal relationships** to coordinate timely interventions and ongoing care, the concept that became the second theme I developed. Moreover, although the role of leadership is not explicit in this theme, I noted its importance as a catalyst in optimising collaboration.

4.3.6 Theme 3: Immobility of Systemic Determinants of Open Fracture Care

Interviewees provided insight into the variety of systemic factors that inevitably influence the management of patients with open fractures. The existence of parallel private

and public health systems was cited as a major cause of inequities in accessing what is considered standard of care:

> *In a private hospital I can access a surgical theatre within hours of admission. On the contrary, in a public hospital the reality is different. Despite your best efforts to get to theatre, usually there is no availability due to more pressing emergencies, or there is not enough staff. There are no resources which results in patients waiting long hours even days to have their debridement. – Orthopaedic surgeon, Country A*

In middle- and low-income countries, endemic poverty is still a major limitation to accessing healthcare, including treatment of open fractures, and affects not only the treatment that can be provided but even patients' ability to seek care in centres with the capacity to manage this type of injury:

> *The barrier is poverty. That is the financial ability of the patient. Because to travel from a rural community to [Tertiary centre] it means that patients have to travel by themselves. So, if they have no finances for transport and don't manage to find accommodation for their relatives in [Capital city], then they find it difficult to travel to [Capital city]. – Orthopaedic surgeon, Country C*

Along with health system heterogeneity and scarcity of resources in general, codes referred to other factors that determine patient care and that can be considered systemic, as they surround clinical teams and the institutions at which they work, determining to an extent how these institutions operate. These include financial incentives, centralisation of care, and cultural preferences. For example, in the following extract, the interviewee recognises amputation and prosthetic rehabilitation as a reasonable treatment in certain cases but emphasises the cultural implications of limb loss in their country:

> *People in [Country E], we have a tradition to preserve the limb as much, as far as we can, although the prosthesis is very good for the lower extremity. Patients still prefer to preserve the limb if we have extensive trauma, so we still want to preserve the part of patients they like to preserve. – Plastic surgeon, Country E*

The theme that I considered to best encompass these factors was not exclusively their systemic nature but rather the perception that these are **immobile**. By this, I mean the realistic, and rather pessimistic, impression I gathered from the interviews that these cannot be changed, at least not by the clinicians interviewed or the networks to which they belong. I

perceived a sense of acceptance, with clinicians finding ways around these issues in order to provide adequate care rather than trying to change the system directly. A sense of resignation is evident in the following extract, in which an interviewee describes the corruption present in pre-hospital care in their setting:

> *There is a scam happening here. There is a nexus between the private hospitals and the ambulance drivers. So, they take patients to their preferable hospitals, despite that they may not have adequate facilities, irrespective of whether they have the right specialists or not. This is what is happening in [Country F], and it is very pathetic. – Orthopaedic surgeon, Country F*

However, partially challenging this notion was the precedent set by exceptional clinicians who, through leadership and advocacy, succeeded in modifying healthcare policy in the speaker's setting:

> *The implementation of clinical guidelines in [Country A] has usually been achieved by the effort of individuals, mostly medics, who have fought for standardising care. Usually, these clinicians have ultimately knocked the door of the Health Ministry asking for support while demonstrating how clinical guidelines can reduce associated healthcare costs. – Plastic surgeon, Country A*

4.3.7 Theme 4: Not "a Piece of Paper Hung on the Wall That Everyone Ignores"

The fourth and final theme was developed later in the analysis. Overall, interviewees viewed clinical guidelines as a positive adjunct to improving management of patients with open fractures. These were perceived as reliable resources that are based on up-to-date evidence, foster multidisciplinary collaboration, and prioritise patient management while maintaining focus on providing necessary, time-sensitive interventions:

> *I think a guideline would be tremendously helpful for two reasons. One is that I think that it would provide some evidence, updates, as to what is good care for centres that are maybe not as familiar with the literature. I think also it just helps to keep people focused, you know, these injuries tend to be quite complex and some services are more dialled into these injuries than others and when it's a multi-specialty effort to take good care of complex extremity injuries, when we are all working towards a similar goal or on a certain timeline, I think it really helps to focus their attention. It helps to focus everyone's attention on that patient in a meaningful and a constructive way. – Orthopaedic surgeon. – Country D*

However, the idealised potential benefits contrasted with the reality of implementation in real-world scenarios. When discussing limitations to the implementation of guidelines, the interviewees voiced several apprehensions, including medico-legal ones, bureaucracy, lack of governmental financial support, and infrastructure:

> *Developing a standard protocol is highly impossible. There are many associations which are trying to do this, but those protocols can only be implemented in hospitals where they have all the facilities and right people to do it. We don't have the facility and or right people to do it. It's very difficult to become a standard or uniform. – Orthopaedic surgeon. – Country F*

Given the systemic determinant factors of open fracture care previously discussed, interviewees described clinical guidelines as being at risk of **becoming like a piece of paper hung on the wall that everyone ignores**. The speaker of the next extract hypothesises this possibility:

> *The problem is that in the future, when a patient is admitted to [Regional Hospital] with an open fracture, the protocol may be hung on the wall, but the patient is not necessarily going to be managed accordingly. – Plastic surgeon, Country A*

In the words of another interviewee, in the current context, the lack of auditing and of oversight renders compliance with a protocol or guideline—and hence the protocol or guideline itself—irrelevant. Failure to adhere to proposed best practices when available has neither a consequence nor an incentive:

> *If you follow the guideline or if you don't follow it, it doesn't really matter. It is up to you and your professional standards. But you won't get hit back if you don't follow them. – Plastic surgeon, Country D*

On the other hand, the presence of robust mechanisms to measure and monitor outcomes prevents a clinical guideline's being ignored following its implementation. Moreover, an audit culture raises awareness of the standards of care that a set of guidelines is designed to deliver while also allowing identification of areas in need of continued improvement. Another interviewee's comments on this when discussing guideline implementation emphasised the relevance of this theme:

Coming back to clinical guidelines, you need a permanent feedback system to make sure guidelines are being followed and that it is real. If it is unfeasible, it will be left somewhere, in a drawer. Or even can be used maliciously, politically or medico-legally, economically, it would be a complex situation. – Orthopaedic surgeon, Country A

4.4 Conclusions

The aim of the LINEAGE study was to investigate the attitudes, barriers, and facilitators related to implementation of clinical guidelines for open lower limb fractures. This was achieved by purposive sampling of senior clinicians with extensive experience managing these injuries in six countries lacking guidelines who shared their insights in semi-structured interviews.

Three of the themes developed in the analytic phase of this project relate directly to barriers to the development and implementation of guidelines for open extremity trauma. The themes **individualistic decision-making, reliance on multidisciplinary interpersonal relationships**, and **the immobile determinants of open fracture care** reflect the current dynamics that govern patient care for these injuries in the absence of clinical guidelines. While the **immobile determinants of open fracture care** theme represents a clear set of systemic barriers, the other two characterise what human factors literature describes as *norms,* or "the way things are done," a set of written and unwritten rules that develop over time and that may or may not be fit for purpose.[236]

Figure 4.3 is a revised iteration of the mental map shown previously in **Figure 4.2**. Added to the new version are elements of a Venn diagram representing the organisational and environmental hierarchy associated with the first three themes identified: the clinician sphere, a sphere representing the wider team, and the overarching system sphere. The challenge associated with developing and implementing guidelines involves addressing the barriers that maintain the status quo, which these themes and the spheres in which they operate represent.

Across the interviews, the attitude towards introduction of guidelines was in general positive, due primarily to the hypothetical effects that these would have on the three initial themes representing current practice. Guidelines could influence decision-making by

providing up-to-date, evidence-based recommendations that simultaneously address inter-clinician variability. Furthermore, guidelines may also establish clear referral pathways to normalise the involvement of plastic surgeons so that teams need not rely exclusively on the quality of interpersonal relationships between teams. Although guidelines could not address all the systemic factors that play a role in lower limb care, they can provide a roadmap to future improvements.

The generic, positive attitude of the interviewees toward guidelines was tinted, however, with scepticism. Regardless of the improved care of patients with open fractures that clinical guidelines offer, the fourth theme developed in the analysis threatens the potential benefits of guideline implementation. The metaphor "**a piece of paper hung on the wall that everyone ignores"** represents a scenario in which, despite the time and finances invested in robustly constructed guidelines, clinicians fail to follow them, and so they have no impact on patient outcomes. If implementers of guidelines are not conscious of the four themes presented above that represent barriers to effective guideline introduction, a well-intended initiative may well succumb to these and fail to breach the inertia of the status quo. In other words, failure to appreciate the interactions these themes represent would only widen the gap between "work as imagined" and "work as done."[237]

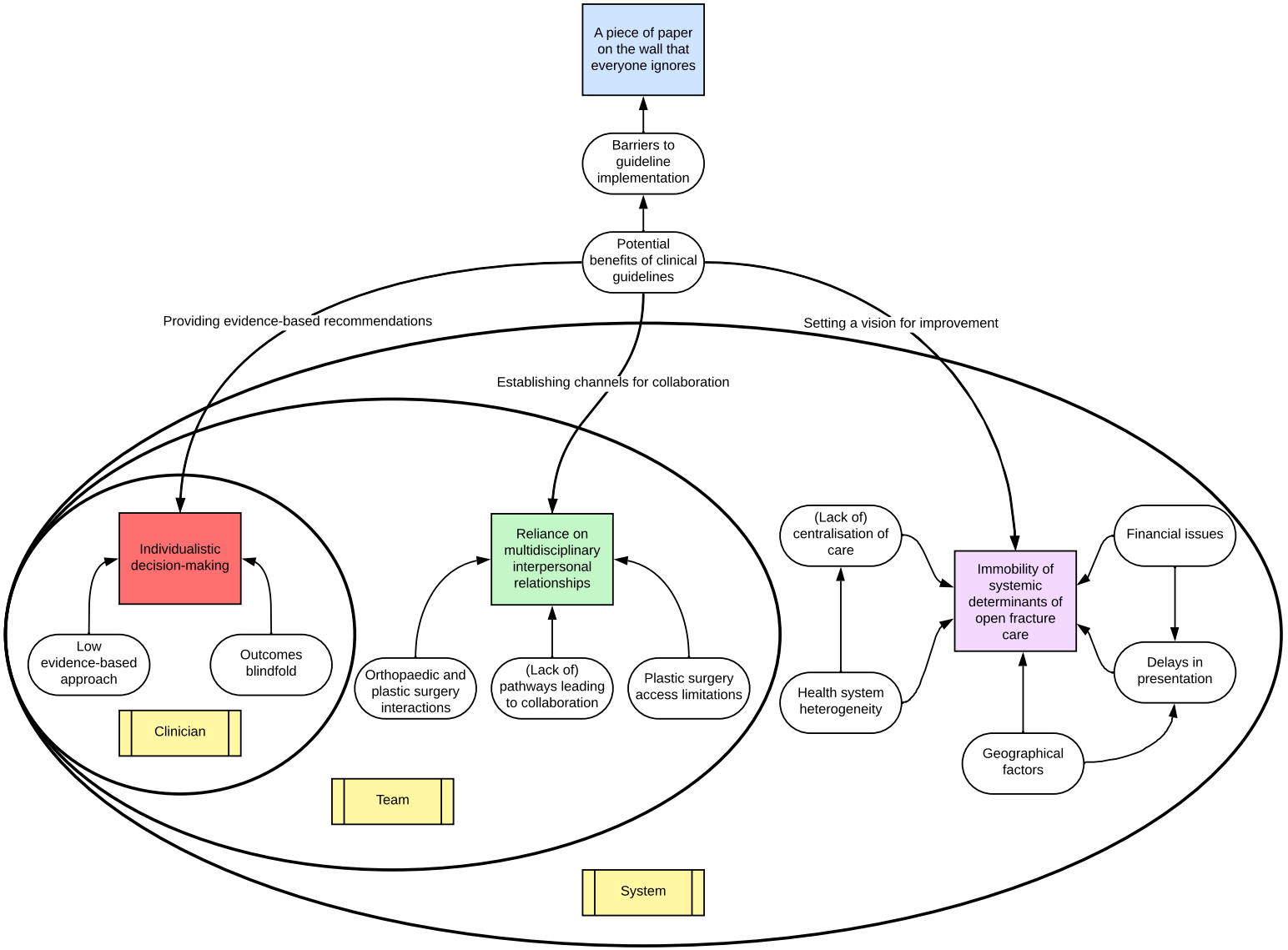


Figure 4.3: Mind map relating the themes identified in the analysis for the LINEAGE study

Conversely, my analysis also identified certain facilitators that could potentially address these hurdles. In terms of clinician factors and decision-making, providing recommendations would not suffice in the absence of effective feedback mechanisms. Auditing processes and patient outcomes provides unparalleled data with which to measure compliance and promote improvement.[238] With respect to team dynamics, guidelines may establish clear pathways for collaboration. However, my findings highlight the importance of leadership in enhancing partnership and team building.[239] Although the data implies that there are systemic factors that are unlikely to be changed over the short term, guidelines nonetheless present a vision and a basis for advocacy with the right stakeholders.[84]

Prior to conducting the analysis for the LINEAGE study, I thought that the interviews would revolve primarily around the actual processes behind the development and implementation of clinical guidelines. However, the analysis provided a wider overview of the factors at play, which existing frameworks do not necessarily address. The results showed that even a robustly constructed guideline may fail to change practice and improve outcomes, especially if the relevant barriers to its implementation are ignored.

The issue of guideline compliance has been addressed in the literature, including in the context of settings with adequate capacity and readily available resources. Prior et al. (2008) conducted a systematic review of guideline implementation strategies to enhance recommendation compliance. [240] They identified a series of proposed approaches including continuing medical education; traditional educational meetings; workshops and practical sessions; educational outreach activities; audit, feedback, and peer-review; mass media dissemination strategies; decision-support systems; local opinion leaders' endorsement; and, finally, financial incentives. The authors of this review found that multi-faceted interventions are more successful in achieving guideline compliance than single approaches. Unsurprisingly, they advocated for simplicity of presentation in guidelines, as complex ones are less likely to be followed.

The LINEAGE study's goal was not to address the challenge of developing and implementing clinical guidelines for lower limb open fractures. Instead, it was intended to be the first step to better understanding the factors that play a role in this process. As a qualitative study, the analysis and results are the product of my interaction with the data in attempting to address this project's objective. Although senior clinicians and leaders in their field provided data with the necessary depth to proceed with the analysis, future studies may consider involving other types of stakeholders such as healthcare managers, allied health professionals, patients, carers, and the wider public. This would allow further exploration of the contexts that surround open lower limb fracture care.

Although the purpose of the analysis presented in this chapter was not the effective implementation of clinical guidelines for open lower limb fractures internationally, the LINEAGE study themes provide the necessary elements for development of a framework for achieving this goal in settings that do not yet have guidelines in place. However, the next chapter of this thesis addresses the fourth and final objective of my doctoral research, design and development of a guideline-implementation framework.

Chapter 5 Development and Validation of a Framework for Implementation of Guidelines for Open Lower Limb Fractures

This chapter presents my efforts to address the final objective of my doctoral research—development and validation of an implementation framework for open lower limb fractures. In it, I provide an overview of conceptual frameworks and the role that these tools can play in implementation science. After discussing their development and validation, I present the process I employed to develop a framework to aid in implementation of clinical guidelines for management of open lower limb fractures. The themes identified in the LINEAGE study and discussed in the last chapter provided the basis for this process.

Due to the importance of validation, also described in this chapter is my use of the Delphi technique to validate my proposed framework. Thus, I elicited structured feedback from senior clinicians based in countries currently without guidelines until a consensus regarding my proposal was reached.

This chapter presents the resulting validated framework and a strategy to optimise the uptake of evidence to improve the management of and patient outcomes for open lower limb fractures.

5.1 Background

5.1.1 Use of Frameworks in Implementation Science

Implementation science is defined as the rigorous study of methods to achieve systematic adoption of evidence into policy and routine practice.[241] It is based on the premise that the uptake of research findings is not automatic and can be variable across different settings.[242] The aim of discipline of implementation science, broadly speaking, is to identify the challenges and develop strategies to improve quality and effectiveness of healthcare services.

Over the last two decades, the importance of establishing a theoretical basis for implementing change has been recognised and the important role qualitative research can play in developing theories, models, and frameworks to identify barriers to improvement and how these can be addressed. [243] Whereas *theories* are a set of principles to explain a phenomenon of interest— in this case addressing why certain variables lead to predicted outcomes, *models* offer a simplification of the phenomenon, and the distinction between theories and models may not always be clear. *Frameworks*, on the other hand, are a structured graphical or narrative representation of a system, including the concepts or variables that interact in relation to the phenomenon of interest. [243]

In implementation science, the usefulness of frameworks relies on their ability to guide the process of translating evidence into practice, including description of the factors that play a role in the implementation process and the evaluation of the outcomes resulting from process.[242] In general, frameworks are specific to the topic of interest, identify all necessary information, are simple to understand and apply, provide a practical insight, encourage deeper understanding of the factors at play, and facilitate communication by providing a shared language among users.[244] Able to accommodate multiple levels of the determinants that influence potential outcomes and their relation to each other, frameworks acknowledge the systemic nature of achieving change.[245]

5.1.2 Development and Validation of Frameworks

In implementation science, development of frameworks is the result of qualitative theorisation. In an attempt to synthesise reality, ontological and epistemological assumptions have to be made as each concept is developed, and, as each evolves during this process, differences in and relationships with other concepts are established, collectively gaining meaning as the framework is assembled.[246] Stated differently, a framework is not merely a collection of concepts or ideas but rather a construct designed to interpret an observation and made up of interrelating concepts. However, frameworks do not necessarily provide a causal

or deterministic explanation but rather postulate an understanding, as these are usually the result of inductive qualitative analysis.[247]

Different qualitative methods can be used for the development of frameworks, as they can provide the necessary depth of understanding required for synthesising reality to create a framework.[248] However, as discussed previously for the LINEAGE study, the outcome of qualitative analysis is the intersection between data and the researcher at a given point in time, making it unique and not necessarily reproducible. Consequently, authors have advocated validation of frameworks, thereby allowing other scholars, peers, and users to appraise an evolving piece while also obtaining necessary feedback.[246]

The literature contains no consensus regarding framework validation, as a recent systematic scoping review indicates. [249] Although in theory informal discussion with relevant stakeholders can achieve validation, structured methods such as case studies, consensus meetings, and Delphi studies are also available, and any of these can provide further insight into the framework, allowing further reflection, refinement, and optimisation.

5.2 Framework for Development and Implementation of Open Lower Limb Guidelines

Following the completion of the LINEAGE study, I considered myself prepared to conceptualise a framework for development and implementation of guidelines for open lower limb injuries. To undertake this process, I took relevant elements of the LINEAGE analysis and organised them. My aim was to develop a framework that acknowledges current challenges while also proposing a strategy to facilitate uptake of evidence to improve care of patients having such injuries. The outcome of this reflective process was the development of interacting, individual concepts that functioned as a whole to explain the intricacies of developing and implementing an open fracture guideline. **Figure 5.1** summarises my initial framework proposal.

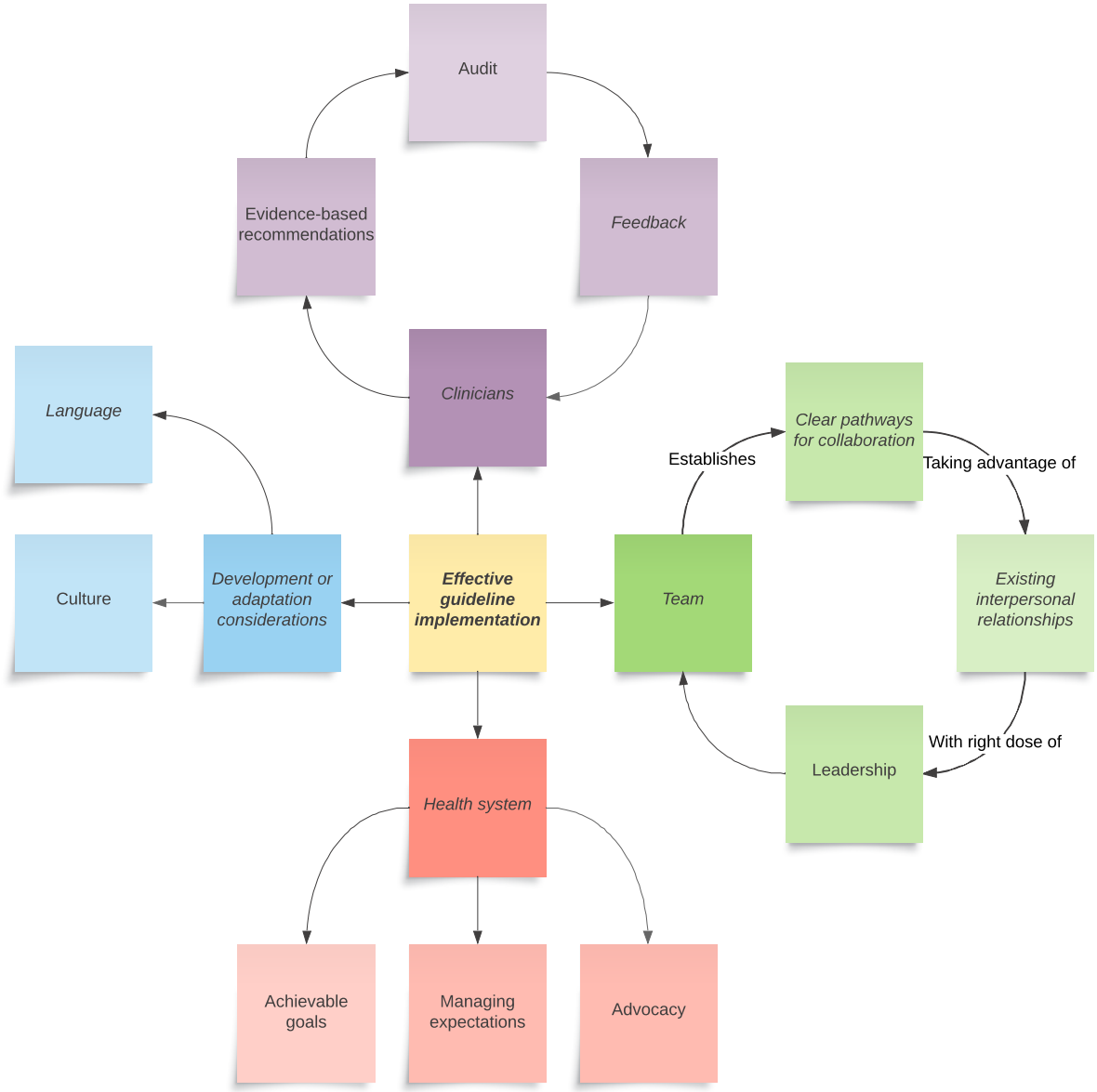


Figure 5.1: A framework for the effective implementation of open fracture guidelines

At the centre of the proposed framework is a single concept epitomising the framework's main goal: effective guideline implementation. Around this principal concept are four clusters of ideas, each one playing a role in the success of the aim shown at the diagram's centre in yellow. These clusters represent the translation into practice of the themes contained in each of the spheres presented in the last chapter in relation to the LINEAGE study (**Figure 4.3**).

Above the central aim of this framework is the concept clinician. This item acknowledges the role of clinicians and their decision-making in defining the treatment of patients with open fractures. As previously discussed, guidelines offer evidence-based recommendations and so can modify clinicians' behaviour. However, LINEAGE highlighted the importance of auditing practice to avoid a robustly developed guideline' not being followed. Awareness of the quality of care delivered allows not only measurement of adherence to recommendations but also provides feedback for future improvement.

Towards the right side of **Figure 5.1**, the cluster in shades of green indicates the importance of multidisciplinary collaboration and team dynamics. The LINEAGE findings highlighted lack of clear pathways for collaboration as an impediment to delivering timely and coordinated care to patients with open fractures. Implementing a guideline can address this by establishing when and how different specialties should intervene in this process.

However, LINEAGE also revealed the benefits of positive interpersonal relationships in delivering patient care. Instead of assuming that guidelines replace natural human interaction, the framework proposal acknowledges the importance of team building to achieve its goal. Similarly, this cluster stresses the importance of the concept leadership, which can act as a catalyst in this process. Effective leaders occupy the best position to address factors that interfere with team dynamics, provide support when challenges are encountered, and ensure that patient treatment is at the expected standard.

At the bottom of **Figure 5.1**, I include a third cluster also associated with a theme previously discussed in the LINEAGE analysis: the immobile systemic factors that directly limit effective implementation of guidelines. This aspect of the framework is intended to provide a realistic approach to achieving its goal. Prioritising achievable goals may be necessary when implementation of all evidence-based recommendations is not feasible, a situation which could occur in settings where minimal systemic conditions have not yet been met. In these circumstances, the focus should instead be on implementing a reduced number

of achievable recommendations. Aligned with this is managing expectations to avoid unrealistic assumptions and the frustration associated with failing to deliver the "ideal" package of care. However, awareness of the role that systemic limitations play in treating patients with open fractures would also enable clinicians in advocating for system improvement with the relevant stakeholders.

Finally, and placed at the left of the central aim of the framework shown in **Figure 5.1**, I included a series of concepts which have been recognised in the literature as key elements in the introduction of novel guidelines. Not necessarily related to the healthcare system factors discussed previously, these include the cross-cultural differences that may affect implementing evidence-based recommendations. This part of the framework is not intended to address whether users should develop a guideline *de novo* or adapt an existing one; the pros and cons of this were discussed in the background section of Chapter 4. Independent of the chosen modality, local culture should always be considered, as patient and clinician attitudes towards the same recommendation may vary in different settings. Language considerations are especially important if a foreign guideline is adopted, even more so if translation is required.

Once development of this framework was complete, external review and validation by potential future users of this proposal was needed. In the following section, I present how this was achieved with a Delphi study. In this way, I obtained structured feedback regarding my proposal while developing a consensus regarding the concepts included in the framework and its overall structure.

5.3 Delphi Methodology

5.3.1 Origin and Rationale for Delphi Studies

The Delphi method is a survey-based technique developed shortly after the end of the Second World War. This technique emerged within Project RAND, an American, not-for-profit initiative created by the U.S. Army Air Forces under contract with Douglas Aircraft

Company that later became Rand Corporation. Project Rand's aim was preserving the momentum of scientific discoveries achieved during the war.

Researchers at Project RAND sought to develop a method for achieving expert consensus. They recognised that, in traditional group-based decision-making, certain individuals or groups tend to dominate the discussion, favouring their own views. Furthermore, these modalities often fail to give participants the opportunity to retract their views, even if during the discussion they are persuaded to change them.[250] These limitations motivated the development, led by Norman Dalkey and Olaf Helmer, of a novel method which they named Delphi after the ancient Greek city where the Oracle of Delphi resided.[251]

In general, Delphi studies establish a structured group-communication process to address a matter of interest. This process employs an iterative approach in which participants respond to the same set of questions in multiple rounds until the research question is successfully addressed. In a classical Delphi study design, the first round involves asking the chosen participants to answer a series of open-ended questions about the matter of interest. These are then analysed qualitatively to generate the foundations of what is later tested in subsequent rounds. A modified Delphi design presents an alternative to this approach in which researchers utilise a qualitative research methodology and the available literature as a starting point instead of a first round of open-ended questions.[252]

In both the classical Delphi and modified Delphi strategies, the aim of the first round is to develop a series of statements that describe the research question. These are then presented in a survey for participants to complete in the Delphi's second round. Accompanying each statement is a Likert-style question that allows participants to express their level of agreement or disagreement in an ordinal fashion.

Answers obtained during the second round of a Delphi study are then analysed with participants are anonymous. Preserving anonymity is crucial in Delphi studies to control for the peer-pressure and subject bias that is inherent in other consensus-building strategies.[253]

The results obtained are then summarised and returned to the participant experts embedded in a new questionnaire, allowing them to revise their answers in light of emerging data if they so wish.[252]

The number of Delphi rounds required for a successful study depends both upon the goals predetermined by the researchers and the responses obtained, with no strict rules presented in the literature.[254] However, most authors agree reaching consensus is crucial to decide to deciding whether further rounds are needed.[253] Regrettably, however, defining "consensus" has been a contentious matter among researchers, leading to variations in its measurement.[255] Independent of the definition used and as has been stressed in the literature, researchers should be transparent about their chosen consensus criteria when participating in Delphi studies.[256]

In general, consensus in the context of a Delphi study is defined as a majority of respondents' expressing their agreement with a particular statement, where "majority" is a pre-established proportion of participants, i.e., a "consensus threshold."[257] This required level of agreement is not fixed and can vary depending on the particular topic of study. Consensus thresholds between 70% and 80% are commonly reported in the literature.[258] This criterion can be further augmented by measuring response dispersion, as reporting standard deviation or interquartile range can provide insight into the degree to which opinions diverge, another measure that can also be used to define "consensus."[255]

A Delphi study can end when either a consensus has been reached for all proposed statements or when, after subsequent rounds, number of responses for and against remains constant. In this latter case, the results are compiled, and those statements that met the criteria for consensus and those that did not after subsequent iterations are identified.[259]

5.3.2 Use of Delphi Methodology to Validate Framework Proposal

I conducted a modified Delphi study to validate the framework presented earlier in this chapter. Before commencing, I prepared a study protocol that was shared with the

University of Oxford CUREC for evaluation and reviewed by the Medical Sciences Division Ethics Committee. On the 13th of September 2024, I was informed that no further ethical considerations were required for this study design.

Participants eligible for this study were fully qualified orthopaedic, plastic, or general surgeons with a clinical interest in open fractures. Utilising a purposive sampling strategy, I contacted all senior INTELLECT investigators based in countries with no current guidelines and invited them to participate. I also circulated an invitation in ICOPLAST and International Microsurgery Club channels to allow snowballing recruitment. In addition, I used the JISC Online Survey platform (JISC, UK) to design a virtual registration form that allowed me to collect updated contact details and eligibility information from prospective respondents.

The first round of the modified Delphi study consisted of development of a series of statements that summarised each of the concepts included in the framework proposal previously presented. In subsequent rounds, these were phrased so as to allow respondents to express their level of agreement using Likert-style answers. Using the Online Surveys platform, I compiled these statements, structuring them as a virtual Delphi survey.

The first page of this online document included a patient information sheet, and following this was a consent form. After a succinct demographic and professional background questionnaire, participants were presented with the proposed framework, including the diagram in **Figure 5.1**. For each of the statements presented, respondents were provided with a five-level Likert-style selection box, allowing them to state their degree of agreement or disagreement with each statement individually. The survey concluded with five statements regarding their reactions to the framework proposal in general, including its clarity and applicability. Finally, a free text box was included to provide them with the opportunity to give further feedback (Appendix 20: Framework Proposal and Delphi Validation Survey).

Once this online survey went live, I proceeded with the second Delphi round. For this, participants were sent a unique link to the Delphi questionnaire and given a deadline of two

weeks to respond. In accordance with our study protocol, I sent them a reminder after one week. The results were exported into a password-protected Excel spreadsheet stored on the University of Oxford OneDrive. Using SPSS software and the information obtained, I performed a descriptive statistical analysis to profile the participating sample of experts. For each Likert-style question, I calculated frequencies and proportions along with the corresponding mean and IQR values.

In order to determine whether subsequent Delphi rounds were needed, I defined three criteria to be met to achieve consensus, as **Figure 5.2** shows. Statements that exceeded an agreement threshold of 80%, had an associated IQR of 1 or less in their Likert answers, and had a mean Likert response of 4.5 were considered automatically validated, with no further testing required. Statements that did not initially meet these three criteria qualified for a third Delphi round, thus allowing me to assess response stability. In the further questionnaire, participants were presented with any statement that had not yet achieved validation, along with the previous round response percentages and means. Statements that maintained agreement levels above 80% and an IQR of 1 or less in the third round were also considered validated. Any statements that did not meet these criteria were discarded from the framework proposal.

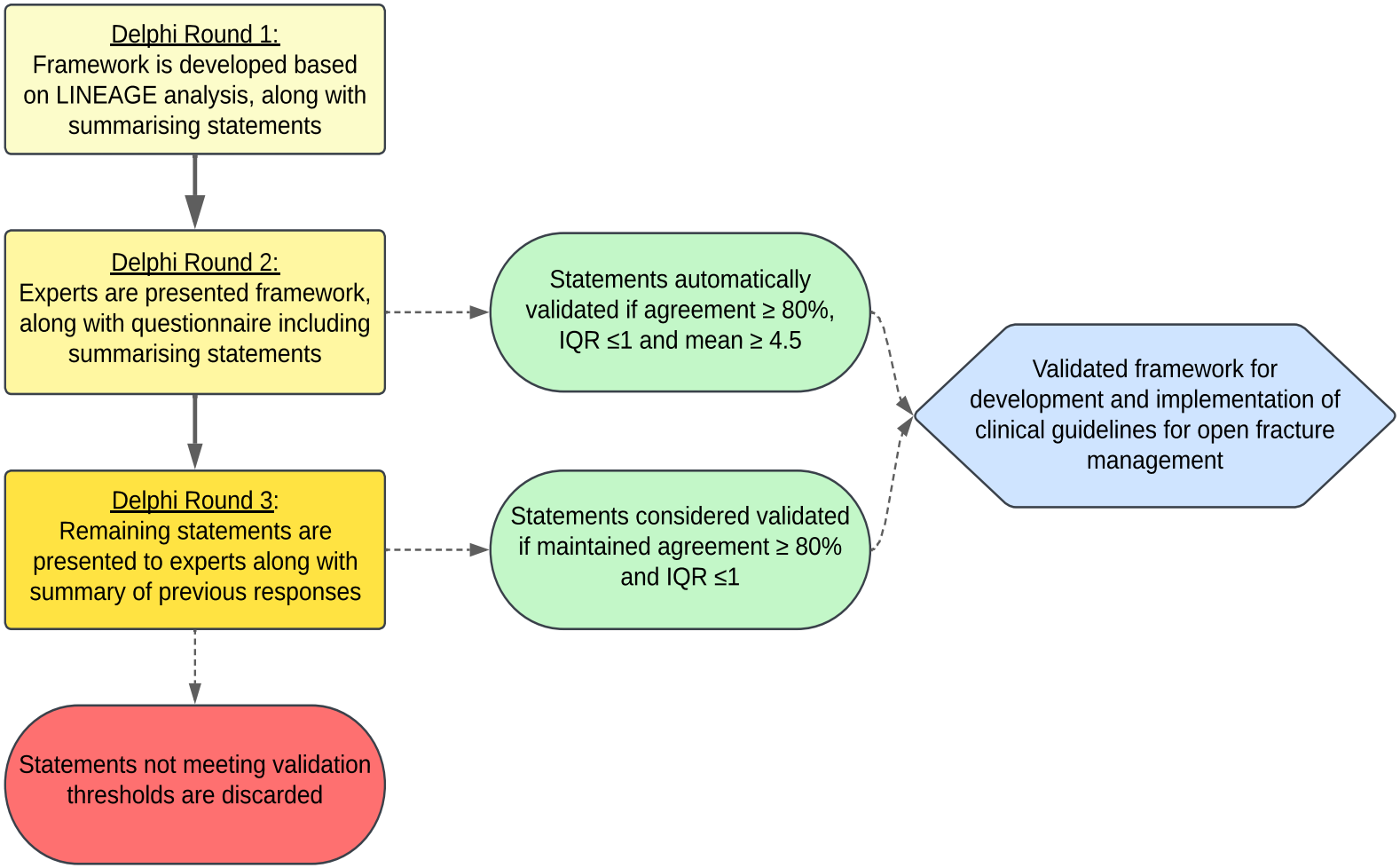


Figure 5.2: Delphi study for framework validation flowchart

5.4 Results of Delphi Study

5.4.1 Validation of Individual Concepts

The initial participant recruitment phase for the Delphi study ran from the 25th of September through the 2nd of October 2024. During this period, a total of 53 plastic, orthopaedic, and general surgeons expressed their intention to participate, all complied with the pre-defined inclusion and exclusion criteria.

The second Delphi round, and the first to obtain expert feedback, took place from the 2nd through the 16th of October 2024. Of the 53 invited participants, 43 completed their enrolment by providing consent and fully answering the questionnaire. Twenty (47%) of the respondents identified themselves as orthopaedic surgeons, and 23 (53%) as plastic and reconstructive surgeons, with 14 (33%) of participants female. Median reported time in practice after specialist certification was nine years. Enrolled participants were based in fifteen different countries, including the United States (n=7), Canada (n=2), Spain (n=9), Italy (n=3), Germany (n=1), Poland (n=1), Sweden (n=1), Israel (n=2), Syria (n=1), Pakistan (n=1), Taiwan (n=2), Kenya (n=2), Chile (n=9), Trinidad and Tobago (n=1), and Australia (n=1). Not all participants agreed to be acknowledged for their participation, and instead wished to remain anonymous (Appendix 21: Delphi Panel of Experts for Framework Validation).

All statements received a positive response overall (**Table 5.1**). Eight of these achieved the pre-defined threshold for validation, including all statements related to clinician factors and team factors. Additionally, the health system statement regarding the role of advocacy also met this threshold. Although the remaining statements had agreement levels above 80%, their mean response was below 4.5 and so, as per our protocol, required further testing in a subsequent Delphi round.

Table 5.1: Second round Delphi results. Validated statements highlighted in green

	1	2	3	4	5	Mean	IQR
Clinician factors							
1. Recommendations should be based in best available evidence to positively influence clinician decision-making.	0%	0%	0%	19%	81%	4.8	0
2. Continuous audit of care and outcomes should be encouraged as part of implementation.	0%	0%	2%	19%	79%	4.8	0
3. Feedback from audits should be used to measure guideline compliance, as a driver for continuous quality improvement.	0%	0%	5%	19%	77%	4.7	0.2
Team factors							
4. Open fractures should be managed within multidisciplinary teams able to provide complex interventions, addressing bone and soft tissues.	2%	0%	2%	21%	74%	4.7	0.8
5. Clear pathways for collaboration across specialties are desirable to optimise patient care, while reducing variability.	0%	0%	2%	28%	70%	4.7	1
6. The positive effect of good interpersonal relationships among clinicians favouring teamwork and inter-specialty collaboration should be recognised.	0%	0%	2%	40%	58%	4.6	1
7. Positive leadership is necessary to facilitate collaboration among a multi-disciplinary team.	0%	0%	0%	35%	65%	4.7	1
Health system factors							
8. Open fracture management is inevitably influenced by health system factors that clinicians cannot easily change.	0%	7%	7%	51%	35%	4.1	1
9. Health system factors should be considered when developing an open fracture guideline, so that any recommendation is feasible in real-world scenarios.	0%	0%	9%	42%	49%	4.4	1
10. Expectations should be managed when implementing an open fracture guideline, especially when foreign guideline adaptation is being considered.	0%	2%	12%	53%	33%	4.2	1
11. Although gold-standard care may not always be feasible, awareness of ideal best practice is important, so that effective advocacy is possible.	0%	0%	2%	23%	74%	4.7	0.8
Socio-cultural factors							
12. Appreciating cultural and language factors is crucial in the development of guidelines for open fracture management. This is especially relevant when an adaptation is considered.	2%	5%	12%	33%	49%	4.2	1
1: strongly disagree / 2: disagree / 3: undecided / 4: agree / 5: strongly agree							

On the 24th of October 2024, participants were contacted again via email and presented with the results of the previous questionnaire. For this third Delphi round, a shorter version of the questionnaire was used, focusing on the statements that had not previously achieved validation. Statements regarding overall framework validation were kept in order to assess response stability. As previously, participants were given two weeks to respond.

A total of 37 participants completed this subsequent questionnaire. The results showed strong and persistent validation of three of the four statements assessed (**Table 5.2**). Statement number eight, which referred to the fact that open fracture management is inevitably influenced by health system factors, did not achieve the threshold for validation and was discarded from the framework proposal.

Table 5.2: Third round Delphi results. Validated statements highlighted in green.

	1	2	3	4	5	Mean	IQR
8. Open fracture management is inevitably influenced by health system factors that clinicians cannot easily change.	3%	11%	8%	65%	14%	3.8	0
9. Health system factors should be considered when developing an open fracture guideline, so that any recommendation is feasible in real-world scenarios.	0%	0%	0%	35%	65%	4.6	1
10. Expectations should be managed when implementing an open fracture guideline, especially when foreign guideline adaptation is being considered.	0%	0%	3%	70%	27%	4.2	1
12. Although gold-standard care may not always be feasible, awareness of ideal best practice is important, so that effective advocacy is possible.	0%	8%	0%	43%	49%	4.3	1
1: strongly disagree / 2: disagree / 3: undecided / 4: agree / 5: strongly agree							

5.4.2 General Framework Validation

In terms of general framework validation, participants were presented with statements that assessed comprehensiveness, conceptualisation, ease of understanding, logic, practicality, and applicability. These statements were measured twice, in the second and third Delphi rounds, to capture the overall impression of the experts regarding the framework proposal. On

both occasions, a positive response was recorded for all of these global validation statements. As expected, as the Delphi progressed, responses tended towards moderation and fewer outliers while maintaining levels of agreement above 80% (**Table 5.3**).

Table 5.3: Overall framework validation results

Overall framework validation	**1**	**2**	**3**	**4**	**5**	**Mean**	**IQR**
This framework provides a comprehensive overview of the key elements that should be considered in the process of developing and implementing guidelines for open lower limb fractures.	Delphi round 2:						
	0%	0%	12%	44%	44%	4.3	1
	Delphi round 3:						
	0%	0%	0%	49%	51%	4.5	1
This framework conceptualises the process of guideline development and implementation, so that it can be applied in settings where no guidelines exist at present.	Delphi round 2:						
	0%	0%	7%	53%	40%	4.3	1
	Delphi round 3:						
	0%	0%	5%	59%	36%	4.3	1
It is easy to understand the concepts included in this framework, along with their relevance in the process of guideline development and implementation.	Delphi round 2:						
	0%	7%	12%	49%	33%	4.1	1
	Delphi round 3:						
	0%	0%	3%	70%	27%	4.2	1
The relationships between the concepts included in this framework are logical and practical.	Delphi round 2:						
	0%	2%	12%	46%	40%	4.2	1
	Delphi round 3:						
	0%	3%	5%	68%	24%	4.3	0.5
This framework has the potential of being a useful resource in the development and implementation of open fracture guidelines.	Delphi round 2:						
	0%	2%	14%	44%	40%	4.2	1
	Delphi round 3:						
	0%	0%	3%	62%	35%	4.3	1
1: strongly disagree / 2: disagree / 3: undecided / 4: agree / 5: strongly agree							

5.5 Conclusions

This chapter concludes the results section of my dissertation. It introduced a framework to aid in the development and implementation of clinical practice guidelines for lower limb open fractures, and, in this way, I provide a concrete answer to the main goal of my doctoral research, a framework to optimise the uptake of evidence to improve management and outcomes for these patients.

The Delphi study described in this chapter demonstrated the consensus achieved by a panel of experts with the elements of this proposal. All but one of the framework statements included in the Delphi questionnaire were successfully validated. Furthermore, participants consistently responded positively to the framework as a whole with respect to its

comprehensiveness, logic, and applicability. These results suggest that the analysis and conclusions of the LINEAGE study provided the necessary conceptualisation and so foundation for the framework proposal.

Although Delphi methodology offers a pragmatic strategy for seeking consensus among experts, the approach has limitations. For purposes of the study presented in this chapter, I defined an expert as any orthopaedic or plastic surgeon with an interest in open lower extremity fractures. I viewed this as a reasonable definition, given that clinicians that have completed undergraduate and postgraduate specialist training are usually considered experts in their field.[253] Furthermore, I specifically sought physicians of this type as they would be potential early adopters of this framework and so would be in the best position to provide it peer-validation. However, this study did not include feedback from other stakeholders, such as patient representatives, managers, and policymakers. Further research including these groups would provide valuable insight to improve and further validate the framework presented in this chapter.

My approach to participant selection was pragmatic, as I reached out to previous collaborators and their adjacent networks. Although this strategy was successful in terms of recruitment and engagement, it may have introduced selection bias, as clinicians who had previously participated in open fracture research may have had a positive attitude towards the uptake of evidence in open lower limb trauma care. I sought to address this by introducing heterogeneity in respondent choice through use of snowball sampling recruitment to reach clinicians with whom I had had no previous contact. Unfortunately, there is no consensus regarding the ideal strategy for recruitment in Delphi methodology.[258] Similarly, no guidance is available concerning the ideal size of a panel of experts for this kind of study, and no evidence suggests that a larger sample would be beneficial to achieve consensus.[257]

While the Delphi study's results validated most of the elements of my framework proposal, it also allowed me to identify areas that needed to be further addressed. One

statement, that open fractures are inevitably influenced by health system factors that clinicians cannot easily change, did not achieve the threshold for validation. Although the majority of respondents agreed with this to an extent, identifying the primary source of disagreement regarding it was challenging. Considering that the remaining health system factor statements were validated, I hypothesise that the source of the dispute was not the assertion that health systems play a role but rather that I included the statement "that clinicians cannot easily change." Some respondents may have had a more positive attitude than myself regarding the capacity of clinicians to change the systems in which they work. Since this slightly contentious statement was not validated in the Delphi study, I removed it from the framework proposal.

Despite the outcome of the Delphi study, this framework may require further testing and refinement before and after it is put into practice. Although this validated framework provides an answer to the aim of my doctoral research, measuring its impact in real-world scenarios was beyond the scope of my thesis.

In the conclusion chapter that follows, I summarise the work conducted for my DPhil that led to the development and validation of the framework presented in this chapter. Moreover, I use this opportunity to discuss not only the overall limitations of my research but also my plans for future work to address these challenges along with attending to a number of unanswered questions that arose during my doctoral studies.

Chapter 6 Discussion

This final chapter is the conclusion of my thesis. In it, I provide an overview of the main findings of my doctoral research, presenting how my work addressed the goal and specific objectives of my thesis research. Although I have already discussed the specific limitations of each project, in this chapter I share my reflections on the overall challenges I faced and the lessons learned.

As expected, during the course of my studies, a number of new research questions arose that were beyond the scope of my dissertation. In this chapter, I present these and how I plan to address them in the future.

6.1 Main Research Findings

The aim of my doctoral thesis was to optimise the uptake of evidence in order to improve the treatment management and patient outcomes of open lower limb fractures. To achieve this goal, I defined four specific research objectives, which I refined as my research progressed and which are presented in the first chapter of this thesis. I based the structure of my thesis on these objectives. Each was addressed individually in a specific chapter of my dissertation, and a summary of this work is presented below.

6.1.1 Large International Survey of Management and Outcomes of Patients with Open Lower Limb Injuries

My first objective was to investigate the treatment management and outcomes of patients with open lower limb fractures on a global scale. I saw this as the necessary first step in understanding the care currently being provided and the disparities occurring in differing settings. The INTELLECT and QUINTET studies, both presented in Chapter 2, addressed this objective using different methodologies.

INTELLECT was a retrospective study that reported data for more than 2,700 cases of open lower limb fractures. This was possible only through the support provided by a

collaborative network of clinicians spanning sixteen countries. To the best of my knowledge and at the time of publication, this study represented the largest international series of open fractures in the literature.[111]

Despite the methodological limitations associated with analysing retrospectively collected health records, INTELLECT demonstrated the variations in the management of patients in low- and middle-income countries, high-income countries with no guidelines, and high-income countries with guidelines. The INTELLECT dataset revealed how, after adjusting for World Bank country income-group classification, treatment in a setting with clinical guidelines was a protective factor for both deep tissue infection ($OR = 0.66$, $p = 0.04$) and non-union ($OR = 0.66$, $p = 0.043$).

QUINTET, on the other hand, involved a much smaller sample of patients, who were followed prospectively. This study design provided a tighter control over the data-collection process, while allowing me to investigate the impact of open fractures on QOL in an international cohort of participants. The QUINTET analysis described the reduction in PROMs after open fractures and also allowed me to explore the relationship between gender and age on these patients' quality-of-life perceptions. In the context of the ageing population in developed economies, QUINTET highlighted the need for future research focused on treatment and outcomes for patients with fragility fractures, which are primarily sustained by females.[113]

6.1.2 Systematic Scoping Review and AGREEII Analysis to Determine the Current Availability and Quality of International Clinical Guidelines

Following the conclusion of the INTELLECT and QUINTET studies, I recognised the value of clinical guidelines as a means of introducing evidence-based practice into lower extremity trauma care. I trained as a plastic surgeon in the UK, so clinical guidelines for this type of injury have always been part of my professional practice. However, this was not always the case in this country.[103] I therefore selected determining current availability and

quality of international clinical guidelines for management of lower limb fractures worldwide as the second objective of my thesis research. The positive association between guidelines and patient outcome in the INTELLECT study made this only more relevant to my doctorate.

The research presented in Chapter 3 addressed this objective. First, I designed and conducted a systematic scoping review to establish how many national clinical guidelines for open lower limb fractures had been published to date. Unexpectedly, I found that clinical guidelines for this type of injury are the exception rather than the rule, with only five countries having produced such documents at the time of my review. Moreover, only nine of the twelve clinical guidelines provided a comprehensive overview for the management of open fractures. The remainder focused solely on antibiotic prophylaxis.[157]

The results of this scoping review provided the necessary foundation for a detailed comparison of those identified comprehensive guidelines. Using the AGREEII methodology, I found that clinical guidelines for open lower limb fractures have improved in quality over time. Not surprisingly, robustly developed guidelines tend to present very similar recommendations, as these are ultimately based on the same body of primary evidence. That finding led to the concept of guideline adaptation, as it presents a cost- and time-saving strategy for guideline implementation. The Malawian guideline, developed collaboratively between MOA and the AO Alliance,[177] is an encouraging precedent on how this can be achieved, along with the more recent Spanish experience and the publication of Spain's new guideline in late 2024.

6.1.3 Qualitative Study to Investigate the Attitudes, Barriers, and Facilitators for Implementation of Clinical Guidelines for Open Fractures

Next, I investigated the reasons for the limited availability of open fracture guidelines internationally. In Chapter 4, I presented my investigation of the attitudes, barriers, and facilitators for implementation of clinical guidelines to improve management of patients with open lower limb fractures. In particular, I sought to understand why so few countries have

developed guidelines and what factors may be restricting their implementation in settings currently without them. A qualitative research methodology was best suited to address this question and represented a departure from the methods previously I had used previously in my thesis research.

Interviewing senior clinicians from across the world and conducting a reflexive thematic analysis of the data enabled me to the challenges associated with guideline implementation. My analysis led to the development of three initial themes, each related to a specific domain: individual decision-making in the clinician sphere, reliance on multidisciplinary relationships in the team sphere, and immobility of systemic determinants of open fracture care in the wider system. Additionally, a fourth theme evolved, i.e., how even a robustly constructed guideline may be disregarded or, as in one interviewee's metaphor, be like a piece of paper hung on the wall that everyone ignores.

6.1.4 Delphi Study to Validate a Framework for Development and Implementation of Open Fracture Guidelines

The LINEAGE qualitative analysis[202] provided the conceptual background to address the final objective of my thesis: designing a framework to aid in the development and implementation of open fracture guidelines. This research enabled me to formulate key concepts that may facilitate the effective development and implementation of guidelines for lower limb fractures.

Understanding the need for external review, I validated this initial framework by conducting a Delphi study. An expert panel of 43 orthopaedic and plastic surgeons with an interest in open fractures participated in this project, and Chapter 5 summarises their evaluation, which resulted in validation of eleven out of the proposed framework's twelve components.

6.1.5 Conclusions

Globally, my research identified significant variability that differences in availability of resources alone did not explain in the management and patient outcomes of open fractures. Moreover, promotion of evidence-based practice through use of clinical guidelines can be an important driver for improving outcomes and reducing variability. However, these evidence-based resources for open lower limb fractures are still relatively uncommon.

One challenge to guideline development is cost, and guideline adaptation may therefore be a cost-effective alternative. Independent of the chosen strategy, it is important to recognise the role that clinician, team, health system, and cultural factors play in the management of open fractures. The finalised framework presented in **Table 6.1** provides a practical tool to optimise the uptake of evidence-based practice in lower limb open trauma, and this framework addresses the overall aim of my DPhil.

Table 6.1: Validated framework proposal

Clinician factors
1. Recommendations should be based in best available evidence to positively influence clinician decision-making.
2. Continuous audit of care and outcomes should be encouraged as part of implementation.
3. Feedback from audits should be used to measure guideline compliance, as a driver for continuous quality improvement.
Team factors
4. Open fractures should be managed within multidisciplinary teams able to provide complex interventions, addressing bone and soft tissues.
5. Clear pathways for collaboration across specialties are desirable to optimise patient care, while reducing variability.
6. The positive effect of good interpersonal relationships among clinicians favouring teamwork and inter-specialty collaboration should be recognised.
7. Positive leadership is necessary to facilitate collaboration among a multi-disciplinary team.
Health system factors
8. Health system factors should be considered when developing an open fracture guideline, so that any recommendation is feasible in real-world scenarios.
9. Expectations should be managed when implementing an open fracture guideline, especially if foreign guideline adaptation is being considered.
10. Although gold-standard care may not always be feasible, awareness of ideal best practice is important, enabling effective advocacy.
Socio-cultural factors
11. Appreciating cultural and language factors is crucial in the development of guidelines for open fracture management.

6.2 Limitations of Thesis Research

Throughout the chapters of this dissertation, I have discussed the limitations of the research conducted for my DPhil. Instead of repeating these here, I am dedicating this section to summarise the overall weaknesses of my research projects and suggest ways to address these weaknesses in future research.

6.2.1 Methodological Limitations

The clinical studies contained in the large survey of outcomes presented in Chapter 2 presented challenges in terms of data obtention and analysis. Despite the large amounts of data gathered to complete INTELLECT, its retrospective design limits the conclusions that can be drawn from the study's findings. On the other hand, QUINTET presented less than ideal recruitment and representation of the populations of interest. As per our statistical analysis plan, we employed nonparametric tests after confirming that the data did not follow the normal distribution. These tests rely on fewer assumptions than do parametric tests, and so their use may minimise Type 1 error, i.e., the probability of rejecting a true hypothesis, from what it would be if a parametric test were wrongly applied to data that failed to meet the assumptions needed for its application.

The quality and characteristics of retrospectively collected data from patient health records are inevitably linked to local practices. Although we based our data-gathering instrument on the core set of outcomes defined by Aquilina et al. (2023),[30] under INTELLECT, we were unable to reliably collect these, including time to weight-bearing or time to return to work or previous life roles following an open fracture. QUINTET partially addressed the gap in patient reported outcomes for this group. However, a larger sample with longer follow-up time would be required to adequately record the outcomes that matter to patients most.[54]

I was able to conduct INTELLECT and QUINTET despite my restricted budget by using a collaborative-research data-gathering methodology. Although I succeeded in my research objectives, I appreciate that this strategy poses challenges from a research governance perspective. In collaborative research, the process of obtaining local approval and of data collection is outsourced, reducing the capacity of the core team of researchers to exercise oversight. This model is based on the belief that collaborators ultimately share the values and rigour of the principal investigator and their close associates. I tried to mitigate the

risk of deviation from study protocols by actively engaging with partners in the UK and overseas, emphasising the role of local data guarantors and due procedures for data validation.

Although in collaborative research most collaborators have altruistic motives, all are ultimately rewarded with an acknowledgement based on the number of records uploaded and not necessarily their quality. The RSTN has developed expertise in using collaborative research methods and has an extensive track record of successful projects. However, as I have discussed with its leadership, further work is required to ascertain and define best practices for collaborative studies.

Chapter 3 presented two studies that are based on the available literature: a systematic scoping review and, following, a detailed quality appraisal of all comprehensive lower limb open fracture guidelines using the AGREEII approach. In an effort to control risk of bias and adhere to best practice, the former adhered to the PRISMA statement for scoping reviews. I interrogated EMBASE and MEDLINE databases for this project but may, however, have missed guidelines with this approach, as would be the case if additional guidelines were disseminated in non-indexed publications. Examining additional databases might have reduced this risk, but at the cost of an increased workload. However, I mitigated the risk of missed guidelines by conducting a rigorous reference check of eligible articles.

The AGREEII methodology is not the only existing tool for guideline appraisal but is considered one of the most comprehensive available.[158] Although it requires two assessors to grade each item in parallel to reduce the risk of bias, the assessment itself is qualitative in nature, an issue that has been reported as inevitably reducing reproducibility.[260]

The part-time DPhil in Evidence-Based Health Care in which I have been enrolled since 2019 allows its students to complete their theses within eight years of commencing. In the context of the rapidly expanding body of medical literature,[261] I accepted upon matriculation that research conducted in the early stages of my DPhil would possibly be outdated by the time I submitted my dissertation. The two projects contained in Chapter 3

exemplify this phenomenon, as new guidelines have emerged since their completion—for example, the new Spanish guideline, which is discussed below.[262] I do not view this as necessarily being a limitation but rather as a sign of progress and of the engagement of dedicated clinicians committed to improving the care of patients with open extremity trauma by applying evidence-based principles.

Finally, both the qualitative study presented in Chapter 4 and the resulting framework proposal included in Chapter 5 represented a paradigm shift relative to the positivist methods used in the research described in previous chapters. Although possible bias is a crucial consideration in appraising the quality of quantitative research, it does not have the same negative connotation in constructivist studies. In qualitative projects, it is accepted that the researcher, having their own views and agendas, has an active role in the analysis and outcomes. Furthermore, the aim of qualitative research is not to numerically represent all available views to reach meaningful conclusions but, rather, to select participants who will provide data with the necessary depth to facilitate analysis and adequately address the research question. In the reflexivity exercise in Chapter 4, I discussed how each participant's and my own background shaped the analysis being conducted.

The Delphi study that validated my framework proposal involved a panel of experts consisting of plastic and orthopaedic surgeons with an interest in lower limb trauma and working in countries with no guidelines at that point in time. As these two specialties have a leading role in the care of patients sustaining open fractures, I obtained feedback from members of these groups. However, additional feedback is needed. For the proposed framework to succeed, further research, refinement, and validation is required from allied medical specialties, health professionals, managers, patients, and carers. I do not claim that the findings and proposals contained in my thesis are definitive but believe that they do represent a step towards optimising the uptake of evidence and improving the care of patients with open fractures.

6.2.2 Chicken or Egg. What Comes First: A Guideline or a System That Enables It?

A recurring theme in my thesis is the influence of the wider health system on the delivery of care for patients admitted with open extremity fractures. The complex interaction between evidence-based recommendations and systemic factors was key in the LINEAGE analysis presented in Chapter 4, leading to its inclusion in the framework proposal. However, the hierarchy between guidelines and health system remains elusive.

According to INTELLECT's findings, better patient outcomes were observed in countries with clinical guidelines. However, it was impossible for me to determine if those better outcomes were the result of the guidelines' existence or were due to the patients' being treated in a system that had evolved to the point of enabling guideline development and implementation. Using the UK as an example, remaining unanswered is whether the superior level of care provided is the result of the implementation of the NICE and BOA/BAPRAS guidelines or whether it is due to patients' being treated within a system that has fostered three decades of orthoplastic collaboration. What came first: the chicken or the egg? The system or the guideline? Although the research contained in this thesis does not provide an answer to this question, a safe assumption to accept would be that both are equally important and are, in fact, linked.

As discussed in Chapter 4, clinical guidelines for open lower limb fractures can influence the wider system in the same way that the wider system can facilitate or limit guideline implementation. It is my belief that work on both fronts is required to optimise the care of patients with open fractures, an assumption supported by the results of the Delphi study, especially regarding the consensus generated around the concept of advocacy for health system improvement in relation to open fractures.

6.3 Dissemination and Impact

As a part-time DPhil student and full-time clinician, I have required over five years to complete the research presented in my doctoral thesis. However, from early on, my supervisors encouraged me to engage in peer-review and dissemination of my findings. This effort resulted in a number of publications, which I included in the prologue of this thesis. Furthermore, I am grateful for the opportunity to have delivered seven podium presentations at different forums, including BAPRAS; the Royal Society of Medicine; the European Association of Plastic Surgeons; the European Society of Plastic, Reconstructive and Aesthetic Surgery; the Caribbean Association of Plastic, Reconstructive and Aesthetic Surgeons; and the Chilean Society of Plastic Surgery. The feedback received allowed me to refine my work while ascertaining that the product of my studies was of a doctoral standard.

Besides the academic achievements arising from this thesis, I am pleased to see how the aim of my doctoral research has resonated in the international community of clinicians with an interest in open fractures. While conducting the INTELLECT study, I realised how most of my international partners had never previously undertaken a formal audit of their practice. By engaging with INTELLECT, they had the opportunity, for the first time, to measure their service and outcomes, thus allowing them to establish a foundation for future local improvement. Although not directly involved, I was delighted to see how some of my collaborators used their INTELLECT experience to further inquire into their practice. Examples of this are the thesis written by Dr Ana Ortega Columbrans and supervised by Dr Javier Martínez Ros for the award of Master of Science at the University of Murcia in Spain[263] and the cost-of-illness study for open lower limb fractures in the Netherlands published by Noorlander-Borgdorff et al. in 2024.[264]

Although the impact of INTELLECT has been more tangible, due to the large collaborative network involved and to the two years that have elapsed since its publication, I am optimistic that both the LINEAGE study results and the proposed framework will have a

similar impact. I was pleased to learn that Dr Alina Ortega Briones, part of the INTELLECT steering team, and her colleagues have recently published an adaptation of the BAPRAS/BOA guideline for Spain. To achieve this, she gained the support of both the Spanish Society of Plastic, Reconstructive and Aesthetic Surgery and the Spanish Society of Orthopaedic Surgery and Traumatology. I look forward to learning from the Spanish implementation experience and seeing how they navigate the introduction of evidence-based principles in a well-established comprehensive health system. In due course, it will be interesting to audit the impact of these guidelines on patient outcomes.

6.4 Future Professional and Academic Work

After completing my training and working as consultant plastic surgeon in the UK, I now wish to continue my academic career in the United States. For this purpose, I have recently assumed the position of assistant professor within the Division of Plastic and Reconstructive Surgery of The University of Texas Health Science Center in San Antonio, Texas. In addition to my responsibilities as a reconstructive surgeon, I will lead implementation of a multidisciplinary lower limb reconstruction service in a setting that lacks one at present. I see this as an opportunity to place the knowledge and skills I gained during my DPhil at the service of the local population, while advocating for the use of evidence-based principles in lower extremity trauma and continuing my progression as an independent researcher.

I will be using the framework presented in **Table 6.1** to implement an evidence-based protocol for the management of open lower limb fractures at University Hospital, one of the two major trauma centres in San Antonio. Understanding the difference between work as imagined and work as done, I plan to document this experience by measuring costing data along with process and patient outcomes. The resulting case study will provide further feedback on this framework, allowing me to further refine it, while reflecting on its

applicability in the wider American healthcare system. I am optimistic that a positive experience will contribute to the wider dissemination of this proposal.

Besides my work directly related to the implementation of clinical guidelines, I am also interested in contributing to the body of primary research on open lower limb fractures. More specifically, I am interested in determining the extent to which certain groups have been partially overlooked in open fracture research. To address the issue of underrepresentation of certain populations in open fractures research, I plan to conduct a systematic review. Reviewing all clinical studies that include patients with these injuries will enable me to assess not only reporting quality but also age and gender distribution of the reported subjects. I hypothesise that underrepresentation of females and elderly patients have led to a skewed body of evidence that favours the reporting of younger males. Exposing these potential findings could help raise awareness of the importance of researching underrepresented groups.

Fragility fractures in the elderly affecting primarily females have gained wider attention recently in the context of ongoing population ageing in developed countries.[124,126,153,154] Furthermore, the latest BAPRAS/BOA guidelines recognise the challenges involved in managing these patients, warning that they may not benefit from recommendations arising primarily from studies skewed towards younger populations suffering high-energy injuries.[39,265]

It is my position that any efforts towards building a consensus for the managing of these injuries needs to consider the unique experience, values, and expectations of this special group of patients[266]. Bearing in mind that this is still a meaningful gap in the literature, I view as crucial improving our understanding of what outcomes are most important to patients suffering fragility open fractures, as it is reasonable to hypothesise that these may differ from those of their younger, working-age counterparts. My plan is to use the qualitative research skills I acquired during my DPhil to lead this exploratory exercise so as to inform further

efforts in generating high-quality evidence to improve the care of elderly patients presenting open fractures.

Beyond open fracture research, it is also my intention to continue leading and sharing my expertise in improving the conduct of collaborative studies. As previously mentioned, I recognise the need to define and standardise best practices for this research approach. By this, I mean promoting adequate governance, transparency of processes, accountability of the parties involved, data validation, and training of investigators so as to enable delivery of high-quality studies.

Taking advantage of the accumulated expertise of the RSTN and the precedent set by the EQUATOR network, I plan to lead the development of a reporting guideline for collaborative research studies. This will comprise a qualitative research study arising from a focus group discussion involving principal investigators, data-gathering collaborators, scientific journals, and patient representatives. The resulting analysis will be used for the development of best practices and reporting guidelines that will be subjected to later validation in a Delphi study.

6.5 Summary

Open fractures affecting the lower extremities are severe and disabling injuries that require resource-intensive and multidisciplinary attention. The research reported in this thesis provides insight into inequities in management and patient outcomes internationally. It also highlights how clinical guidelines can act as a vector for optimising uptake of evidence, standardising management, and improving outcomes. This thesis explored the factors preserving the status quo in contexts lacking evidence-based recommendations at present and provided a validated framework to aid in the development and implementation of clinical guidelines.

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Appendices

Appendix 1: INTELLECT Data-Gathering Instrument

Confidential

Data gathering instrument

Record ID	_____
Inclusion criteria: Patients with open lower limb fractures Injured between 1st of January 2017 and 31st December 2018 Exclusion criteria: Patients that were initially treated in participating centre, but definitive treatment happened somewhere else Note: For the "Record ID" entry, please enter your local patient study number. Avoid using patient name or hospital number which are considered identifiable information	
Date of birth	_____
Gender	◯ Male ◯ Female
Where did the patient first present?	◯ At participating hospital ◯ Referred from a different hospital in same country ◯ Referred from a hospital in a different country
Date/time of injury	_____
Mechanism	_____
Anatomical location of open fracture(s)	☐ Femur ☐ Tibia/Fibula ☐ Foot skeleton
Gustillo Classification	◯ I ◯ II ◯ III A ◯ III B ◯ III C
Co-morbidities	☐ None ☐ Hypertension ☐ Diabetes mellitus ☐ Ischaemic heart disease ☐ Chronic obstructive pulmonary disease ☐ Asthma ☐ Peripheral vascular disease ☐ Cerebrovascular disease
Other co-morbidities	_____
Smoking status	◯ Yes ◯ No ◯ Unknown

Date/time first dose antibiotics	_____
Date/time first debridement surgery	_____
Specialties of surgeon(s) leading debridement	☐ Orthopaedic surgeon ☐ General surgeon ☐ Plastic surgeon ☐ Non-specialist medical doctor ☐ Other
Seniority of surgeon(s) leading debridement surgery	◯ Resident / Registrar ◯ Fellow ◯ Attending / Consultant
Soft tissue reconstruction required?	◯ Yes ◯ No
Date/time definitive soft tissue cover	_____
Method of soft tissue reconstruction used	☐ Conventional dressings ☐ Topical negative pressure dressings ☐ Skin graft ☐ Local flap (random pattern) ☐ Regional flap (perforator or axial pattern) ☐ Cross-leg flap ☐ Free flap
Flap choice	◯ Propeller flap ◯ Sural nerve flap ◯ Gastrocnemius flap ◯ Peroneus brevis flap ◯ Medial plantar flap ◯ Free ALT flap ◯ Free MSAP flap ◯ Free radial forearm flap ◯ Free SCIP flap ◯ Free gracilis flap ◯ Free latissimus dorsi flap ◯ Free rectus abdominis flap ◯ Free scapular/parascapular flap ◯ Free lateral arm flap ◯ Other regional muscle flap ◯ Other regional fasciocutaneous flap ◯ Other fasciocutaneous free flap ◯ Other muscle/musculocutaneous free flap
Flap salvage required?	◯ No ◯ Yes. Due to arterial insufficiency ◯ Yes. Due to venous congestion ◯ Yes. Due to haematoma ◯ Yes. Due to a different reason ◯ Yes. Due to an unknown/unclear reason
Flap reconstruction outcome	◯ Total flap survival ◯ Partial flap failure ◯ Total flap failure

Deep venous thrombosis diagnosed at any point?	◯ Yes ◯ No
What date was the DVT diagnosed?	_____
Date/time of definitive skeletal immobilisation/fixation	_____
Modality of definitive skeletal immobilisation/fixation	☐ Casting ☐ External fixation with rods and pins ☐ External fixation with frame ☐ Plates and screws ☐ Intramedullary nail ☐ Kirschner wires ☐ Other
Wound infection developed?	◯ Yes ◯ No (Defined as redness and swelling, with or without discharge, that was treated with antibiotics. If surgery was performed, no evidence of infection was found deep to muscle fascia)
Date of diagnosis of wound infection	_____
Deep tissue infection developed?	◯ Yes ◯ No (Defined as infections below muscle fascia, including bone, that require surgical exploration for lavage, removal of metalwork and/or further bone debridement)
Date of diagnosis of deep infection	_____
Was osteomyelitis diagnosed?	◯ Yes ◯ No (Defined as proven bone infection based on clinical, radiographic or microbiological findings)
Date of osteomyelitis diagnosis	_____
Date hospital discharge	_____ (This is the date when the patient was first discharged after definitive fixation and soft tissue cover were achieved. Avoid putting the date of subsequent hospitalisations, readmissions or when patient was discharged from further treatment.)
Date return to work	_____

Date to full weight bearing	_____
Non-union	◯ Yes ◯ No (Lack of union requiring unplanned surgical intervention after definitive wound closure or incomplete radiographic healing at 1 year)
Amputation	◯ Not required ◯ Immediate amputation (within 24 hours of injury) ◯ Early amputation (between 24 hours and 3 months post-injury) ◯ Late amputation (after 3 months of injury)
Last follow-up appointment	_____
Comments	_____

Appendix 2: List of INTELLECT Participating Centres and Collaborators

Collaborating hospital	Collaborators
Imperial College Healthcare NHS Trust (UK)	Grant Nolan, Harsh Samarendra, Arvind Mohan, Kerri Cooper
Hospital del Trabajador de Santiago (Chile)	Nicolás Pereira, Günther Mangelsdorff, Josefa Venegas, Álvaro Layseca
University Hospitals Coventry and Warwickshire NHS Trust (UK)	Joanna Skillman, Anne-Marie Kennedy, Arham Qureshi, Katy Wallis
Queen Victoria Hospital NHS Foundation Trust / Brighton and Sussex University Hospitals NHS Trust (UK)	Lorraine Harry, Ahmed Hagiga, Shimaa Ibrahim, Mohamed Albendary, Khalid A Shah
Hull University Teaching Hospital NHS Trust (UK)	Cher Bing Chuo, Chie Katsura
Hospital Sótero del Río (Chile)	José Ramón Rodríguez Astudillo, Aldo López Ortega, Juan Pablo Henríquez Rissios, Matías Nova Nova
University Hospitals Plymouth NHS Trust (UK)	Juliana Hughes, Chris Wearn, David Peberdy, Beatrice Ho, Kajal Gohil
Cambridge University Hospitals NHS Foundation Trust (UK)	Ahid Abood, Nicholas Rabey, Metin Nizamoglu, Garance Biosse-Duplan, Ken To
Ganga Hospital (India)	S Raja Sabapathy, Monusha Mohan, Hari Venkatramani, Shanmuganathan Rajasekaran
Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation. Tzu Chi University (Taiwan)	Honda Hsu
Hospital Civil de Guadalajara (Mexico)	Ana Rosa Ambriz Plascencia, Luis Enrique Escalona Ramirez, Cesar Alfredo Zepeda Torres
Hospital General "Dr. Manuel Gea González" (Mexico)	Eric Santamaria, Sergio Vallejo Toro
Leeds Teaching Hospitals NHS Foundation Trust (UK)	Christopher West, Waseem Bhat, Ciarstan McArdle, Stefan Louette, Sameena Hassan
Elisabeth-TweeSteden Ziekenhuis (Netherlands)	Pim W. van Egmond, Wouter J.J. Bekkers
ASST Grande Ospedale Metropolitano Niguarda (Italy)	Dario Capitani, Luigi Troisi, Tazio Talamonti, Paolo Capitani, Vincenzo Cerbone, Giovanni Materazzi, Luca Ballini
Vall d'Hebron Barcelona Hospital Campus (Spain)	Jordi Tomas-Hernandez, Juan Antonio Porcel-Vazquez, Yaiza Garcia-Sanchez, José Vicente Andrés-Peiró, Jordi Teixidor-Serra, Jordi Selga-Marsà
Morriston Hospital, Swansea Bay University Health Board (UK)	Hywel Dafydd, Stephen Ali, Robert Slade, Sam Tarassoli
Hospital Universitario de Canarias (Spain)	Beatriz Olías López, Juan Boluda Mengod, David González Martín
The Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)	Asim Bashir, Alex Dearden, Vinay Itte, Fiona Smith, Chang Woo Lee
Radboud UMC (Netherlands)	Vera A.A. Paulus, Patrick Romijn, Tjarda N. Tromp, Tim de Jong
The Alfred Hospital (Australia)	Satomi Koide, Kaiyang Lim, Frank Raiola, Scott Ferris
Uppsala University Hospital (Sweden)	Andrés Rodríguez, Eva Lindell Jonsson, Sebastian Holm, Olof Wolff
Ribat University Hospital and Ibrahim Malik Teaching Hospital (Sudan)	Ahmed Abugarja, Hassan Elbahari, Hytham K. S. Hamid, Mohamed Awadelkarim
Complejo Hospitalario Universitario Insular Materno Infantil (Spain)	Julen Erdocia Pascual, Luis Bahillo O'Mahoney, Manuel Aniel Quiroga Bilbao, Marta Felipe Peña
South Tees Hospitals NHS Foundation Trust (UK)	William Eardley, Anthony Egglestone, Suhib Taher, Nicholas Wei
Hospital Clínico Universitario " Virgen de la Arrixaca" (Spain)	Javier Martínez Ros, Gregorio Valero Cifuentes, Antonio Ondoño Navarro, Alonso Escudero Martínez, Ana Ortega Columbrans
Hospital de la Santa Creu i Sant Pau (Spain)	Paúl Zamora, Jaume Masiá, Andree Ibarra, Manuel Fernández
Sheffield Teaching Hospitals NHS Foundation Trust (UK)	Victoria Giblin, Andrew Kilshaw, Benjamin Wood, Matthew Wyman
Hospital of Divine Savior (Austria)	Ines E. Tinhofer, Elena Seidl, Chieh-Han J. Tzou
AUVA Traumazentrum (Austria)	Stefan Quadlbauer, Jürgen Reichetseder, Heinz Bürger, Thomas Hausner
Medisch Spectrum Twente (Netherlands)	Sacha van Miltenburg, Iris Beijk, Wiebe Verra, Reinier de Groot

Masaryk's hospital (Czechia)	Vojtěch Kunc, Lubomir Kopp
Salisbury NHS Foundation Trust (UK)	Alexandra Crick, Chris Mitchell, Terry-Ann Curran, Rachel Kuo, Salma Eltoum Elamin
Hospital 12 de Octubre (Spain)	Pedro Caba Doussoux, Diego Alonso Tejero, Jorge Gómez Alcaraz, Juan María Pardo García
Medisch Centrum Leeuwarden (Netherlands)	Kevin Kooi, Ralph Poelstra
Asan Medical Center (South Korea)	Joon Pio Hong, Minyoung Jang, Dae Won Hong, Jin Geun Kwon
Hospital Universitario de Gran Canaria "Doctor Negrín" (Spain)	Mónica Francés Monasterio, Javier Fernández-Palacios Martínez, Adrián Suarez Cabañas, Manuel Marrero Martínez-Carlón
Ziekenhuisgroep Twente (Netherlands)	Wouter ten Cate, Juliette E.D. Jacobs
Royal Perth Hospital (Australia)	Jeremy Rawlins, Jessica Haley
Hospital Clínico Pontificia Universidad Católica de Chile (Chile)	Joaquín Palma, Álvaro Cuadra, Hugo Demandes, Sebastián Canahuate, Daniel Moreno
Norfolk and Norwich University Hospitals NHS Foundation Trust (UK)	Sam Norton, Joshua Thompson, George Lafford
Hospital Universitari Josep Trueta (Spain)	Diana Noriego Muñoz, Aina Teixido de la Cruz, Miguel Vázquez Gómez
Policlinico Umberto I - Sapienza University of Rome (Italy)	Andrea Mingoli, Diego Ribuffo, Giovanni Marruzzo, Pierfrancesco Lapolla
Al Azhar Hospital (Egypt)	Wael Ayad, Amr Elbatawy, Mohamed Ouf
Hospital Universitari Mútua de Terrassa (Spain)	Pablo Castillón. Carlos García, María Surroca
Hospital Clínico San Carlos (Spain)	Javier Garcia-Coiradas, Fernando Marco
Universita degli studi dell'Insubria (Italy)	Mario Cherubino, Leonardo Garutti
Hospital Consorci Sanitari Moises Broggi (Spain)	Guillem Molina Olivella, Amaia Endemaño Lucio
Amsterdam UMC (Netherlands)	Kamilcan Oflazoglu, Femke Lutgendorff, Matthijs Botman, Georgios Giannakopoulos
Haaglanden Medisch Centrum (Netherlands)	Rens Dams, Peer van der Zwaal
Hospital Universitario San Cecilio (Spain)	Ramon Moral-Nestares, Francisco Requena
Hospital Parc Tauli (Spain)	Nuria Fernández-Poch, Jaume Cámara-Cabrera
Mutual de Seguridad (Chile)	Fernando Macán, Marcelo Standen
Sanatorio Otamendi (Argentina)	Federico Flaherty, Macarena Vizcay
Sanatorio de la Trinidad (Argentina)	Diego Yerson
Sanatorio Finochietto (Argentina)	Enzo Sperone
Sanatorio Sirio Libanés (Argentina)	Fernando Bidolegui, Sebastian Pereyra
Sanatorio Dupuytren (Argentina)	Eugenio Chouhy, Miguel Jaureguialzo
Ospedale di Cattinara (Italy)	Zoran Arnez, Vito Cazzato
Hospital Universitario Vírgen del Rocío (Spain)	Miguel Ángel Giraldez, Raúl Moreno Domínguez, Beatríz Martínez Sañudo
NHS Lothian (UK)	Luca Lancerotto, Sanita Sandhu
Ulster Hospital, South Eastern Health and Social Care Trust (UK)	Andrew Robinson, Clare Digney

Appendix 3: Multivariate Logistic Regressions for Deep Infection and Non-Union

Dependent variable	Independent variables	
	Process variable	Other co-variable
Deep_infection	Initial_presentation	National_guidelines
	Hours_to_antibiotics	Country_income_group
	Hours_to_debridement	Age
	Days_to_fixation	Gender
	Multidisciplinary_debridement	Gustilo_classification
	Surgeon_seniority	
	Days_to_closure	

Logistic regression — Number of obs = 884; LR chi2(7) = 76.94; Prob > chi2 = 0.0000; Log likelihood = -368.81561; Pseudo R2 = 0.0945

Deep_infection	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Days_cover_cat						
4-7 days	2.611244	.7839725	3.20	0.001	1.449745	4.703306
8-14 days	4.09034	1.272694	4.53	0.000	2.222856	7.52675
15-28 days	1.998228	.6963221	1.99	0.047	1.009316	3.956062
>=29 days	7.408652	2.206293	6.72	0.000	4.13287	13.28087
1.countries_guidelines	.6597426	.1337572	-2.05	0.040	.4434051	.9816313
Gender						
Male	1.684246	.4155927	2.11	0.035	1.038411	2.731757

Dependent variable	Independent variables	
	Process variable	Other co-variable
Non-union	Initial_presentation	Countries_guidelines
	Hours_to_antibiotics	Country_income_group
	Hours_to_debridement	Age
	Days_to_fixation	Gender
	Multidisciplinary_debridement	Gustilo_classification
	Surgeon_seniority	
	Days_to_cover	

Logistic regression — Number of obs = 870; LR chi2(7) = 45.44; Prob > chi2 = 0.0000; Log likelihood = -347.62998; Pseudo R2 = 0.0613

Non_union	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Days_cover_cat						
4–7 days	2.780182	.7461229	3.81	0.000	1.642989	4.704483
8–14 days	2.264872	.6858491	2.70	0.007	1.251073	4.100197
15–28 days	.8445973	.3155653	-0.45	0.651	.406085	1.756639
>=29 days	1.520159	.4857476	1.31	0.190	.8126405	2.843674
1.countries_guidelines	.657357	.1360214	-2.03	0.043	.4381969	.9861281
Gender						
Male	1.962642	.548205	2.41	0.016	1.13523	3.393116

Appendix 4: RSTN COVID–INTELLECT Data-Gathering Instrument

Confidential

Data Gathering Instrument

Record ID	_____
Inclusion criteria: Patients with open lower limb fractures treated on or after the 1st of January 2020 until the 31st May 2020, in the context of the COVID pandemic Exclusion criteria: Patients that were initially treated in participating centre, but definitive treatment happened somewhere else Note: For the "Record ID" entry, please enter your local patient study number. Avoid using patient name or any other patient identifiable information	
Date of birth	_____
Gender	◯ Male ◯ Female
Where did the patient first present?	◯ At participating hospital ◯ Referred from a different hospital in same country ◯ Referred from a hospital in a different country
Date/time of injury	_____
Mechanism	_____
Anatomical location of open fracture(s)	☐ Femur ☐ Tibia/Fibula ☐ Foot skeleton
Gustillo Classification	◯ I ◯ II ◯ III A ◯ III B ◯ III C
Co-morbidities	☐ None ☐ Hypertension ☐ Diabetes mellitus ☐ Ischaemic heart disease ☐ Chronic obstructive pulmonary disease ☐ Asthma ☐ Peripheral vascular disease ☐ Cerebrovascular disease
Other co-morbidities	_____
Smoking status	◯ Yes ◯ No ◯ Unknown

Date/time first dose antibiotics	_____
Date/time first debridement surgery	_____
Specialties of surgeon(s) leading debridement	☐ Orthopaedic surgeon ☐ General surgeon ☐ Plastic surgeon ☐ Non-specialist medical doctor ☐ Other
Seniority of surgeon(s) leading debridement surgery	◯ Resident / Registrar ◯ Fellow ◯ Attending / Consultant
Soft tissue reconstruction required?	◯ Yes ◯ No
Date definitive soft tissue cover	_____
Method of soft tissue reconstruction used	☐ Conventional dressings ☐ Topical negative pressure dressings ☐ Skin graft ☐ Local flap (random pattern) ☐ Regional flap (perforator or axial pattern) ☐ Cross-leg flap ☐ Free flap
Flap choice	◯ Propeller flap ◯ Sural nerve flap ◯ Gastrocnemius flap ◯ Peroneus brevis flap ◯ Medial plantar flap ◯ Free ALT flap ◯ Free MSAP flap ◯ Free radial forearm flap ◯ Free SCIP flap ◯ Free gracilis flap ◯ Free latissimus dorsi flap ◯ Free rectus abdominis flap ◯ Free scapular/parascapular flap ◯ Free lateral arm flap ◯ Other regional muscle flap ◯ Other regional fasciocutaneous flap ◯ Other fasciocutaneous free flap ◯ Other muscle/musculocutaneous free flap
Flap salvage required?	◯ No ◯ Yes. Due to arterial insufficiency ◯ Yes. Due to venous congestion ◯ Yes. Due to haematoma ◯ Yes. Due to a different reason ◯ Yes. Due to an unknown/unclear reason
Flap reconstruction outcome	◯ Total flap survival ◯ Partial flap failure ◯ Total flap failure

Date of definitive skeletal immobilisation/fixation	_____
Modality of definitive skeletal immobilisation/fixation	☐ Casting ☐ External fixation with rods and pins ☐ External fixation with frame ☐ Plates and screws ☐ Intramedullary nail ☐ Kirschner wires ☐ Other
Complications during hospital stay:	_____
Unexpected return to theatre in first 30 days	◯ Yes ◯ No
Reason for unexpected return to theatre	
Was amputation required?	◯ Not required ◯ Immediate amputation (within 24 hours of injury) ◯ Early amputation (between 24 hours and 3 months post-injury)
Was patient COVID-positive upon admission?	◯ Yes ◯ No
Did the patient become COVID-positive during hospital stay?	◯ Yes ◯ No
Was patient symptomatic for COVID?	◯ Yes ◯ No
Date for positive COVID test	_____
Which diagnostic modalities for COVID were used for this patient?	☐ PCR ☐ CT-scan ☐ Antibodies test (quick test)
Did usual management of this kind of injury changed due to COVID pandemic?	◯ Yes ◯ No
How?	_____
Date hospital discharge	_____ (This is the date when the patient was first discharged after definitive fixation and soft tissue cover were achieved. Avoid putting the date of subsequent hospitalisations, readmissions or when patient was discharged from further treatment.)

Follow up arrangements made for this patient

_____

Appendix 5: List of RSTN COVID–INTELLECT Participating Centres and Collaborators

Collaborating hospital	**Collaborators**
Hospital del Trabajador (Chile)	Nicolás Pereira, Gonzalo Bastías, Josefa Venegas
Imperial College Healthcare NHS Trust (UK)	Harsh Samarendra
Ribat University Hospital (Sudan)	Hassan Elbahari, Hytham K. S. Hamid
Norfolk and Norwich University Hospitals NHS Foundation Trust (UK)	Samuel Norton, George Lafford, Joshua Thompson
The Hull University Teaching Hospitals NHS Trust (UK)	Cher Bing Chuo, Chie Katsura
Hospital Universitario de Gran Canaria "Doctor Negrín" (Spain)	Mónica Frances Monasterio, Ivan Beirutti, José Miguel Casarrubios Barrera
Dalin Tzu Chi Medical Center (Taiwan)	Honda Hsu
Medisch Spectrum Twente (The Netherlands)	Kamilcan Oflazoglu, Iris Beijk
South Tees Hospitals NHS Foundation Trust (UK)	William Eardley, Anthony Egglestone
Asan Medical Centre, University of Ulsan (South Korea)	Joon Pio Hong, Jin Geun Kwon
Hospital Clínico Universitario "Virgen de Arrixaca" (Spain)	Javier Martinez Ros, Ana Ortega Columbrans
Ibrahim Malik Teaching Hospital (Sudan)	Ahmed Abugarja, Mohamed Awadelkarim
Hospital General "Dr. Manuel Gea González" (Mexico)	Eric Santamaria, Sergio Vallejo
Università degli Studi dell'Insubria (Italy)	Mario Cherubino, Leonardo Garutti
Salisbury NHS Foundation Trust (UK)	Marios Nicolaou, Terry-Ann Curran, Jack Pearce

Appendix 6: AO UK&I Major Grant Notification

South Tees Hospitals
NHS Foundation Trust

Directorate of Trauma & Orthopaedics
Specialist & Planned Care Centre
The James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW

24th October 2020

Dear Dr Berner

AOUK&I R&PD Major Grant 2020 funding round

I'm very grateful to you for submitting your work to us for review and for consideration of funding by AOUK research.
We had far more applications this year than usual and all were of a high calibre. I'm delighted to inform you that your application for funding has been successful. The panel of six senior research active consultants reviewed all applications and scored yours as appropriate to fund.

We will be unable to fulfil the entirety of your grant request. This is due to the number of applications and also due to restrictions placed upon us due to the pandemic situation. For instance we are restricting the funding of travel and conference fees etc in order to enable other studies to have key elements covered. I trust you will understand this situation and I do not believe, as with all the other applications that have been scaled back, that this will interfere in any way with the delivery of your work. We will grant you £8,500 towards your study.
Thank you for your submission and I wish you all the best with your work. I look forward to seeing your work published and we require you to present the work to us in the next year or two at the AOUK&I AGM.

Yours sincerely



Mr W Eardley - GMC No: 4499792
MD, MSc, PgCertMedEd, DipSEM(UK&I),FRCSEd(Tr&Orth)
Consultant Orthopaedic Surgeon

Appendix 7: East of England – Cambridge South Research Ethics Committee Approval

Health Research Authority

East of England - Cambridge South Research Ethics Committee
Equinox House
City Link
Nottingham
NG2 4LA

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

19 October 2021

Professor Abhilash Jain
Nuffield Department of Orthopaedic, Musculoskeletal and Rheumatological Sciences
B4495
Oxford
OX3 7LD

Dear Professor Jain,

Study title:	**Quality of life after open extremity trauma (QUINTET): a prospective, multi-centre, international study.**
REC reference:	**21/EE/0197**
Protocol number:	**1.0**
IRAS project ID:	**295778**

Thank you for your letter of 06 October 2021, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Appendix 8: NHS Health Research Authority Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Prof. Abhilash Jain
Nuffield Department of Orthopaedic, Musculoskeletal and Rheumatological Sciences
B4495
Oxford
OX3 7LD

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

19 October 2021

Dear Prof. Abhilash Jain

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Quality of life after open extremity trauma (QUINTET): a prospective, multi-centre, international study.**
IRAS project ID:	**295778**
Protocol number:	**1.0**
REC reference:	**21/EE/0197**
Sponsor	**University of Oxford / Clinical Trials and Research Governance**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Appendix 9: QUINTET Study Participant Information Sheet

Mr Juan E Berner / juan.berner@kellogg.ox.ac.uk

Trainee Lead for QUINTET

[Name of chief local investigator and email]

PARTICIPANT INFORMATION SHEET

QUINTET: Quality of life after open extremity trauma study **Quality of life after open extremity trauma (QUINTET): a prospective, multi-centre, international study.**

We'd like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. If there is anything that is not clear, or if you *would like more information, please ask us.*

What is the purpose of the study?

The aim of this study is to better understand how patients feel their quality of life is impacted after sustaining an open fracture in their lower extremities.

Why have I been invited?

- You have been invited to take part considering that you have been recently been admitted with a lower extremity fracture
- We are intending to recruit 200 patients with similar injuries from different centres around the world. This will allow us to better understand how individuals in different settings cope after trauma.

Do I have to take part?

- No, your participation is completely voluntary. The treatment you receive will not change in any way if you participate or not.
- You can withdraw from the study at any point. If you wish to do so, you will be able to choose if you want us to use or destroy any data that we may have gathered from you prior to your decision to withdraw from the study
- Withdrawal will not affect the clinical care you receive in any way.

Appendix 10: QUINTET Study Consent Form

Mr Juan E Berner / juan.berner@kellogg.ox.ac.uk
Trainee Lead for QUINTET
[Name of chief local investigator and email]

Study Code: *Site ID Code:* *Participant identification number:*

CONSENT FORM

Study Title: Quality of life after open extremity trauma (QUINTET): a prospective, multi-centre, international study.

Name of Researcher:	*If you agree, please initial box*
1. I confirm that I have read the information sheet dated 05/7/2021 (version 1.0) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities, from the host organisation [HOSPITAL NAME], where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to be contacted by the investigators to remind me of follow-up appointments and to be contacted for the purpose of this study	
5. I agree to take part in this study.	
6. I would like to be sent a copy of the study findings once complete	

_____	_____	_____
Name of Participant	*Date*	*Signature*
_____	_____	_____
Name of Person taking Consent	*Date*	*Signature*

**1 copy for participant; 1 copy for researcher site file*

Appendix 11: QUINTET Data-Gathering Instrument

Confidential

Data Gathering Instrument

Record ID	_____
Date of birth	_____
Gender	◯ Male ◯ Female
Where did the patient first present?	◯ At participating hospital ◯ Referred from a different hospital in same country ◯ Referred from a hospital in a different country
Date/time of injury	_____
Mechanism	◯ Road traffic accident ◯ High-energy fall ◯ Low-energy fall (from standing or seating) ◯ Work-related injury ◯ Gunshot injury ◯ Sports-related injury ◯ Other
Anatomical location of open fracture(s)	☐ Femur ☐ Tibia/Fibula
Gustillo Classification	◯ I ◯ II ◯ III A ◯ III B ◯ III C
Co-morbidities	☐ None ☐ Hypertension ☐ Diabetes mellitus ☐ Ischaemic heart disease ☐ Chronic obstructive pulmonary disease ☐ Asthma ☐ Peripheral vascular disease ☐ Cerebrovascular disease
Other co-morbidities	_____
Smoking status	◯ Yes ◯ No
Date/time first dose antibiotics	_____
Date/time first debridement surgery	_____

Specialties of surgeon(s) in attendance for debridement	☐ Orthopaedic surgeon ☐ General surgeon ☐ Plastic surgeon ☐ Non-specialist medical doctor ☐ Other
Soft tissue reconstruction required?	◯ Yes ◯ No
Date definitive soft tissue cover	_____
Main method of soft tissue reconstruction used	◯ Conventional dressings ◯ Topical negative pressure dressings ◯ Skin graft ◯ Local flap (random pattern) ◯ Regional flap (perforator or axial pattern) ◯ Cross-leg flap ◯ Free flap
Flap choice	◯ Propeller flap ◯ Sural nerve flap ◯ Gastrocnemius flap ◯ Peroneus brevis flap ◯ Medial plantar flap ◯ Free ALT flap ◯ Free MSAP flap ◯ Free radial forearm flap ◯ Free SCIP flap ◯ Free gracilis flap ◯ Free latissimus dorsi flap ◯ Free rectus abdominis flap ◯ Free scapular/parascapular flap ◯ Free lateral arm flap ◯ Other regional muscle flap ◯ Other regional fasciocutaneous flap ◯ Other fasciocutaneous free flap ◯ Other muscle/musculocutaneous free flap
Flap salvage required?	◯ No ◯ Yes. Due to arterial insufficiency ◯ Yes. Due to venous congestion ◯ Yes. Due to haematoma ◯ Yes. Due to a different reason ◯ Yes. Due to an unknown/unclear reason
Flap reconstruction outcome	◯ Total flap survival ◯ Partial flap failure ◯ Total flap failure
Deep venous thrombosis diagnosed at any point?	◯ Yes ◯ No
What date was the DVT diagnosed?	_____
Date of definitive skeletal immobilisation/fixation	_____

Modality of definitive skeletal immobilisation/fixation	☐ Casting ☐ External fixation with rods and pins ☐ External fixation with frame ☐ Plates and screws ☐ Intramedullary nail ☐ Kirschner wires ☐ Other
Wound infection developed?	◯ Yes ◯ No (Defined as redness and swelling, with or without discharge, that was treated with antibiotics. If surgery was performed, no evidence of infection was found deep to muscle fascia)
Date of diagnosis of wound infection	_____
Deep tissue infection developed?	◯ Yes ◯ No (Defined as infections below muscle fascia, including bone, that require surgical exploration for lavage, removal of metalwork and/or further bone debridement)
Date of diagnosis of deep infection	_____
Date hospital discharge	_____ (This is the date when the patient was first discharged after definitive fixation and soft tissue cover were achieved. Avoid putting the date of subsequent hospitalisations, readmissions or when patient was discharged from further treatment.)
Has patient returned to work?	◯ Yes ◯ No
Date return to work	_____
Is patient full weight-bearing?	◯ Yes ◯ No
Date to full weight bearing	_____
Non-union	◯ Yes ◯ No (Lack of union requiring unplanned surgical intervention after definitive wound closure or incomplete radiographic healing at 1 year)
Date of diagnosis of non-union	_____

Amputation	◯ Not required ◯ Immediate amputation (within 24 hours of injury) ◯ Early amputation (between 24 hours and 3 months post-injury) ◯ Late amputation (after 3 months of injury)
Last follow-up appointment	_____
Comments	_____

Appendix 12: QUINTET Study Telephone Follow-Up Script

Mr Juan E Berner / juan.berner@kellogg.ox.ac.uk

Trainee Lead for QUINTET

[Name of chief local investigator and email]

TELEPHONE COMMUNICATION SCRIPT

QUINTET: Quality of life after open extremity trauma study **Quality of life after open extremity trauma (QUINTET): a prospective, multi-centre, international study.**

Script 1: Telephone follow-up for EQ-5D-3L and SF-12 assessment

Investigator (I): Good morning/afternoon, my name is [local investigator] and I am calling you from [participating hospital]. May I speak with [participant name]?

Participant (P): [Confirms name]

I: Just for data protection could you confirm your participant identification number?

P: [Confirms information]

I: Thank you. I am calling you today regarding the QUINTET study you decided to take part in. You opted for a telephone call as a follow-up following your recent injury. Is this a good time to go through a series of questions?

P: [Agrees to proceed with assessment]

I: [Reads out loud the introductory sentence for EQ-5D-3L followed by the first question along with all the options. A response is recorded. This proceeds until the whole instrument is completed. The SF-12 is completed aftewards]

I: Thank you very much for your time. Do you have any questions about your answers or the study in general?

P: [Participant may or may not ask a question]

I: If you do not have any further questions we are ready to end this phone call. Have a good day.

Appendix 13: List of QUINTET Participating Centres and Collaborators

Collaborating hospital	Collaborators
St George's University Hospital NHS Foundation Trust (UK)	Alex Trompeter, Bethany Kenny, Charlotte Brookes, Belal Amini, Aisha Jeffers, Sally Fisher, Sara Dardak, Roshan Rupra, Rhody Asirvatham, Maria Dadabhoy, William Swadling
University Hospitals Coventry and Warwickshire NHS Trust (UK)	Joanna Skillman, Palashika Bhat, Mahalakshmi Ishwar, Rehnuma Hossain
Imperial College Healthcare NHS Trust (UK)	Shakeel Rahman, Susan Hendrickson, Terry-Ann Curran, Chiwen Lin, Stephanie Ivie, Adam Misky
Hospital Universitario de Canarias (Spain)	Beatriz Olías López, Alejandro Herrera-Rodríguez, Juan Boluda-Mengod
Hull University Teaching Hospital NHS Trust (UK)	Cher Bing Chuo, Kae Sian Tay, Chie Katsura, Joshua Totty, Isla Shariatmadari, John Kiely, Harjoat Riyat, Irfan Jumabhoy, Kim Dearnley
The Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)	Stuart Watson, Christine Dobb, Kelly Atkinson, Lauren Hutchinson, Heidi McColm
Hospital del Trabajador de Santiago (Chile)	Nicolás Pereira, Leonardo Parada, Nicolas Franulic, Maximiliano Rivera, Gonzalo Bastias
Ribat University Hospital (Sudan)	Hytham Hamid, Ahmed Abugarja

Appendix 14: Search Strategy for Open Fracture Guidelines Systematic Scoping Review

# ▲	Searches	Results
1	exp FRACTURES, OPEN/	6175
2	(open adj2 fracture*).ab,kw,ti.	7648
3	(compound adj2 fracture*).ab,kw,ti.	681
4	(Gustilo* and Anderson*).ab,kw,ti.	366
5	(Gustilo* and fracture*).ab,kw,ti.	946
6	(open and fracture*).kw,ti.	5904
7	(compound and fracture*).kw,ti.	330
8	1 or 2 or 3 or 4 or 5 or 6 or 7	13521
9	PRACTICE GUIDELINE/	448061
10	(guideline* or guidance or consensus or recommendation* or standard*).kw,ti.	370547
11	9 or 10	706976
12	8 and 11	260
13	limit 12 to conference abstracts	28
14	from 12 keep 1-260	260

Appendix 15: LINEAGE Study University of Oxford CUREC Approval

MEDICAL SCIENCES INTERDIVISIONAL RESEARCH ETHICS COMMITTEE
Research Services, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB
Tel: +44(0)1865 616575
ethics@medsci.ox.ac.uk

CONFIDENTIAL

Associate Professor Abhilash Jain & Mr Juan Berner
Department of Continuing Education
University of Oxford
Rewley House, 1 Wellington Square
Oxford

27 April 2023

Dear Associate Professor Jain and Juan,

Research Ethics Approval - CUREC 1

Ethics Approval Reference: R85977/RE001

Study title: Limitations to the Implementation Open Trauma Guidelines (LINEAGE) study

The above application has been considered on behalf of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) in accordance with the University's procedures for ethical approval of all research involving human participants.

I am pleased to inform you that, on the basis of the information provided to the IDREC, the proposed research has been judged as meeting appropriate ethical standards, and approval has been granted for a period of **18 months**, commencing on **27th April 2023.**

Amendments

Should there be any subsequent changes to the study, you should submit details to the MS IDREC for consideration and approval. Details of changes must be listed on an amendment form.

Yours Sincerely

DocuSigned by:
Leah Butts
9F14889D2BC549A...

Mrs Leah Butts
Research Ethics Administrator

for
Dr Helen Barnby-Porritt
Research Ethics Manager

Appendix 16: LINEAGE Study Recruitment Email Script

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)

Professor Abhilash Jain
Botnar Institute for Musculoskeletal Sciences
Mr Juan Berner, DPhil in Evidence-Based Healthcare Student
Telephone: 01865 741155
Email: juan.berner@kellogg.ox.ac.uk.



Study Title: Limitations to the Implementation Open Trauma Guidelines (LINEAGE) study

RECRUITMENT TEXT

Central University Research Ethics Committee Approval Reference: [R85977/RE001]

Dear _____,

We hope this email finds you well. We would like to invite you to take part in the "Limitations to the Implementation of Open Trauma Guidelines (LINEAGE) study. Your contact details were passed on to us by the Secretariat of the professional organisation in which you have a senior role. The aim of the study is to investigate the barriers and limitations to the development and implementation of clinical guidelines for lower limb open fractures, at global scale. To achieve this, we are interviewing representatives of orthopaedic and plastic surgery scientific societies internationally. For this reason, we are very interested in getting to know your perspective in this matter.

We have taken the liberty to attach a Participant Information Sheet and a Consent Form you would have to sign if you are willing to take part in this study. This document covers in detail how we will be conducting the study, including how we are protecting participants anonymity. If you have any queries and would like to discuss further, please let us know.

Kind regards,

Mr Juan Berner MD, MSc(Oxon), FRCS(Plast)

DPhil Student in Evidence-Based Healthcare

University of Oxford

Prof. Abhilash Jain PhD, FRCS(Plast)

Nuffield Department of Orthopaedic, Rheumatology and Musculoskeletal Sciences

University of Oxford.

Appendix 17: LINEAGE Study Participant Information Sheet

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)

Professor Abhilash Jain
Botnar Institute for Musculoskeletal Sciences
Mr Juan Berner, DPhil in Evidence-Based Healthcare Student
Telephone: 01865 741155
Email: juan.berner@kellogg.ox.ac.uk.



Study Title: Limitations to the Implementation Open Trauma Guidelines (LINEAGE) study

PARTICIPANT INFORMATION SHEET

Central University Research Ethics Committee Approval Reference: [R85977/RE001]

1. Introductory paragraph

You are being invited to take part in a research project. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

2. Why is this research being conducted?

Severe injuries to the legs can be devastating for people who suffer them. Open fractures are very difficult to treat, as they require the involvement of multiple specialties such as orthopaedic, plastic surgery, radiology, microbiology, physiotherapy, and specialist nursing. In order to standardise how these injuries a few countries have developed clinical practice guidelines for clinicians looking after these patients. However, these documents are not available in most settings.

The purpose of this study is to investigate the barriers and limitations to the development and implementation of clinical guidelines for lower limb open fractures, at global scale. Secondarily, we are researching what barriers and limitations to the conduction of international clinical research on open extremity fractures.

3. Why have I been invited to take part?

You have been invited because you are considered a senior stakeholder as a Council Member of a national Orthopaedic or Plastic Surgery scientific society.

We are intending to recruit 10 to 12 participants holding a similar position in your and other countries.

4. Do I have to take part?

No. It is up to you to decide whether to take part. You can withdraw yourself from the research, without giving a reason, by advising us of this decision.

5. What will happen to me if I take part in the research?

If you decide to take part, you will have to sign a consent form to document your agreement. Following this you will be invited to participate in a 45 to 60-minute virtual interview. During this interview, you will be asked to discuss your professional views about open lower limb fractures guidelines and open fractures research.

Appendix 18: LINEAGE Study Consent Form

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)

Professor Abhilash Jain
Botnar Institute for Musculoskeletal Sciences
Mr Juan Berner, DPhil in Evidence-Based Healthcare Student
Telephone: 01865 741155
Email: juan.berner@kellogg.ox.ac.uk.

UNIVERSITY OF OXFORD

Consent to take part in the Limitations to the Implementation Open Trauma Guidelines (LINEAGE) study

Central University Research Ethics Committee (CUREC) approval reference: R85977/RE001

Purpose of Study: The purpose of this study is to investigate the barriers and limitations to the development and implementation of clinical guidelines for lower limb open fractures, at global scale.

	Please initial each box if you agree with the statement
I confirm that I have read and understand the information sheet for the above research. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any point, without giving any reason.	
I understand who will have access to personal data provided, how the data will be stored and what will happen to the data at the end of the project.	
I understand that I will not be identifiable from any publications, presentations, or thesis.	
I consent to being audio recorded.	
I understand how audio recordings will be used in research outputs.	
Use of quotations: Please indicate your preference (select *one* option): a) I do not wish to be quoted. **or** b) I agree to the use of quotations in research outputs if I am not identifiable. **or**	
I understand how to raise a concern or make a complaint.	
I agree to take part.	

Template written consent form, version 4.2, November 2022

Appendix 19: LINEAGE Study Semi-Structured Interview Script

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)

Professor Abhilash Jain
Botnar Institute for Musculoskeletal Sciences
Mr Juan Berner, DPhil in Evidence-Based Healthcare Student
Telephone: 01865 741155
Email: juan.berner@kellogg.ox.ac.uk.

Study Title: Limitations to the Implementation Open Trauma Guidelines (LINEAGE) study

SEMI-STRUCTURED INTERVIEW

Central University Research Ethics Committee Approval Reference: [R85977/RE001]

Introduction

Thank you for agreeing to participate in this virtual interview. The aim of this study is to better understand current barriers and limitations to the development and implementation of open lower limb fractures in different countries. There are no right or wrong answers to any of these questions as we interested to better understand your local situation.

Participation in this study is voluntary and we have sent you ahead a participant information sheet and consent form that you have already signed. This interview should take between 45 minutes and one hour. We would like to ask you for your consent to audio record this interview to capture all the details arising in our conversation. All responses will remain confidential, and we will de-identify your contribution before any analysis is conducted or results shared with other members of the team. We would like to reassure you that your participation will remain anonymous in the resulting publications, presentations or any other research outputs resulting from this project. You may decline to answer any question or stop the interview at any time. Are there any questions you may want me to answer before we start?

You may wish to turn on your video camera if you want, although this will not be recorded. May I turn the audio recording on?

As a semi-structured interview, we will here present the main themes to be discussed and some prompts to initiate discussion of certain topics. We are also planning to use non-leading prompts to allow participants to explore ideas further, for example "Would you be able to tell me a bit more about that?"

Opening question

Before we begin, it would be nice if you could tell me about your professional background. What is your clinical specialty and what is your role in your professional organisation?

1. Current management of open lower limb fractures

Could you tell me how open lower limb fractures are usually treated in your country?

Prompts: Are there different healthcare systems in your country? Are open fractures treated differently in these systems?

Appendix 20: Framework Proposal and Delphi Validation Survey



Developing a framework for the introduction of open fracture guidelines: a Delphi study

1. Introduction

You are being invited to take part in a research project. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

2. Why is this research being conducted?

Open lower limb fractures can be devastating injuries with long-term physical and psycho-social consequences for people who sustain them. The INTELLECT study showed how clinical practice guidelines may play a role in improving the care of patients, leading to better outcomes. We have developed a framework to aid in the development and implementation of open fracture guidelines in countries that do not have one at the moment. The aim of this study is to obtain feedback from senior clinicians dealing with these injuries routinely, to further refine this framework and identify areas of consensus.

3. Why have I been invited to take part?

You have been invited to participate as a clinician and expert in the management of open fractures of the lower limb. You have been approached based on our previous academic interaction. We are expecting that 50 participants will take part on this study.

4. Do I have to take part?

No. It is up to you to decide whether to take part. You can withdraw yourself from the research, without giving a reason, by advising me of this decision. If you decide to withdraw we will remove any provided information from our records. However, following this deadline this may not be possible as the analysed data will be submitted as a doctoral thesis / publication.

5. What will happen to me if I take part in the research?

This research study will take place virtually. If you decide to participate you will have to complete a virtual consent form. Following this you will be granted access to brief questionnaire designed to collect basic demographic information about yourself. This is followed by Delphi survey in which you will be presented with Likert-style questions for you to answer. This will allow for you to score your degree of agreement or disagreement with elements of this framework for the development and implementation of open fracture guidelines. You will also be able to write free-text comments along these questions, to further assist us in the refinement of this framework. The expected time required to complete this survey will be of 5 to 10 minutes.

After obtaining the responses from yourself and other participants we will aggregate this scores. You will be then invited to participate on a further Delphi round in which the same questions will be included, along with a summary of the previously obtained aggregated scores in percentages. No other participants will know your exact answers through this process. We will send you a maximum of two kind reminders if we do not hear back from you and no more than 3 Delphi rounds will be conducted. We are expecting that your involvement in this study will not take longer than 3 months.

7. What information will be collected and why is the collection of this information relevant for achieving the research objectives?

Your personal contact information will be gathered and stored for the duration of the study. This will be used to contact you for the subsequent Delphi rounds. Once the study is finished you may choose to be acknowledged in any resulting publications or remain anonymous. Either way, we will not disclose your individual answers but an aggregate for all participants. The data collected will be in the form of Likert-style answers, and free text if you wish to contribute in that way. There will be no question regarding personal or sensitive matters.

The research team will have access to the research data. Identifiable data (including consent forms) will be stored in the same secure platform you will use to answer the questionnaire (Jisc Online Surveys). Once data gathering is complete, unidentifiable research data will be exported and stored in a secure Oxford server for up to 5 years and then will be destroyed.

8. Will the research be published? Could I be identified from any publications or other research outputs?

The findings from the research will be written up as part of the main investigator doctoral thesis, and will also be published in an academic journal. As previously mentioned, you will be entitled to be acknowledged for your participation, if you wish.

9. Further Information and Contact Details

If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

Dr Juan Berner. Kellogg College, University of Oxford. University email: juan.berner@kellogg.ox.ac.uk

Consent Form

Please read the statements below. Proceeding to the next page will be interpreted that you have confirmed these three items:

1. I confirm that I have read the information provided for this study. I have had the opportunity to consider the information, ask questions, and have these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.
3. I agree to take part in this study.

Demographics and professional background

As previously stated, we would appreciate if you could answer this brief demographic questionnaire before proceeding to the Delphi survey

1. In which country is your clinical practice based? *

2. What is your medical/surgical specialty? *

- ◯ Orthopaedic Surgery
- ◯ Plastic and Reconstructive Surgery
- ◯ Trauma Surgery
- ◯ General Surgery

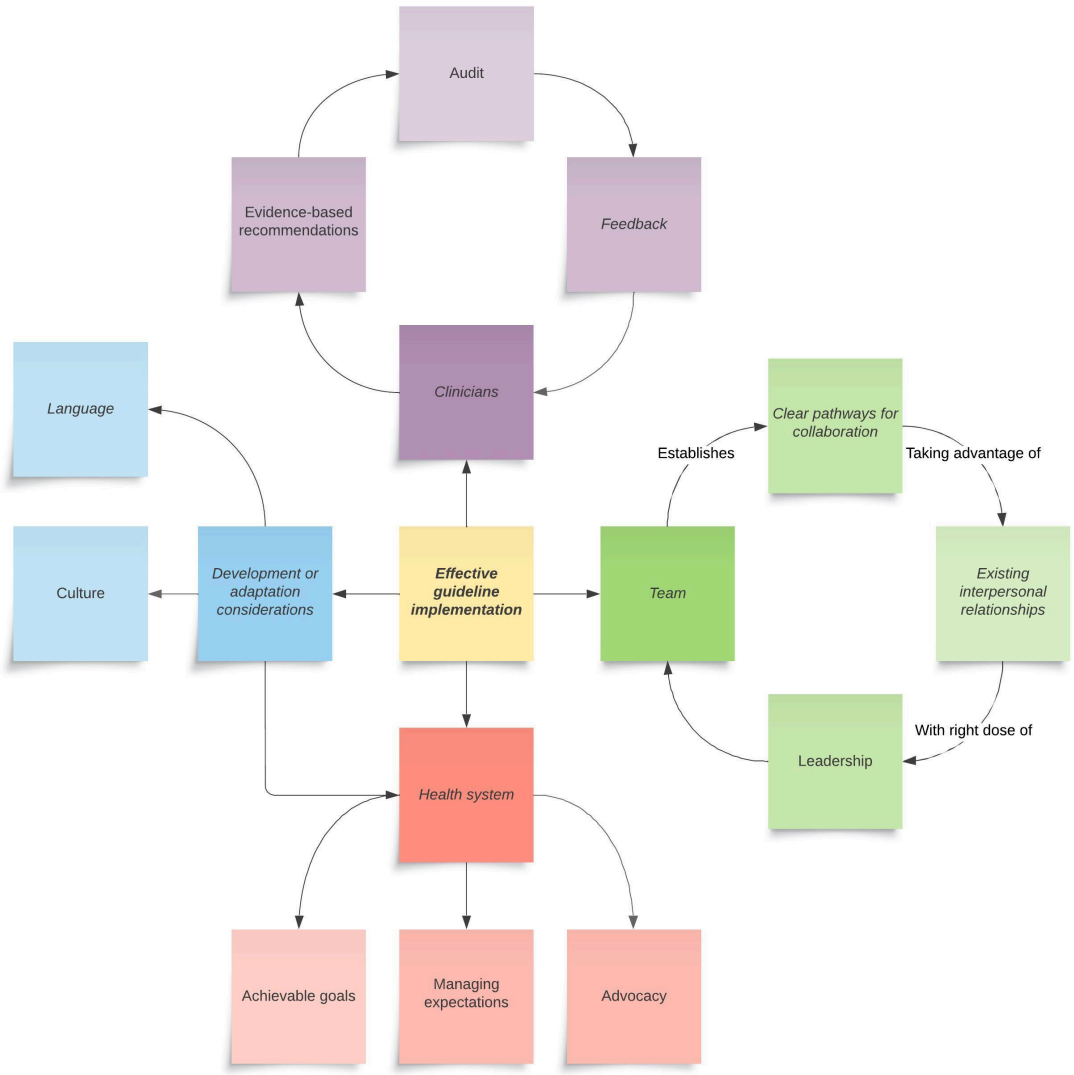
3. How many years have you been practicing as a specialist? *

4. Which of the following best represents your gender? *

- ◯ Male
- ◯ Female
- ◯ Non-binary
- ◯ My gender is not listed
- ◯ Prefer not to say

Framework proposal

In this section you will be presented with an overview of the proposed framework for effective implementation of guidelines for the management of open fractures. This will be the basis for the Delphi survey that will follow.



The central concept of this diagram is to achieve effective guideline implementation for open lower limb fractures. Around it, four domains are presented: clinician factors (purple), team factors (green), health system factors (red) and general cultural considerations (blue).

In terms of clinician factors, guidelines intend to guide decision-making by providing evidence-based recommendations for managing open fractures. This framework, however, highlights the importance of an auditing practice for this to be effective. Measuring process and patient outcomes is able to provide valuable feedback for continuous improvement, while assuring compliance.

Moving on to team factors, we emphasise the importance of a multidisciplinary team for treating open lower limb fractures. While clinical guidelines can establish clear pathways for collaboration, this framework appreciates how interpersonal relationships inevitably play a role, negatively or positively. In this context, we see how positive leadership can influence this dynamic, upholding that protocols for collaboration are followed, while incentivising positive working attitudes across members of the team.

This framework also recognises how many of the systemic factors that play a role in the management of open fractures may be difficult to change in the short-term. Any effective guideline implementation should consider these in order to find creative solutions to these limitations. In relation to this, establishing achievable goals and managing expectations is crucial to succeed in terms of implementation.

The wider context social context is also included in this guideline, paying attention to both cultural and language considerations when preparing a guideline for implementation.

Delphi survey

In this page you will be presented with a series of statements in relation to the framework introduced previously. Please mark an answer for each one, depending on your level of agreement or disagreement for each item.

Clinician factors

5. Recommendations should be based in best available evidence, to positively influence clinician decision-making. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

6. Continuous audit of care and outcomes should be encouraged as part of implementation. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

7. Feedback from audits should be used to measure guideline compliance, as a driver for continuous quality improvement. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree

◯ Strongly agree

Team factors

8. Open fractures should be managed within multidisciplinary teams able to provide complex interventions, addressing bone and soft tissues. *

◯ Strongly disagree
◯ Disagree
◯ Undecided
◯ Agree
◯ Strongly agree

9. Clear pathways for collaboration across specialties are desirable to optimise patient care, while reducing variability in terms of how this is delivered. *

◯ Strongly disagree
◯ Disagree
◯ Undecided
◯ Agree
◯ Strongly agree

10. The positive effect of good interpersonal relationships among clinicians favouring teamwork and inter-specialty collaboration should be recognised *

◯ Strongly disagree
◯ Disagree
◯ Undecided
◯ Agree
◯ Strongly agree

11. Positive leadership is necessary to facilitate collaboration among multi-disciplinary team members. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

Health system factors

12. Open fracture management is inevitably influenced by healthy system factors that clinicians cannot easily change. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

13. Health system factors should be considered when developing an open fracture guidelines, so that any recommendation is feasible in real-world scenarios. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

14. Expectations should be managed when implementing an open fracture guideline, especially when foreign guideline adaptation is being considered. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree

- ◯ Strongly agree

15. Although gold-standard care may not always be feasible, awareness of ideal best practice is important, so that effective advocacy is possible. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

Socio-cultural factors

16. Appreciating cultural and language factors is crucial in the development of guidelines for open fracture management. This is especially relevant when adaptation of a foreign guideline is being considered. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

Delphi survey

17. In terms of overall structure, this framework provides a comprehensive overview of the key elements that should be considered in the process of developing and implementing guidelines for open lower limb fractures. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

18. This framework conceptualises the process of guideline development and implementation, so that it can be applied in settings where no guidelines exist at present. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

19. It is easy to understand the concepts included in this framework, along with their relevance in the process of guideline development and implementation. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

20. The relationships between the concepts included in this framework are logical and practical. *

- ◯ Strongly disagree

- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

21. The framework here presented has the potential of being a useful resource in the development and implementation of open fracture guidelines, in settings that do not have one at present. *

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Undecided
- ◯ Agree
- ◯ Strongly agree

22. The purpose of this Delphi exercise is to refine the framework here presented. Please use the space below to write any feedback, criticism and suggestions.

Thank you

This is the end of the Delphi survey. Thank you for taking the time to answering these questions. Once the results have been analysed we will contact you again to share the results and ask for further feedback.

23. Your answers will remain anonymous. We will not disclose your answers to other participants or the wider public. However, we would like to offer participants the chance of being acknowledged for their participation in this exercise. This is optional and we would appreciate if you could let us know your decision by selecting an option below: *

- ◯ I would prefer not to be named in any resulting reports or publications
- ◯ I would prefer to be acknowledged in any resulting reports and publications

Appendix 21: Delphi Panel of Experts for Framework Validation

Participating panel of orthopaedic and plastic surgeons for Delphi study: Alina Ortega-Briones, Ata Ul Haq, Álvaro Zamorano, Beatríz Olías López, Carlos Fonfach, Chad Chang, Carlos Prada, Diana Crego-Vita, Ernesto Ewertz, Anton Fries, Gonzalo Aranda, Yung-Chen Chiu, Oriana Haran, Hari Castro, Héctor Aguado, Javier Martínez Ros, Juan de Dios Errázuriz, Joaquín Palma, Leonardo Parada, Lily Mundy, Antonella López, Luigi Troisi, Macarena Vizcay, Mania Mani, Roberto Martínez, Fernando Nangole, Nicolás Pinto, Pierlugi Tos, Asimb Bashir, Patrick Will, Quillan Young Sing, Raquel García Albea, Sarah Lonie, Richard Thomson, José Valle Cruz, Vicente Guimera, Virginia García Virto, Aleksandra Winiarska.

Appendix 22: Research Collaborations

	Research task	Performed by
Chapter 2: INTELLECT	Inception	JEB
	Protocol development and registration	JEB
	Study set up and management	JEB
	Data cleaning and validation	JEB, RT, AN
	Data analysis	JEB, MO
Chapter 2: INTELLECT - COVID-	Inception	JEB
	Protocol development and registration	JEB
	Study set up and management	JEB
	Data cleaning	JEB
	Data analysis	JEB
Chapter 2: QUINTET	Inception	JEB
	Protocol development and registration	JEB
	Ethical approval	JEB
	Study set up and management	JEB
	Data cleaning	JEB
	Data analysis	JEB, MO
Chapter 3: Systematic scoping review	Inception	JEB
	Protocol development and registration	JEB
	Literature searches	JEB, TP
	Article screening	JEB, SA
	Data extraction	JEB, PW, SA
	Data analysis	JEB
Chapter 3: Guideline comparison	Inception	JEB, EV
	AGREEII assessment	JEB, EV, KO
	Recommendation comparison	JEB, EV
Chapter 4: LINEAGE	Inception	JEB
	Protocol development	JEB
	Ethical approval	JEB
	Data gathering	JEB
	Data processing	JEB, AP
	Data analysis	JEB
Chapter 5: Delphi study	Inception	JEB
	Protocol development	JEB
	Ethical discussion (no approval needed)	JEB
	Data gathering	JEB
	Data analysis	JEB

AN: Alfonso Navia, AP: Adele Pope, EV: Elfi Verheul, KO: Kamil Oflazoglu, MO: Manuel Ortiz-Llorens, TP: Tatjana Petrinic, RT: Rodrigo Tejos, SA: Stephen Ali