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Spontaneous Osteonecrosis of the Knee:

Systematic Review & Delphi Study

by

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A thesis submitted in partial fulfilment for the requirements for the degree of Master of Science by Research at the University of Central Lancashire

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Student Declaration

Type of award: Master of Science by Research
Awarding School: Faculty of Clinical and Biomedical Sciences

I declare that while registered as a candidate for the research degree, I have not been a registered candidate or enrolled student for another award of the University or other academic or professional institution

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Abstract

Background: Numerous treatments for Spontaneous Osteonecrosis of the Knee (SONK) have been described, but there is little guidance regarding which joint-preserving treatments to use for different disease stages.

Aims: To assess the effectiveness and appropriateness of non-operative and operative joint-preserving treatments for SONK as a whole, as well as for different disease stages.

Methodology: A systematic review with narrative synthesis of four bibliographic databases was undertaken to identify studies evaluating the effectiveness (clinical, radiological outcomes and failure rates) of joint-preserving treatment for SONK. The findings of the review were then used to inform a 2-round Delphi study involving an international expert panel to establish consensus on preferred first and second-line treatments for different disease stages.

Results: Twenty eligible studies were identified: 8 described non-operative measures and 14 surgical interventions (2 studies described several treatments). One study was a randomised controlled trial evaluating foot orthoses, which proved more effective than usual treatment with analgesia and physiotherapy. Supportive treatment with analgesia and restricted weight bearing, bisphosphonates and most other joint-preserving surgical interventions had promising results from small case series.

Nineteen experts contributed to the first round of the Delphi study and 14 to the second round. Consensus was achieved for 3 months of rest and analgesia as first-line treatment in early and intermediate-stage disease, without consensus on the most appropriate second-line treatment. For late-stage disease, consensus was not reached for first-line treatment although 50% agreed against joint-preserving therap. For second-line treatment, 78.6% would use arthroplasty.

Conclusions: Rest and analgesia with or without restricted weight-bearing appears to be an appropriate, and often effective first-line treatment for early or intermediate-stage disease. Arthroplasty, rather than joint-preserving therapy is the most commonly utilised treatment for late-stage disease. However, existing research is limited, and higher-level evidence is required before being able to definitively state which joint-preserving treatments are most effective for SONK of different stages.

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Abbreviations

	Abbreviation	Meaning
F	FTA	Femorotibial angle
H	HSS	Hospital for Special Surgery rating system
	HTO	High Tibial Osteotomy
J	JOA	Japanese Orthopaedic Association
K	KSS	American Knee Society Score;
L	LOE	Level of Evidence
M	MINORS	Methodological Index for Non-Randomised Studies
	MRI	Magnetic Resonance Imaging
O	OATS	Osteochondral Autograft Transfer System
	OD	Osteochondritis Dissecans
	ON	Osteonecrosis
R	RCT	Randomised controlled trial
	ROM	Range of Motion
S	SONK	Spontaneous Osteonecrosis of the Knee
T	TKR	Total Knee Replacement
	TO	Transient Osteoporosis
V	VAS	Visual Analogue Scale
W	WBL %	Weight Bearing Line Percentage

CHAPTER ONE: INTRODUCTION

This chapter provides an overview of the anatomy of the knee and the resulting pathological processes that can occur in the joint resulting in disease, with a specific focus on spontaneous osteonecrosis. The proposed theories regarding underlying pathophysiology as well as the differing features and clinical findings in comparison to other similar disease processes occurring around the knee joint will be discussed, followed by a brief overview of the existing treatment modalities used in current practice.

1.1. Anatomy of the Knee

The knee is the largest and most superficial synovial joint in the body and is made up of three articulations; two femorotibial articulations between the lateral and medial femoral and tibial condyles, and one patellofemoral articulation between the femur and patella. (Moore & Dalley, 2006).

The knee has an extensive arterial blood supply, derived primarily from five main branches of the popliteal artery. The superior medial and lateral, the middle (posterior), and the inferior medial and lateral genicular arteries form a rich anastomosis to supply the knee joint (figure 1.1), (Shim & Leung, 1986). The highly vascular structure of the knee is involved in all aspects of growth, repair and metabolism (Brandi & Collin-Osdoby, 2006). There is increasing evidence to suggest that abnormalities in blood supply around the knee can be directly related to either the initiation or progression of numerous disease processes and has been implicated in the development of both osteoarthritis and osteonecrosis (Findlay, 2007).

1.2. Spontaneous Osteonecrosis

Spontaneous osteonecrosis of the knee (SONK) was first described as a clinical entity in 1968 by Ahlbäck et al. It is a condition characterised by bone necrosis, with subchondral fracture, subsequent segmental collapse and arthrosis (Ahlbäck, et al., 1968). SONK usually presents with acute onset of severe pain localised to the medial side of the knee, with the absence of any risk factors associated with osteonecrosis such as steroid use, alcohol excess or associated autoimmune diseases (Ahlbäck, et al., 1968; Karim, et al., 2015). The knee is the second most common site to be affected by spontaneous osteonecrosis, after the hip, and constitutes 10% of all cases (Mont, et al., 1997; Mont, et al., 2000). The medial femoral condyle is by far the most commonly affected area in the knee, being involved in up to 94% of cases (Al-Rowaih, et al.,

1993); SONK can also involve the tibial plateau and patella (Ecker & Lotke, 1994; Lotke, et al., 2004; Pollack, et al., 1987).

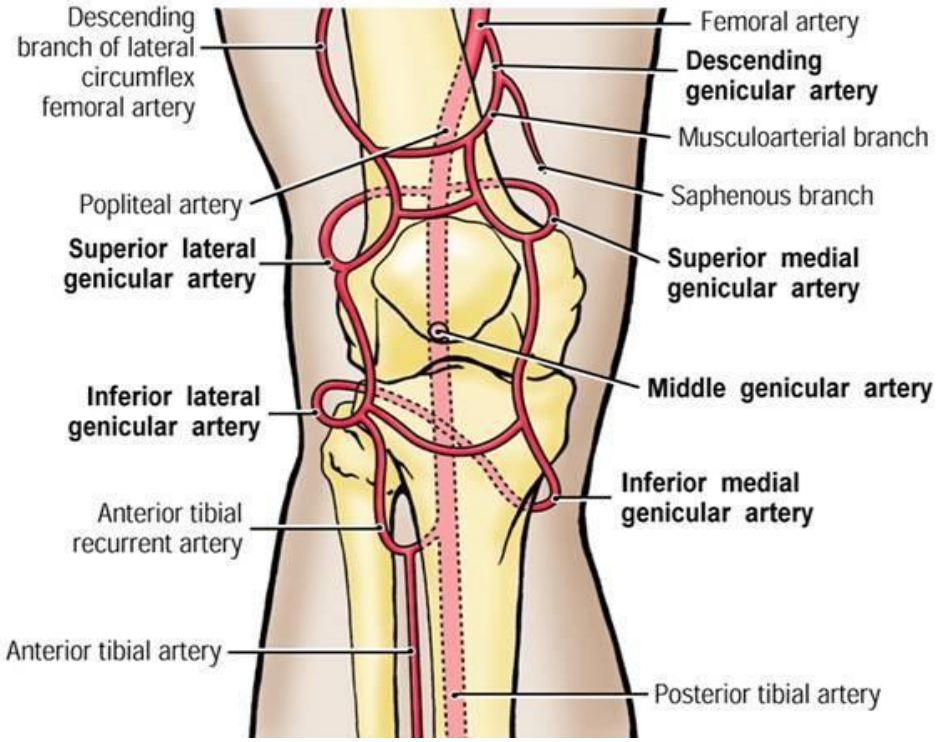

Figure 1-1: Genicular anastomosis, providing blood supply to the knee joint (Moore KL, 2009)
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1.3. Aetiology

The aetiology of SONK is still not fully understood and several differing views on the pathogenesis have been proposed. One theory is that a raised intra-osseous pressure secondary to local inflammation or vascular insufficiency from impaired microcirculation leads to ischaemia and eventual osteonecrosis. The evidence for this theory is limited to a small number of studies (Aglietti, et al., 1983; Ecker & Lotke, 1994; Karim, et al., 2015; Marcacci, et al., 2016). A cadaveric study of twelve knees demonstrated that the medial femoral condyle had a limited blood supply, compared to the extensive intra and extra-osseous blood supply of the lateral femoral condyle (Reddy & Frederick, 1998). This further supports the link between vascular insufficiency and SONK, given the increased incidence of disease in the medial compared to the lateral femoral condyle (Al-Rowaih, et al., 1993).

A mechanical or traumatic theory has also been proposed, suggesting a connection between subchondral insufficiency fractures and the onset of SONK (Marcacci, et al., 2016; Yamamoto & Bullough, 2000). Subchondral insufficiency fractures are atraumatic fractures, often occurring in overweight, elderly patients with osteoporosis. If such fractures occur and fail to heal, repetitive micromotion can lead to infiltration of

synovial fluid, with subsequent detachment and fragmentation of an osteochondral fragment, leading to necrotic changes in this disconnected area (Marcacci, et al., 2016). This theory was initially described by Lotke et al (1977) and has since been supported by further studies, including those evaluating magnetic resonance imaging (MRI) and histopathological findings (Hall, 2005; Muscolo, et al., 2006; Nakamura, et al., 2002; Norman & Baker, 1978; Takeda, et al., 2008). In addition to osteoporosis, the development of such subchondral fractures has also been related to abnormal loading across the knee joint secondary to meniscal injury, malalignment or underlying degenerative changes (Robertson, et al., 2009).
The definitive pathogenesis of SONK, however, remains debated and may indeed be multi-factorial in nature, evolving from a combination of underlying pathological abnormalities described in these theories.

1.4. Clinical Presentation

SONK is a relatively uncommon disease, most frequently occurring in middle-aged to elderly patients. It affects females up to three times more often than males (Aglietti, et al., 1983; Ahlbäck, et al., 1968; Karim, et al., 2015; Rozing, et al., 1980). There is limited epidemiological data published regarding the incidence and prevalence of SONK; one study described an incidence of 3.4% in patients under 50 years old, rising to 9.4% in those over 65 (Pape, et al., 2002).

The condition frequently presents with acute onset of severe pain, often localised to the affected area, usually without history of trauma (Karim, et al., 2015). Patients often complain of increased pain on weight-bearing, along with persistent rest pain (Forst, et al., 1998). Examination of the knee may reveal evidence of an effusion with localised tenderness over the affected area, usually the medial femoral condyle (Karim, et al., 2015; Lotke P A, 1982). During the initial, acute stages of disease, patients may have a restricted range of motion compared to the normal knee. In more long-standing cases, a fixed flexion deformity may occur (Patel, et al., 1998).

1.5. Diagnosis

The diagnosis of SONK can often be made based on clinical history and radiographic changes alone. However, plain radiographs are often normal in the first stages of the disease. Further magnetic resonance imaging (MRI) may be needed (Zywiel, et al., 2009), which can detect early subtle changes in the bone marrow as early as 72 hours after symptom onset (Yates, et al., 2007). It can provide more detailed information on the degree and distribution of bone marrow involvement and the presence of cartilage

damage due to bone collapse, which relates to prognosis (Fotiadou & Karantanas, 2009; Yates, et al., 2007). MRI has greatly improved early diagnosis of the disease, and is the imaging modality of choice for diagnosis, staging and disease monitoring (Dogan, et al., 2012; Lotke, et al., 2000; Yates, et al., 2007).

1.6. Differential Diagnosis

Osteonecrosis of the knee can be broadly divided into four groups: spontaneous osteonecrosis of the knee (SONK, also described as primary osteonecrosis), secondary osteonecrosis (also called idiopathic, ischaemic or atraumatic osteonecrosis), post-arthroscopic and post-traumatic osteonecrosis (Mont, et al., 2000; Zywiel, et al., 2009). SONK is the most common type of osteonecrosis and affects an older age group (Pape, et al., 2002), in comparison to secondary osteonecrosis, which is associated with other underlying medical problems or medication. Alcohol, steroid use, sickle cell disease, myeloproliferative disorders and renal disease have all been implicated in the development of secondary osteonecrosis (Karim, et al., 2015). Post-arthroscopic osteonecrosis is thought to be the rarest form, with an onset following arthroscopic knee surgery, more specifically, after meniscectomy (Cetik, et al., 2009; Karim, et al., 2015). In post-traumatic osteonecrosis, as the name suggests, there is a history of trauma or surgery preceding symptom onset, leading to bone death, usually in an isolated area of the knee (Mont, et al., 2000).

In addition to the different forms of osteonecrosis, there are other intra-articular pathologies of the knee to be considered when diagnosing SONK: osteochondritis dissecans, transient osteoporosis and traumatic bone marrow lesions must be ruled out as they often share common clinical and pathological findings (Mont, et al., 2000). It can sometimes be difficult to differentiate these conditions from the history and clinical examination alone and radiological findings can also be misleadingly similar. Certain characteristics, such as the age of the patient, location of the lesion, clinical symptoms, histology, general lack of intra-articular loose bodies and relatively delayed appearance of changes on plain radiographs may help to differentiate SONK from other conditions (Marcacci, et al., 2016).

Osteochondritis dissecans (OD) is a condition affecting articular cartilage and subchondral bone. It results in varying pathological abnormalities, beginning with softening of the articular cartilage, early cartilage separation and partial or, in some cases, complete separation of an osteochondral fragment (Pape, et al., 2010). It affects the posterolateral aspect of the medial femoral condyle in most cases. OD often affects

adolescents and young adults, whereas SONK is most common in middle-aged and elderly patients (Williams, et al., 1998).

Transient osteoporosis is another differential diagnosis. It is an uncommon, usually self-limiting syndrome of unknown aetiology, characterised by joint pain and osteopenia (Sastre, et al., 2007). Unlike SONK, it is more commonly located in the lateral femoral condyle and gives a characteristic appearance of focal osteopenia within eight weeks of symptom onset (Crespo, et al., 2001; Hayes, et al., 1993).

Lesions and bone marrow oedema following trauma also sometimes need to be considered as a possible diagnosis; this can either be associated with acute trauma, or with more subacute injuries related to overload, such as stress fractures (Roemer, et al., 2009).

Specific features on imaging can be used as an aid to diagnose SONK. One of the most important differences between early SONK and bone marrow oedema (as seen with transient osteoporosis or trauma) is the presence of a focal subchondral lesion on MRI (Björkengren, et al., 1990; Lecouvet, et al., 1998). The focal nature of the lesion in early stage SONK suggests that a pathological process is taking place at this site, rather than a more diffuse disease process throughout the femoral condyle, as seen in bone marrow oedema related to transient osteoporosis or trauma (Yates, et al., 2007). The location of the disease also helps to differentiate between conditions; the lateral femoral condyle is the most commonly affected site in transient osteoporosis, the lateral side of the medial femoral condyle is commonly affected in OD, whereas the medial aspect of the femoral condyle and the tibial plateau are most commonly involved in SONK (Mont, et al., 2000). Contour flattening is also seen more often in SONK. (Gil, et al., 2006). A comparison of SONK and other conditions to be considered in the differential diagnosis are summarised in table 1.1.

	Spontaneous Osteonecrosis	Osteochondritis dissecans	Transient osteoporosis	Secondary osteonecrosis
Patient age group	>55 years	Young-middle age	Young-middle age	<55 years
Associated co-morbidities	None	None	None	Corticosteroid use, renal disease, alcohol excess
Other joint involvement	Rare	Uncommon	Common (in a migratory pattern)	60-90%
Condylar involvement	Usually medial side of medial femoral condyle)	Posterolateral aspect of medial femoral condyle in 70%	Usually lateral femoral condyle	Multiple
Laterality	99% unilateral	Bilateral in ~30%	Usually unilateral	>80% bilateral
Clinical features	Usually sudden onset of severe pain	Insidious onset. Prior knee trauma in 40%	Progressive mechanical pain	Usually insidious onset of pain
Radiological features	Dependent on stage, see table 1.2	Well circumscribed area of subchondral bone separated from femoral condyle by crescent shaped radiolucent line.	Diffuse osteopenia, preservation of joint space. Absence of necrosis on MRI	Lesions much larger and area of osteonecrosis more diffuse than in SONK

Table 1.1: A comparison of SONK and similar pathologies affecting the knee.
Information adapted from: Clanton & DeLee, 1982; Mont et al, 2000; Soucacos, et al, 1997

1.7 Staging of Disease

Koshino et al (1982) described a four-tiered radiological classification of SONK based on plain radiographic appearances, which was later modified by Aglietti et al (1983) to include a fifth stage of disease, describing the appearance of degenerative changes of the knee (table 1.2, figure 1.2). This is the classification system still widely in use to stage SONK.

In stage 1 disease, also described as the incipient stage, patients usually describe significant knee pain which can last for several weeks. Plain radiographs are usually normal. After a variable period, the pain may spontaneously resolve, and patients become asymptomatic, or the disease may progress to subsequent stages (Koshino, 1982).

Stage	Radiographic changes
1	No changes on plain radiographs
2	Flattening of the weight bearing portion of the femoral condyle
3	Flattening of the femoral condyle with sclerotic halo around area of disease
4	Sclerotic ring becomes more defined, with associated subchondral collapse
5	Narrowing of the joint space, osteophyte formation ± tibial subchondral sclerosis

Table 1.2: Stages of SONK as described by Koshino (1982) & later modified by Aglietti (1983).

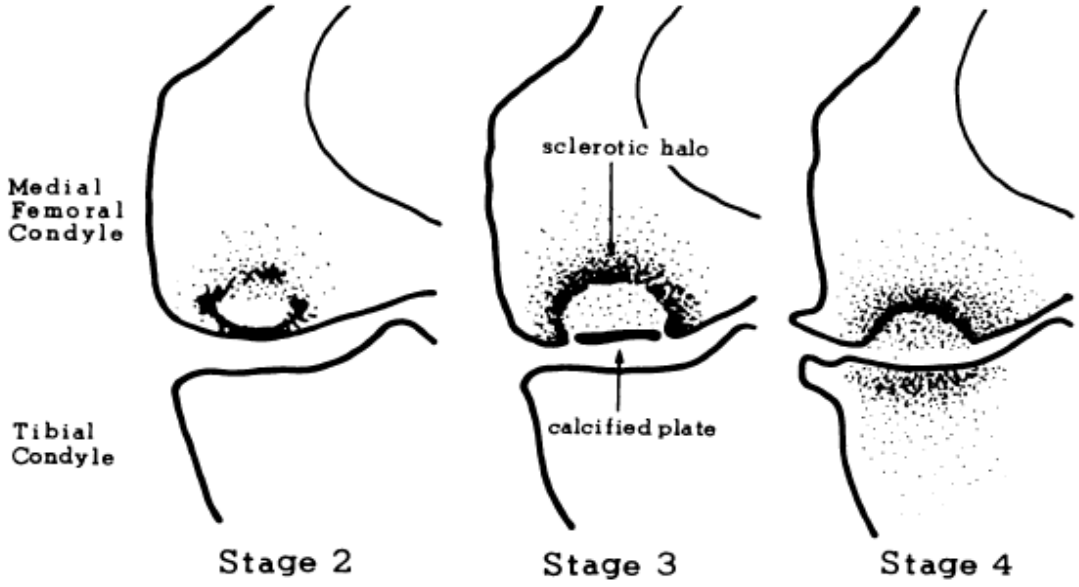

Figure 1-2: Original illustrations of medial femoral condyles with Koshino stage 2, 3 and 4 SONK as they would appear on radiographs (Koshino, 1982). *Permission granted for reproduction from Wolters Kluwer (appendix 11).*

Stage 2 disease is characterised by the appearance of flattening of the medial femoral condyle on plain radiographs, with MRI scanning being able to provide further information regarding the overall size of the area of osteonecrosis (Soucacos, et al., 2004).

The onset of stage 3 disease is defined by the appearance of a sclerotic ring on plain radiographs. This lesion represents segmental necrosis of the subchondral bone with detachment of the overlying articular cartilage (Soucacos, et al., 2004).

Further sclerosis along with articular cartilage destruction and subchondral collapse represents the progression to stage 4 disease, which may extend across the width of the femoral condyle resulting in loss of joint congruity and articular collapse. This may lead to significant malalignment of the knee (Soucacos, et al., 2004).

Patients with stage 5 disease demonstrate characteristic features of degenerative disease of the joint. Plain radiographs show narrowed joint space, osteophyte formation with subchondral sclerosis in some cases (Aglietti, et al., 1983).

For cases of SONK which have progressed to degenerative changes, the arthritis grading systems, described by Ahlbäck (1968) or Ficat and Arlet (1980) can also be used to grade the severity of disease (table 1.3).

Stage	Ahlbäck classification	Ficat & Arlet classification
0	No signs of arthrosis	
I	Diminished joint space	Knees with normal appearance
II	Obliteration of joint space	Cystic or sclerotic lesions, or both. Normal joint contour, no subchondral fractures
III	Erosion <5mm	Crescent sign & subchondral collapse
IV	Erosion between 5-10mm	Reduced joint space, subchondral cysts and osteophytes
V	Erosion >10mm and lateral subluxation	

***Table 1.3: Classification systems used to describe degenerative changes associated with SONK* (Ahlbäck, et al., 1968; Ficat & Arlet, 1980).**

1.8 Natural History and Prognosis

The clinical course of SONK is variable. Some cases spontaneously resolve after a period of rest, analgesia and physiotherapy, whereas others can rapidly progress to joint collapse and subsequent osteoarthritis (Nelson, et al., 2014). This is largely dependent on the stage of disease at presentation, with earlier-disease being more likely to resolve spontaneously (Al-Rowaih, et al., 1993; Mont, et al., 2000). Prognosis has also been linked to the size of the lesion, measured by taking the largest width in the antero-posterior radiograph and the largest length in the lateral radiograph (Lotke & Ecker, 1988). It is thought that small lesions measuring less than 3.5 centimetres squared will typically resolve; intermediate sized lesions (3.5 to 5 cm^2) are less predictable and may or may not progress, whereas large lesions involving more than 5cm^2 of the femoral condyle are more likely to progress to severe disease with condylar collapse, subsequent knee malalignment and secondary arthritis (Muheim & Bohne, 1970; Soucacos, et al., 2004). A second prognostic indicator has been described, using the ratio of the width of the lesion to the width of the affected femoral condyle; if this is more than 40%, patients will often have a poorer outcome, requiring surgical intervention (Ahuja & Bullough, 1978).

1.9 Treatment

Several treatment modalities have been described for SONK, depending on the site, size and progression of osteonecrosis. They represent a wide spectrum, varying from non-operative measures to joint-preserving and joint replacement surgery. For the purposes of this thesis, the term 'joint-preserving treatment' will be used to describe any treatment not involving arthroplasty, both non-operative and operative measures. Regardless of treatment type, the overall aim is to provide a pain-free, mobile knee with good function (Pape, et al., 2010; Patel, et al., 1998).

1.9.1 Non-operative, joint-preserving interventions

Several non-operative treatments have been described for small, early lesions, not affecting the contour of the joint. (Karim, et al., 2015; Mont, et al., 2000). Measures include a combination of symptomatic control with non-steroidal anti-inflammatory medication with or without restriction in weight-bearing. Physiotherapy is also used to strengthen quadriceps, hamstrings and modify forces across the knee (Strauss, et al., 2011).

Medical therapy with bisphosphonates has also been described. Bisphosphonates inhibit bone resorption and are already widely used for various metabolic bone diseases (Russell, 2006). In osteonecrosis, structural defects and failure are thought to result from resorption of the necrotic area of bone during the period of revascularisation, before new bone is formed (Yamamoto & Bullough, 2000). It has been proposed that reducing bone resorption with the use of bisphosphonates during the phase of revascularisation may decrease the incidence of structural failure and joint collapse associated with SONK (Kraenzlin, et al., 2010).

1.9.2 Surgical options for joint preservation

Varying indications for progression from non-operative measures to surgical management have been described, including persistent severe pain, a large lesion, collapse of the femoral condyle and the presence of varus deformity of the knee (Patel, et al., 1998). Surgery aims to provide symptomatic relief and halt disease progression to avoid joint collapse and secondary arthritis (Karim, et al., 2015).

Numerous joint-preserving surgical treatments have been described, including arthroscopy with drilling, perforation and decompression of the lesion; resurfacing the lesion either with microfracture or transplant techniques and high-tibial osteotomy with or without bone grafting (Flynn, et al., 1994; Karim, et al., 2015; Mont, et al., 1997; Mont, et al., 2000).

1.9.2.1 Core Decompression/Drilling of the lesion

Core decompression or drilling of the area of osteonecrosis aims to relieve the increased pressure within the lesion, which is thought to contribute to the local ischaemia (Mont, et al., 1997). It is also thought that this technique will provide a vascular channel into the area of osteonecrosis to promote healing (Zywiel, et al., 2009).

1.9.2.2 Biological Resurfacing: Microfracture

Arthroscopic microfracture of the subchondral bone is a bone-marrow stimulation technique, which was initially developed for the treatment of chondral defects but has since been used in small studies for SONK (Steadman, et al., 2001). This technique involves making small intra-articular holes through the affected area of the joint under direct vision using an arthroscope; the underlying bone marrow brings blood and associated factors into the area of the defect to promote healing (Zywiel, et al., 2009).

1.9.2.3 Biological Resurfacing: Transplant

Osteochondral transplantation into knee defects has also been described; this is commonly known as OATS (osteochondral autograft transfer system). This technique provides autologous hyaline cartilage to resurfacing the defect within the knee and reconstruct the joint surface using a graft with similar biomechanical properties (Karataglis, et al., 2006). A graft consisting of articular cartilage and subchondral bone is harvested from a non-weight bearing portion of the knee, usually the lateral or medial edge of the trochlea, or notch and transplanted to fill the defect (Zywiel, et al., 2009).

1.9.2.4 Unloading Techniques

High tibial osteotomy is a procedure used to offload to affected knee compartment and is often used in the setting of varus or valgus deformity, to realign the knee and redistribute the forces across the joint (Preston, et al., 2005). This technique aims to provide pain relief, while preserving the knee joint itself (Saito, et al., 2014). A wedge of bone is either removed from the proximal tibia, or an opening cut is made, depending on the deformity to offload the affected area and realign the knee. This procedure can be performed alone, or with the addition of intra-articular procedures described above (Koshino, 1982).

1.9.3 Summary of Treatments

There are multiple treatment options available depending on the site, size and progression of osteonecrosis; they represent a wide spectrum, varying from both non-operative and operative joint-preserving measures, to joint replacement surgery. The multitude of treatments available can make it difficult to decide which treatment options to use and when. There is some evidence in the literature describing indications and

outcomes for patients with severe SONK and joint collapse requiring total knee arthroplasty (Bergman & Rand, 1991; Mont M, 2002; Radke, et al., 2005). The difficulty lies with the group of patients who have significant symptoms but do not warrant total knee arthroplasty; there is no consensus or established evidence-base regarding which the most effective joint-preserving treatment is to use in such cases, or recommendations for treatment depending on specific disease stage.

Although there are many potential treatment modalities described in the literature' with the publication of some treatment algorithms (Karim, et al., 2015; Mont, et al., 2000; Zywiel, et al., 2009), a review undertaken at the onset of this study of the British and American Orthopaedic Associations as well as the National Institute for Health and Care Excellence did not reveal any evidence-based guidelines for the treatment of SONK (AAOS, 2015; BOA, 2015; NICE, 2015).

Clinical practice guidelines exist to provide advice on treatment for clinicians, as well as improve care and outcomes for patients with specific conditions (Woolf, et al., 1999). Usually, the initial stages in guideline development involves analysis of existing relevant systematic reviews, or a new systematic review is undertaken if none already exist (Woolf, et al., 2012). At the time of writing, no systematic reviews or consensus studies evaluating both operative and non-operative joint-preserving treatments for SONK were found on a search of the literature. This thesis has therefore set out to identify existing treatments and the evidence to support them using a systematic review, followed by a consensus study to provide further information on which treatments are most suitable for different stages of disease. The thesis then evaluates the findings of these studies in and considers the implications for clinical practice and further research.

1.10 Thesis Aims & Objectives

The aim of this thesis was to evaluate both non-operative and operative joint-preserving treatments for Spontaneous Osteonecrosis of the Knee, to guide clinicians, who may only treat a small number of cases of SONK in making a more informed, evidence-based decision on which treatment is best for their patient.

The objectives of the thesis are as follows:

Research Objective 1

To evaluate the indications and effectiveness of both non-operative and operative treatments for SONK, through assessment of clinical and radiological outcomes.

Research Objective 2

To assess complications and failure rates of joint-preserving treatments, particularly the need for patients to undergo further procedures or joint arthroplasty during the follow-up period.

Research Objective 3

To evaluate existing evidence for the effectiveness of different treatment modalities, both surgical and non-surgical according to severity of disease and establish whether certain treatments are more commonly utilised for specific disease stages.

Two studies were conducted to achieve these research objectives; a systematic review and Delphi study. The combined results of these will be used, where possible, to make recommendations for management and assess the value of future research into the treatment of SONK.

1.11 Outline of the Thesis

This thesis contains four chapters, of which this introduction is the first. Chapter two presents the aims, methodology and results of the systematic review evaluating the effectiveness of joint-preserving treatments for SONK. A discussion of the findings, implications and recommendations for future research then follows. Chapter three gives the Delphi consensus study and includes aims, objectives, and justification for this choice of methodology, results and discussion. Chapter four gives a summary of the overall findings of the thesis and presents the overall conclusions.

CHAPTER TWO: SYSTEMATIC REVIEW OF JOINT-PRESERVING TREATMENTS FOR SPONTANEOUS OSTEONECROSIS OF THE KNEE

Chapter one gave an overview of the underlying pathology of SONK, the diagnosis, staging and potential treatments. It has highlighted that, despite numerous joint-preserving treatments being available, there are currently no clear management pathways or guidelines about which treatment to use when. Before beginning to develop guidelines, it is necessary to review existing evidence for the treatments used for SONK and evaluate their efficacy for different stages of disease. In this chapter, the methods and findings of a systematic review of both operative and non-operative joint-preserving treatments for the treatment of SONK are presented. There is then a discussion regarding the findings of the review, as well as the strengths and weaknesses of the review process, implications and recommendations for future research.

2.1 Aims and Objectives

The systematic review set out to assess the level of existing evidence for joint preserving treatments (both surgical and non-surgical) of SONK. The systematic review objectives are as follows:

1. To identify which joint-preserving treatments for SONK have been evaluated in the literature.
2. To assess the effectiveness of different non-operative treatments for SONK in improving clinical and radiological outcomes and reducing the need for operative intervention.
3. To evaluate the effect of joint-preserving surgery on clinical and radiological outcomes.
4. To review complication and failure rates of both non-operative and operative treatments.
5. To assess the efficacy of treatments according to disease stage.

2.2 Methods

2.2.1 Study Design

The study design was a systematic review; this was chosen over other techniques as the most appropriate method to gather such information. Using pre-defined inclusion criteria reduces the risk of selection bias and individual assessment of included research ensures correct weighting is applied to the most valid research, therefore

producing more reliable findings to inform decision-making (Higgins & Green, 2011; Katikireddi, et al., 2015).

2.2.2 Eligibility Criteria

Condition

Ahlbäck's (1968) definition of SONK, described in section 1.2, was used to identify studies, as this is the most well-known description used in the literature. Descriptions of SONK were analysed in each study to ensure that they were in line with the recognised definition. Studies describing a combination of SONK and post-arthroscopy osteonecrosis of the knee were included as the underlying pathological process, lesion size, location and affected patient population are somewhat similar (Strauss, et al., 2011). Studies with a mixed population, for example, those describing a specific treatment for patients with both spontaneous and secondary osteonecrosis, were only included if it was possible to differentiate the outcomes of the two groups in the results.

Studies solely describing patients with secondary osteonecrosis of the knee were excluded given the differing underlying pathological process, patient population and lesion characteristics (table 1.1).

Types of Participants

All studies with adult patients (over 18 years of age) with SONK were included with no gender or age restrictions. Studies describing patients with all or any of the disease stages as defined by Koshino (table 1.2, section 1.7), Ficat and Arlet (1980) or Ahlbäck (1968) (table 1.3, section 1.7) were eligible for inclusion.

Types of interventions

Studies describing non-operative treatments for SONK, such as lifestyle or activity modification, the use of insoles, physiotherapy, simple analgesia and medical treatment with bisphosphonates were included. Joint-preserving surgical treatments were included for review. This includes, but was not limited to, arthroscopic microfracture, core decompression and drilling, grafting of the lesion (OATS) and offloading procedures, specifically, high tibial osteotomy.

Studies on joint-sacrificing surgery (knee arthroplasty, both uni-compartmental and total knee replacement) were excluded. Studies focusing on alternative and complementary therapies were also excluded, as these are not commonly considered in routine clinical practice.

Comparators

Both studies with comparators and those without were eligible for inclusion in the study, as it was anticipated, from the literature review in the previous chapter, that there would be relatively few comparative studies available.

Research comparing arthroplasty with joint-preserving surgical measures was included, provided the outcomes of the groups were differentiated. In these situations, only the outcomes of the patients undergoing joint-preserving surgery were included. Research comparing non-operative and operative joint-preserving treatments for SONK were sought, along with comparison between different surgical or non-surgical treatments. Studies with arms comparing treatment with placebo or no intervention were also included.

Types of Outcomes

Clinical outcomes were assessed by either improvement or resolution in symptoms or change in function. This was quantified using pre- and post-operative scoring systems assessing pain, functional outcomes and quality of life, either through generic quality-of-life scores, for example, EQ5D (Brooks, 1996), or more specific tools for the knee, for example, the Oxford Knee score (Dawson, et al., 1998). No specific scoring systems were sought, as it was anticipated from the outset that numerous tools would be used, which is often dependent on the country in which the research took place. The focus was on improvement in overall patient and clinical parameters, rather than the type of scoring system used.

Radiological outcomes were recorded; changes in plain radiographs or MRI images before and after interventions were assessed. Any change in the radiological grading of severity of disease, using the different staging classifications (tables 1.2 and 1.3), or change in the size of the osteonecrotic lesion were of interest (Lotke P A, 1982).

Failure was defined as the need for additional intervention following the described treatment. This was further separated into additional joint-preserving surgical intervention, or knee arthroplasty. Other complications were also recorded.

2.2.3 Follow-up

There was no exclusion based on duration of follow-up of the patient cohort. For publications involving the same patient group, but describing different durations of follow-up, the outcomes of each study were reviewed. If these were the same, data from the paper with the longer follow-up time was included.

2.2.4 Types of Studies

Randomised controlled trials were the main focus for inclusion, as these often provide the highest levels of evidence. However, it was anticipated from the outset that few (if any) of these would be available. Comparative methods, such as cohort studies and case-control studies, and non-comparative studies, were therefore also sought. Case series, whether data was collected prospectively or retrospectively, were only included if they described more than five patients for each intervention, as smaller series would be of limited value.

2.2.5 Types of Reports

Articles from peer-reviewed journals were considered; abstracts from conference presentations were excluded, as were PhD theses. Only studies with full texts published in English were included, as resources were not available to accurately translate medical literature to English within reasonable time and costs.
For publications describing different population sizes of the same study, the outcomes of each study were reviewed. If these were the same, data from the paper with the larger population was included. If different outcomes were described, the study information would be collated together and included.

2.3 Search Strategy

The following databases were searched: MEDLINE (OVID); Embase (OVID); Cochrane Library (including CENTRAL, DARE and HTA) and AMED. These databases were chosen as they specifically include orthopaedic and related fields in their subject coverage, are internationally recognised, regularly updated, and they have a longstanding history covering articles as far back as the 1950s (Kluwer, 2017; EBSCO, 2017). The combination of these databases was used to capture the most relevant and up-to-date information related to SONK.

Prior to undertaking the final search, keywords were trialled together to give the most relevant results (for example, knee; knee joint; lower extremity and osteonecrosis; avascular necrosis; aseptic necrosis; bone necrosis respectively). The criteria used in the final search, shown in table 2.1, were found to be the best combination, as this gave the most numerous, but most relevant results from the provisional search. EBSCO was used to search articles in AMED; Embase and MEDLINE were searched together on OVID to minimise duplicate results. There were no limits applied on publication year.

The electronic search strategy shown in table 2.1 was used for MEDLINE, Embase and AMED. The Cochrane Library database was searched using the terms “osteonecrosis” and “knee”.

Keyword	
Knee (SH exploded); Knee joint (SH exploded); Knee (keyword)	
Osteonecrosis (SH exploded); Osteonecrosis (keyword)	OR
Avascular necrosis (keyword)	
Bone necrosis (keyword)	
Aseptic Necrosis (keyword)	
Knee (SH exploded); Knee joint (SH exploded); Knee (keyword)	AND
Osteonecrosis (SH exploded); OR Osteonecrosis (keyword); OR Avascular necrosis (keyword); OR Bone necrosis (keyword); OR Aseptic Necrosis (keyword)	

Table 2.1: Example of search strategy using OVID combined MEDLINE and Embase* search.
*Abbreviations: SH = subject heading (*search terms amended as appropriate for Embase/Emtree subject headings)*

2.4 Study Selection

Screening was performed in three stages independently by two reviewers (MC Killen and CP Charalambous, a supervisor). Titles were screened initially to exclude studies which were not relevant, followed by abstracts against eligibility criteria and then full texts of selected abstracts. Finally, references of included papers were screened to identify any additional texts. It was planned to involve a third reviewer if a decision could not be reached after the full text was reviewed.
Duplicate results between databases were screened using a combination of auto and manual searching. Initially, the tool within OVID for removing duplicates was utilised whilst searching MEDLINE and Embase. Following this, the author and then titles were ordered alphabetically and manually reviewed for duplicates.

2.4.1 Data Extraction

Data was extracted from the included studies using a standardised data collection form (appendix 2); this was developed to ensure that all necessary data was obtained from the selected studies accurately, without introducing reporting bias. The form was designed to obtain general information about the publication, as well as more specific information about the study. An overview of the information gathered is shown in table 2.2.

Study characteristics	Patient characteristics/Treatment/Outcomes
Title	Number eligible and included
Study ID (Author/Year)	Number excluded/withdrawn/lost to follow-up
Study Setting (e.g. Tertiary referral centre)	Number randomised to each group (if applicable)
Aim of Study	Mean age (& range)
Study Design	Gender distribution
Level of Evidence	Stage of disease
Recruitment Method	Details of intervention
Inclusion/Exclusion Criteria	Details of control (if applicable)
Informed Consent	Timing of intervention
Ethical Approval	Primary outcome measure used
Power calculation & statistical methods used	Secondary outcome measure(s) used
	Timing of follow-up (frequency & overall duration)
	Details of results
	Quality assessment/Risk of bias tools

Table 2.2: Summary of data captured from included studies (full data capture proforma in appendix 2).

Each study was reviewed with respect to the type of intervention described, classification system used and disease stage of included patients (where available). Clinical and radiological outcomes and the method of quantifying treatment effect were recorded. The number of patients lost to follow-up was documented and used as part of the risk of bias assessment (discussed below).

A study was considered prospective if it commenced prior to enrolment of the first patient. The relevant data was extracted using the data collection form independently by two reviewers (M Killen and MP Dey, a supervisor), compared and then transferred over to an Excel spreadsheet. A third reviewer was available if there were any conflicting opinions that could not be resolved by discussion.

2.4.2 Quality Assessment & Risk of Bias

Assessment of methodological quality for each included study was undertaken to ensure the results were given appropriate weight according to the strength and reliability of the presented evidence. Level of evidence was assigned in keeping with established criteria (table 2.3), (Phillips, et al., 2009) . This hierarchy was chosen as it

is the most well recognised and utilised in medical literature. For the purposes of this systematic review, only evidence levels 1 to 4 were included.

Level	Type of evidence
1A	Systematic review of randomised controlled trials
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual case-control study
4	Case series (and poor-quality cohort and case-control study)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Table 2.3: A summary of levels of evidence for therapeutic studies and example of each study, from the Centre for Evidence-Based Medicine, http://www.cebm.net.
Abbreviation: RCT=randomised controlled trial

For any randomised controlled trials eligible for inclusion, criteria outlined in the Cochrane Handbook for systematic reviews and interventions (Higgins & Green, 2011) were used to assess quality and risk of bias. The following methodological areas were assessed, with each domain being rated as high, low, unclear (if there was lack of information or uncertainty regarding the risk of bias) or not used:

- "Selection bias: methods of randomisation and concealment of allocation sequence.
- Performance bias: blinding of participants, researchers and outcome assessments.
- Attrition bias: number of participants lost to follow-up (either through withdrawals, drop-outs or changes to protocol)
- Sample size/power calculation: whether performed or adequate explanation of sample size used.
- Results: incomplete outcome data; selective outcome reporting" (Higgins & Green, 2011).

Level of risk of bias within each category was then assigned using the criteria in table 2.4.

Risk of bias	Selection bias	Performance Bias	Attrition Bias	Sample size	Results
Low	Appropriate concealment of allocation	Blinding of participants, researchers and outcome measures	< 5% loss to follow-up	Appropriate explanation of sample size calculation	Full outcome data presented
Moderate	Concealment allocation unclear or inadequate	Blinding unclear	5-20%	Unclear or inadequate sample size calculation	Some minor deficiencies in presentation of outcomes
High	Concealment allocation not used	Blinding not used	>20% lost to follow-up or not recorded	Calculation not recorded or used	Selective reporting of outcomes, incomplete data presented

Table 2.4: Criteria used to determine risk of bias for randomised controlled trials, from the Cochrane Handbook (Higgins & Green, 2011).

For non-randomised studies, criteria outlined by the Methodological Index for Non-Randomised Studies (MINORS) were used to assess quality (table 2.5). MINORS is a validated tool which has a set of criteria to be scored; each domain scores either zero (not reported); 1 (reported inadequately) or 2 (fully reported). An overall global ideal score would be 16 for non-comparative studies or 24 for comparative studies (Slim, et al., 2003). Studies reaching such scores were assessed as having low risk of bias; research with lower scores had increasing risk of bias.

Clearly stated aim?	***For comparative studies:***
Inclusion of consecutive patients?	An adequate control group?
Prospective data collection?	Contemporary groups?
Endpoints appropriate to study aim?	Baseline equivalence of groups
Unbiased assessment of the study endpoint?	Adequate statistical analysis
Follow-up period appropriate?	
Loss to follow-up <5%	
Prospective calculation of study size?	

***Table 2.5: MINORS assessment for non-randomised studies* (Slim, et al., 2003).**

2.4.3 Data Analysis

It was anticipated from the outset that meta-analysis would not be possible from a preliminary search of the available evidence, with limited numbers of randomised controlled trials. Therefore, findings were presented in narrative form including multiple tables and figures to aid in data presentation, where appropriate.

After initial analysis of the results, studies were grouped and sub-analysed according to the treatment type, then stage of disease (using the Koshino or other formal staging systems), if the data was available. This was an important step in working towards evaluating the efficacy of different treatments depending on the severity of disease.

2.5 Systematic Review results

2.5.1 Results of Search

A total of 3501 records were identified from the database searches performed in September 2015. From this initial search, 921 records were removed as duplicates and searches of the references of the included research revealed an additional 7 records, giving a total of 2587 records. Table 2.6 presents the search strategy and number of results for the combined MEDLINE and Embase search; the results of the AMED and Cochrane search are shown in appendix 1.

Keyword		**Number of results**
Knee (SH exploded); Knee joint (SH exploded); Knee (keyword)		120655
Osteonecrosis (SH exploded); Osteonecrosis (keyword)	OR	18224
Avascular necrosis (keyword)		
Bone necrosis (keyword)		
Aseptic Necrosis (keyword)		
Knee (SH exploded); Knee joint (SH exploded); Knee (keyword)	AND	3457
Osteonecrosis (SH exploded); OR Osteonecrosis (keyword); OR Avascular necrosis (keyword); OR Bone necrosis (keyword); OR Aseptic Necrosis (keyword)		

Table 2.6: Search strategy and number of results using OVID MEDLINE and Embase* search.
*Abbreviations: SH = subject heading (*search terms amended as appropriate for Embase/Emtree subject headings).*

Titles were screened for relevance and those obviously not relevant were excluded at this stage. The most common reason for exclusion was due to the cohort relating to osteonecrosis of the hip only, or from stating they were a single case report in the title. Following screening of titles and duplicate removal, 187 were considered potentially relevant and the abstracts were reviewed. There were 41 abstracts considered potentially eligible (or more information was needed) for inclusion by both reviewers on independent review, and after discussion, a further 6 were considered potentially eligible. A total of 47 full manuscripts relating to these abstracts were then reviewed by both reviewers. In total, 21 were considered eligible following review independently, and 20 were included following discussion. A third reviewer was not needed throughout the process. Figure 2.1 shows a summary of the search findings and the exclusions at each stage. Appendix 3 gives information on 27 studies that were excluded following review of the full text.

In summary, 4 were excluded as there were no clinical or radiological outcome measures to quantify their results, 9 were excluded as they only included patients with secondary or steroid-associated osteonecrosis, or other knee pathologies. A further 9 were excluded as they included mixed populations (for example, osteoarthritis and SONK), with no separation of outcomes. Four were excluded as the full text was not available in English. One article was excluded as most of the patient cohort were treated with arthroplasty (figure 2.1).

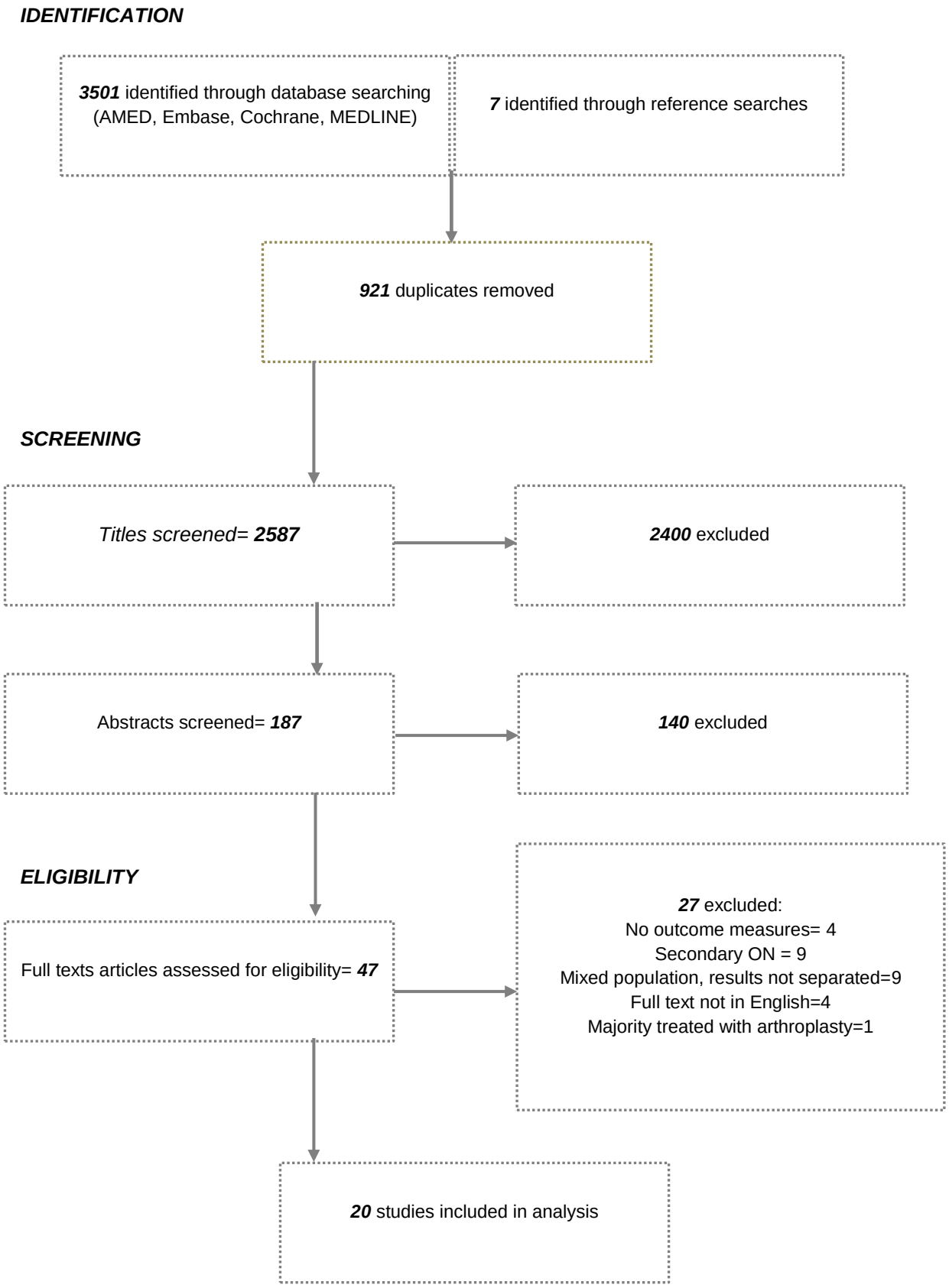

Figure 2.2: Summary of search findings and exclusion at each stage, adapted from PRISMA (Moher, et al., 2009)

2.5.2 Study Characteristics

Twenty studies met the inclusion criteria and were included in the final analysis. There was one unblinded randomised controlled trial (Uchio, et al., 2000). Seven studies were prospective; one was an open-label prospective observational study (Kraenzlin, et al., 2010), the second was a non-randomised comparative prospective study (Marti, et al., 2000) and five were case series with prospective identification of patients (Aglietti, et al., 1983; Johnson, et al., 2014; Jureus, et al., 2012; McDermott, et al., 1985; Miller, et al., 1986) . The remaining twelve studies were either retrospective case series (Akgun, et al., 2005; Valentí Nín, et al., 1998; Yates, et al., 2007), or the nature of the data collection was not stated and so assumed to be to be retrospective (Breer, et al., 2013; Deie, et al., 2008; Duany, et al., 2010; Forst, et al., 1998; Koshino, 1982; Kotani, et al., 2003; Marcheggiani Muccioli, et al., 2013; Takeuchi, et al., 2009; Tanaka, et al., 2009) . The included studies and interventions involved are summarised in table 2.7.

The twenty included studies described outcomes of a total of 465 knees in 442 patients. The mean number of patients included in each study was 22.1 (SD 18.6; range 5-105). The mean age of the patient population (using the mean of the published mean values) was 59.8 years (SD 8.02; range 18-91). All but two studies gave information regarding the gender distribution of included patients (Kraenzlin, et al., 2010; McDermott, et al., 1985); there were 152 males and 250 females, giving a male to female ratio of 1:1.64.

Eleven out of the twenty studies used a combination of plain radiographs and MRI to reach a diagnosis of SONK. The remaining studies used either plain radiographs alone (Johnson, et al., 2014; Koshino, 1982; Miller, et al., 1986; Uchio, et al., 2000), MRI alone (Breer, et al., 2013; Yates, et al., 2007), a combination of MRI findings and histological analysis of tissue (Forst, et al., 1998) or radiographs with scintigraphic studies if needed (Aglietti, et al., 1983). One included study did not describe the method of diagnosis (McDermott, et al., 1985).

Author, Year	Study Design; Level of Evidence	Intervention Described	N=	Knees	Mean age (range)	Mean follow-up (months)
Akgun et al, 2005	Case Series; IV	Arthroscopic microfracture	26	26	48 (16-67)	27
Aglietti et al, 1983	Prospective case Series; IV	Various treatments: protected weight-bearing, analgesia and physiotherapy; arthrotomy and curettage; HTO or TKR	91	105	66 (38-85)	48
Breer et al, 2013	Case Series; IV	Bisphosphonate (Ibandronate) & Vitamin D	5	5	51.8 (±6)	2
Deie et al, 2008	Case Series; IV	Core decompression & artificial bone grafting	12	12	69.6 (59-84)	24.6
Duany et al, 2009	Case Series; IV	Arthroscopic core decompression; OATS	15	15	50 (18-76)	40
Forst et al, 1998	Case Series; IV	Extra-articular drilling	16	16	64.6 (55-81)	35.4
Johnson et al, 2014	Prospective case Series; IV	Autogenous bone grafting	25	26	58 (26-74)	156-228
Jureus et al, 2012	Prospective case series, IV	Bisphosphonate (alendronate)	17	17	68 (48-82)	12
Koshino, 1982	Case Series; IV	High tibial osteotomy ± drilling/bone grafting	36	37	58 (43-78)	61
Kotani et al, 2003	Case Series; IV	OATS	16	16	64.9 (58-74)	67
Kraenzlin et al,2010	Prospective observational study; IV	Bisphosphonates (Pamidronate, Alendronate)	28	28	57.7 (±2.7)	6
Marcheggiani Muccioli et al, 2013	Case Series, IV	Pulsed electromagnetic therapy	28	28	49.8 (46-74)	24.9
Marti et al, 2000	Prospective non-randomised comparative, III	High tibial osteotomy	10	10	59.5 (44-80)	17.5
McDermott et al, 1984	Prospective case Series, IV	Osteochondral allograft	11	11	48	72

Table 2.7: Summary of study design, intervention and patient demographics of included studies

Author, Year	Study Design; Level of Evidence	Intervention Described	N=	Knees	Mean age (range)	Mean follow-up (months)
Miller et al, 1986	Prospective case Series, IV	Arthroscopic debridement	5	5	69.2 (61-80)	31
Takeuchi et al, 2009	Case Series, IV	High tibial osteotomy	30	30	71 (58-82)	37
Tanaka et al, 2008	Case Series, IV	OATS	6	6	54.2 (50-57)	27.7
Uchio et al, 2000	RCT (unblinded) II	Lateral wedge insole	30	31	69 (46-78)	53.5
Valentí Nín et al, 1998	Case Series; IV	Various Treatments: protected weight bearing, analgesia & physiotherapy; arthroscopic washout; arthroscopic drilling; high tibial osteotomy; TKR	21	21	66 (46-91)	41
Yates et al, 2007	Case series, IV	Analgesia, protected weight-bearing or activity restriction	14	20	52 (42-64)	Not stated

Table 2.7: Summary of study design, intervention and patient demographics of included studies (ctd)
Abbreviations: HTO= high tibial osteotomy; OATS=osteochondral autograft transfer system; RCT= randomised controlled trial; TKR=total knee replacement;

Time from diagnosis to treatment was widely variable. One study described that treatment was commenced within 7 days (Marcheggiani Muccioli, et al., 2013). Eleven studies gave numerical values for time from diagnosis to treatment with a range of 0.75-60 months.

Treatments are summarised in table 2.7. With regard to non-operative measures, 3 studies reported outcomes following analgesia with or without physiotherapy and restricted weight bearing (Aglietti, et al., 1983; Valentí Nín, et al., 1998; Yates, et al., 2007), 3 studies described outcomes following bisphosphonate therapy (Breer, et al., 2013; Jureus, et al., 2012; Kraenzlin, et al., 2010), one described results of pulsed electromagnetic field therapy (Marcheggiani Muccioli, et al., 2013) and one reported outcomes following treatment with a lateral wedge insole (Uchio, et al., 2000).

The majority of studies described outcomes following joint-preserving surgical treatment: two described results following either arthroscopic or open joint debridement (Aglietti, et al., 1983; Miller, et al., 1986); four reported outcomes with drilling/decompression of the lesion (Deie, et al., 2008; Duany, et al., 2010; Forst, et al., 1998; Valentí Nín, et al., 1998); one study reviewed results of microfracture (Akgun, et al., 2005) and five reported outcomes after osteochondral transplantation or bone grafting (Duany, et al., 2010; Johnson, et al., 2014; McDermott, et al., 1985; Kotani, et al., 2003; Tanaka, et al., 2009) . Five studies reported results following high tibial osteotomy (Aglietti, et al., 1983; Koshino, 1982; Marti, et al., 2000; Takeuchi, et al., 2009; Valentí Nín, et al., 1998).

Most studies were case series and did not have any comparators. One study was a randomised controlled trial and compared the use of a lateral wedge insole with usual treatment of analgesia and physiotherapy (Uchio, et al., 2000). Three further studies involved some form of comparator: Aglietti et al (1983) described outcomes of various operative and non-operative treatments; Marti et al (1999) compared high tibial osteotomy with a period of partial weight bearing. Koshino (1982) compared outcomes in patients undergoing high tibial osteotomy with or without the use bone grafting. The findings of these different groups have been discussed separately in the appropriate sub-section.

2.5.3 Study Outcome Measures

A variety of tools were used in the included studies to measure outcomes, which can be broadly divided into clinical and radiological outcome measures. The clinical scoring systems can further be sub-divided into general health or quality of life assessments (for example, EQ-5D), assessments specific to pain (for example, Visual Analogue Scale) or more specific knee scores, focusing on knee function and how knee symptoms impact on activities of daily living (for example, Hospital for Special Surgery knee score, American Knee Society Score). Table 2.8 shows each included study and the specific scoring tools used. One study used a scoring tool specific to the type of treatment used, the Fresh Small-Fragment Osteochondral Allografts-Score, which combines a subjective and objective assessment of knee function (McDermott, et al., 1985). A summary of the scoring systems and their parameters is in appendix 5.

A variety of methods were also used to measure radiological parameters. Most included research involved a measurement of the size of the lesion both pre- and post-intervention as a minimum. Some employed more specific measurements to assess joint alignment (for example, femoro-tibial angle), or the Lotke index, which is a ratio expressed as a percentage of joint surface involvement of SONK in relation to the total joint surface of the affected medial or lateral femoral condyle (Lotke P A, 1982).

Author, Year	Clinical outcomes	Radiological Outcomes
Akgun et al, 2005	Lysholm score, activity level of Cincinnati, pain, ROM, effusion, instability, muscle atrophy, satisfaction level	-
Aglietti et al, 1983	Knee evaluation & score; HSS	Radiographic staging
Breer et al, 2013	VAS	Absence of MRI changes
Deie et al, 2008	VAS, JOA scores	Radiographic & MRI changes
Duany et al, 2009	KSS	Radiographic & MRI size of lesion; survival of native knee
Forst et al, 1998	KSS	MRI changes
Johnson et al, 2014	Summary of common complaints Subsequent surgical interventions	-
Jureus et al, 2012	Clinical examination	Lotke index & MRI changes
Koshino, 1982	Ranawat knee score	Radiographic changes
Kotani et al, 2003	JOA score; clinical findings; arthroscopic changes	Radiographic & MRI change
Kraenzlin et al,2010	VAS	MRI ± radiographic staging
Marcheggiani Muccioli et al, 2013	VAS, KSS, Tegner, EQ-5D	MRI staging (WORMS score)
Marti et al, 1999	KSS	Radiographic staging & MRI Changes
McDermott et al, 1984	Fresh Small-Fragment Osteochondral Allografts-Score, Survival of native knee	-
Miller et al, 1986	HSS	Radiographic changes
Takeuchi et al, 2009	KSS & functional score	Radiographic changes: FTA, WBL %.
Tanaka et al, 2008	Lysholm score, histological evaluation	-
Uchio et al, 2000	HSS	Radiographic changes; FTA
Valenti Nín et al, 1998	Ordoñez classification	Radiographic staging
Yates et al, 2007	-	MRI changes

Table 2.8: Clinical and radiological outcome measures used for included studies.
Abbreviations: VAS= visual analogue scale; HSS: hospital for special surgery rating system; KSS= American Knee Society Score; FTA= femorotibial angle; WBL %= weight bearing line percentage; ROM= range of motion; JOA=Japanese Orthopaedic Association.

2.5.4 Risk of Bias

The randomised controlled trial was assessed using the criteria outlined by the Cochrane handbook (Higgins & Green, 2011) and scored as having a high risk of bias in 3 out of the 5 domains; it is an un-blinded trial with no concealment of allocation or power calculation (Uchio, et al., 2000). Given the nature of the intervention, it would not have been possible to blind the participants, but it is not reported whether the assessors were blinded. However, there were no patients lost to follow-up and the results were fully presented, so this study had low risk of bias for these areas. The outcomes and ratings are summarised in table 2.9; as 3 out of 5 areas scored as high, it can be concluded that the overall risk of bias for this study is high.

Domain Assessed	Outcome	Level of risk
Selection bias	Concealment allocation not used	High risk
Performance Bias	Blinding not used for either participants or assessors	High risk
Attrition bias	0% loss to follow-up	Low risk
Sample size	Sample size calculation not reported	High risk
Results	Full outcome data presented	Low risk

***Table 2.9: Risk of Bias assessment for the included randomised controlled trial evaluating use of lateral wedge insole compared with analgesia and physiotherapy* (Uchio, et al., 2000).**

Non-randomised controlled trials were assessed for their risk of bias using the MINORS criteria (summarised in table 2.5). For non-comparative studies, an ideal score would be 16, whereas, for comparative research, an ideal score would be 24 to demonstrate a low risk of bias (Slim, et al., 2003). The scoring for comparative studies is summarised first in table 2.10, followed by non-comparative studies in table 2.11.

Author, Year	Study Design	Treatment Described	MINORS score
Aglietti et al, 1983	Case Series (prospective)	Various treatments	9/24
Marti et al, 1999	Prospective, non-randomised comparative study	High tibial osteotomy versus non-operative treatment with 3 months partial-weight bearing	18/24
Koshino, 1982	Case series	High tibial osteotomy with or without drilling/bone grafting	10/24

Table 2.10: MINORS scoring for included comparative studies.

As demonstrated in table 2.10, none of the included comparative studies reached a score of 24, with values ranging from 9 to 18, demonstrating high risk for all the included studies. A full breakdown of the scoring for each domain in shown in appendix 4.

Author, Year	Study Design	Treatment Described	MINORS score
Akgun at al, 2005	Case Series	Arthroscopic microfracture	10/16
Breer et al, 2012	Case Series	Bisphosphonate	9/16
Deie et al, 2008	Case Series	Core decompression & artificial bone grafting	9/16
Duany et al, 2009	Case Series	Arthroscopic core decompression; OATS	7/16
Forst at al, 1998	Case Series	Extra-articular drilling	7/16
Johnson et al, 2014	Case Series (prospective)	Autogenous bone grafting	8/16
Jureus et al, 2012	Case series (prospective)	Bisphosphonates (alendronate)	12/16
Kotani et al, 2003	Case Series	OATS	8/16
Kraenzlin et al, 2010	Prospective non-comparative observational study	Bisphosphonates	11/16
Marcheggiani et al, 2012	Case Series	Pulsed electromagnetic therapy	16/16
McDermott et al, 1984	Case Series (prospective)	Osteochondral allograft	11/16
Miller et al, 1986	Case Series (prospective)	Arthroscopic debridement	10/16
Takeuchi et al, 2009	Case Series	High tibial osteotomy	8/16
Tanaka et al, 2009	Case Series	OATS	9/16
Valentí Nín et al, 1998	Case Series	Various Treatments	7/16
Yates et al, 2007	Case series	Analgesia, protected weight-bearing	7/16

Table 2.11: MINORS scores for included non-comparative studies.

Only one of the non-comparative studies achieved an ideal score of 16 (Marcheggiani Muccioli, et al., 2013). The retrospective nature and lack of calculation of study size in most of the included studies automatically led to a reduced score, and very few discussed whether consecutive cases were included. In addition to this, only one study used an independent assessor to evaluate outcomes of the patient cohort (Marcheggiani Muccioli, et al., 2013). The remaining studies have only involved the

authors to assess the endpoints, potentially increasing bias and resulting in a lower than ideal global score in the 16 non-comparative studies.

2.5.5 Effect of intervention on outcome

This section sub-analyses included research, firstly by treatment type, then by stage of disease to try and evaluate if certain treatments are more effective depending on the severity of SONK.

2.5.5.1 Clinical outcome by treatment type: Non-operative measures

Six studies reported outcomes following non-operative measures (table 2.12), either with insoles or electromagnetic therapy (Uchio, et al., 2000; Marcheggiani Muccioli, et al., 2013), or with medical treatment using different bisphosphonates (Breer, et al., 2013; Jureus, et al., 2012; Kraenzlin, et al., 2010). Three studies have treated patients with analgesia, with or without weight-bearing restriction and physiotherapy (Aglietti, et al., 1983; Valentí Nín, et al., 1998; Yates, et al., 2007).

Lateral wedge insole

One un-blinded randomised controlled trial evaluated a lateral wedge insole for patients with early disease (Uchio, et al., 2000). Thirty participants were randomised to either a patient-specific insole or no insole. Both groups were treated with a period of non-steroidal anti-inflammatory medication and physiotherapy. There was a significant improvement in the clinical scores of the treatment group compared to the placebo group (HSS score). Radiological improvement in the treatment group was also observed (size of the necrotic area), compared to the placebo group, whose radiological parameters worsened. The authors therefore concluded that the use of a lateral wedge insole is a useful treatment for early stage disease. Complications and treatment failures were not reported in this study.

Pulsed electromagnetic therapy

One case series evaluated self-administered pulsed electromagnetic therapy in the treatment of 30 consecutive patients with early stage SONK (Marcheggiani Muccioli, et al., 2013). Authors found a significant improvement in VAS, KSS and EQ-5D scores at 6 months. Radiological parameters also improved, with significant reduction of total WORMS score and mean femoral bone marrow lesion area on MRI. Four patients required knee arthroplasty at the end of the study (24 months), giving a failure rate of 14.3%.

Bisphosphonate treatment

Three case series evaluated the effectiveness of bisphosphonates (Breer, et al., 2013; Jureus, et al., 2012; Kraenzlin, et al., 2010). Breer et al (2012) reviewed ibandronate with high dose vitamin D supplementation in 5 consecutive patients with early stage disease. Remission of MRI findings was observed in all cases and there was a statistically significant improvement in VAS scoring at both 4 and 8 weeks; the study follow-up was limited to 8 weeks.

Jureus et al (2012) evaluated the outcomes of 17 patients with SONK after administration of weekly oral alendronate for either minimum of 6 months, or until the lesion regained bone density on plain radiography or MRI. Outcomes were divided into three groups; 10 out of 17 patients did not go on to develop arthritis, 4 developed arthritis without joint collapse and 3 developed arthritis and joint collapse. Of the group with joint collapse, 2 out of 3 stopped their treatment prematurely due to side effects and both required knee arthroplasty, the final patient progressed to joint collapse during treatment but had mild symptoms so did not require any further intervention. Clinical outcomes and Lotke ratio (Lotke P A, 1982) evaluating the lesion size were measured as part of the methodology but are not fully reported.

Kraenzlin et al (2010) evaluated intravenous pamidronate followed by oral alendronate in 28 patients. Anti-inflammatory and other analgesics were given throughout. There was a rapid reduction in VAS scoring after 4-6 weeks, with a decrease of 80% by 6 months. Complete symptom resolution was observed in 15 out of 28 patients at 6 months. Bone marrow oedema either resolved (18 patients) or substantially reduced on MRI scan. Treatment failed in 2 patients, who required knee arthroplasty.

In summary, bisphosphonate treatment appears to be effective in reducing symptoms and improving radiological changes in these small studies. From the two studies reporting complications, four patients went on to require knee arthroplasty during the study period, giving an overall failure rate of 8.9%.

Intervention	1st author, *study design*	Comparator (if applicable)	N=	Main clinical outcome used	Pre- treatment value (mean)	Post- treatment value (mean)	Need for additional intervention/surgery n= (%)
Lateral wedge insole	Uchio *Unblinded RCT*	Analgesia and physiotherapy	18*	HSS	Treatment: 58.6 No treatment: 60.8	Treatment: 69.9 No treatment: 57.8	Not reported
Pulsed EM therapy	Marcheggiani *Case series*	n/a	28	VAS	7.3	2.7	4 (14.3%)
Bisphosphonates	Breer *Case series*	n/a	5	VAS	7.4	0.8	Not reported
	Jureus *Case series*	n/a	17	Radiographic outcomes only			2 (11.8%)
	Kraenzlin *Observational study*	n/a	28	VAS	8.2	2.0	2 (7.1%)
Supportive measures: analgesia, physiotherapy	Aglietti *Case series*	Various treatments**	22	HSS	70	82	Not reported
	Valentí Nín *Case series*	Various treatments**	6	Ordoñez	See text		1 (16.7%)
	Yates *Case series*	n/a	14	Radiographic outcomes only			0

Table 2.12: Summary of included studies evaluating non-operative measures for the treatment of SONK.
*Abbreviations: EM- electromagnetic; HSS- Hospital for Special Surgery Knee Score; VAS- visual analogue scale; *=number in treatment group; **=comparators discussed in their respective sections.*

Patients treated with supportive measures

Three studies described patients undertaking a period of supportive measures either as their entire cohort (Yates, et al., 2007), or as part of larger case series (Aglietti, et al., 1983; Valentí Nín, et al., 1998), the results of the control arm of the randomised controlled trial is also discussed here (Uchio, et al., 2000).

Yates et al (2007) evaluated the MRI outcomes of 14 patients with early-disease treated with a period of analgesia (paracetamol and non-steroidal anti-inflammatory medication) and either weight-bearing relief or activity restriction with full weight-bearing until their symptoms resolved. All patients made complete symptomatic recovery at a mean period of 4.8 months (range 3-8 months), with full resolution of MRI changes in all cases (mean time to resolution 8 months, range 3-18 months).

Aglietti et al (1983) described long-term results of 105 knees in 91 patients, treated with different measures. Twenty-two underwent a period of weight-relief, analgesia and isometric quadriceps exercises. The Hospital for Special surgery (HSS) knee score (appendix 5) improved from a mean of 70 (range 48-87) to 82 (range 41-98) following treatment, which was just statistically significant ($p<0.05$). Radiologically, the lesion resolved in 1, reduced in size in 8, remained unchanged in 7 and worsened in 6 patients. Arthritis was present in eleven patients prior to treatment; it remained unchanged in 9, but worsened in 2. Arthritis developed in the remaining 11 knees, giving an overall deterioration of 59%. Failure of treatment requiring further intervention was not reported.

Valentí Nín et al (1998) described outcomes of a subgroup of 6 patients undertaking a period of weight-relief, anti-inflammatory medication and straight leg raises, as part of a larger case series. According to the Ordoñez classification (appendix 5), one patient had a poor outcome, one was fair, and four had good outcomes. One patient required a uni-compartmental knee replacement at a later stage, giving a complication rate of 16.7%, higher than the other patients in this study (0% for arthroscopic washout and high tibial osteotomy, 12.5% for drilling).

The control arm of the study by Uchio et al (2000) described outcomes of patients treated with analgesia and physiotherapy only. There was a slight deterioration in their HSS score, along with an increase in the size and percentage ratio of the lesion, compared to the group treated with an insole, who demonstrated improvements in all domains.

Summary of Failures of Non-Operative Measures

Failure of described treatment was defined by progression of disease and need for further intervention, either additional joint-preserving procedures or knee arthroplasty. Table 2.13 gives a summary of the overall failure rates described for the non-operative measures discussed above. Five out of the 8 studies describing non-operative measures specifically stated their failure rates, the remaining 3 did not describe any need for further surgery nor did they explicitly state no failures occurred. Need for additional joint-preserving surgical procedures was not required in any patients, whereas total knee replacement was required in 9 out of 93 cases where failure was described, giving an overall failure rate of 9.7% (range 0-16.7%).

First author, year ***study design***	**N=**	**Treatment**	**Need for further surgery (native joint) (%)**	**Need for TKR (%)**
Aglietti, 1983 *Case series*	22	Supportive measures	None described	
Breer, 2013 *Case series*	5	Ibandronate & vitamin D	None described	
Jureus, 2012 *Case series*	17	Bisphosphonates	0	2 (11.8%)
Kraenzlin, 2010 *Case series*	28	Bisphosphonate	0	2 (7.1%)
Marcheggiani, 2013 *Case series*	28	Pulsed EM therapy	0	4 (14.3%)
Uchio, 2000 *RCT*	18 vs 13	Lateral wedge insole vs no insole	Not described	
Valentí Nín, 1998 *Case series*	6	Supportive measures	0	1 (16.7%)
Yates, 2007 *Case series*	14	Supportive measures	0	0

Table 2.13: Summary of overall failure rates for non-operative measures

Summary of non-operative measures

This section has described the results of eight studies describing non-operative treatments. An initial period of conservative treatment with weight-bearing relief, analgesia and physiotherapy appears to be effective in the described case series. However, the control arm of the randomised controlled trial does not show the same positive outcomes, with this group having poorer outcomes than the group treated with a lateral wedge insole (Uchio, et al., 2000).

2.5.5.2 Clinical outcomes by treatment type: arthroscopic Interventions, drilling and grafting procedures

There were eleven studies investigating outcomes following arthroscopic or open interventions, along with various debridement, drilling or grafting techniques. Table 2.14 summarises the study designs and clinical outcomes of these studies.

Arthroscopy with washout, debridement/currettage or drilling

Valentí Nín et al (1998) described arthroscopic washout for 4 patients and arthroscopy and drilling for 8 patients as part of a larger series. In the washout group, one patient had an excellent, two had good and one had a fair outcome according to the Ordoñez classification; no further procedures were needed. Radiographic outcomes (Koshino staging) remained static in 3; one deteriorated, but still had a good outcome.
For arthroscopy and drilling, outcomes were excellent in 2, good in 4, fair in 1 and poor in 1. Two out of 8 patients demonstrated radiographic progression, but both had excellent outcomes. One patient required further surgery in the form of high tibial osteotomy.

The outcomes of 5 patients treated with arthroscopic debridement were described by Miller et al (1986). The Hospital for Special surgery scores improved from 52 (50-55) to 81.4 (53-95) post-operatively. Two patients required further surgery; one had a repeat arthroscopy and debridement due to recurrence of pain and one underwent high tibial osteotomy for persisting symptoms.

Aglietti et al (1983) described outcomes of 11 patients undergoing arthrotomy and curretage as part of a larger case series. There was a clinical improvement, but this was not statistically significant (table 2.14). Radiologically, the osteonecrotic lesion disappeared in 1 patient, improved in 1, remained unchanged in 8 and worsened in one. No adverse outcomes or need for further surgery was reported throughout this study for any of the treatment groups.

Arthroscopic Microfracture

Akgun et al (2005) presented outcomes of 26 patients treated with arthroscopic microfracture after 4 months of non-operative measures; 3 patients also underwent high tibial osteotomy due to associated varus malalignment. Both Lysholme scores and the activity level of Cincinatti showed significant improvements post-operatively ($p<0.001$) (table 2.14). Radiographic outcomes (Koshino classification) remained static in 16, 4 worsened and 6 improved. The authors found no correlation between the pre-operative size of the lesion and the functional outcome. No adverse outcomes or failures were reported.

Intervention	1st Author, study design	N=	Main clinical outcome	Pre-op value, (mean)	Post-op value, (mean)	Additional surgery, n= (%)
Arthroscopic Washout	Valentí Nín, *case series*	4	Ordoñez	N/A	Excellent (n=1); good (n=2); fair (n=1)	0
Arthroscopic debridement	Miller, *case series*	5	HSS	52	81.4	2 (40%)
Arthrotomy & curettage	Aglietti, *case series*	11	HSS	69	79	Not described
Arthroscopy & drilling	Valentí Nín, *case series*	8	Ordoñez	N/A	Excellent (n=2); good (n=4); fair (n=1); poor (n=1)	1 (12.5%)
Arthroscopic microfracture	Akgun, *case series*	26	Lysholme score Activity level of Cincinnati	57 6	90 13.54	0
Core decompression ± bone grafting	Deie, *case series*	12	VAS JOA	8.4 43	1.5 80	2 (16.7%)
	Duany, *case series*	7	KSS	61.7	76	2 (28.6%)
	Forst, *case series*	16	KSS	74	187.2	Not reported
Autogenous bone grafting	Johnson, *case series*	25	Summary of common complaints	See text		13 (52%)
Osteochondral autograft transfer (OATS)/Osteochondral Allograft	Duany, *case series*	9	KSS	57.9	80.2	2 (22.2%)
	Kotani, *case series*	16	JOA	68.1	88.8	0
	McDermott *Case series*	11	Fresh Small-Fragment Osteochondral Allografts-Score	3 (27%) classified as successful		8 (73%)
	Tanaka, *case series*	6	Lysholme score	54.7	92.3	Not reported

Table 2.14: Summary of included studies evaluating arthroscopic measures, drilling and grafting for the treatment of SONK.

Abbreviations: HSS=hospital for special surgery knee score; JOA= Japanese orthopaedic association knee score; KSS= American knee society score; VAS=visual analogue score.

Core decompression with bone grafting or Osteochondral Autograft Transfer (OATS)

Deie et al (2008) described clinical and radiological outcomes in 12 patients following core decompression and bone grafting. There was a significant improvement in both JOA scores ($p<0.001$) and VAS ($p<0.05$) post-operatively. Two patients underwent repeat arthroscopy, the indication being persisting swelling in one and not reported in the other. There was radiological progression according to the Kellegren-Lawrence classification in 4 patients, the others remained static (Kellegren & Lawrence, 1957).

Duany et at (2009) reported a series of 15 patients who had failed period of non-operative management. Seven underwent arthroscopy and extra-articular core decompression, with a mean improvement in KSS from 61.7 to 76 post-operatively. Five out of 7 cases were sucessful (71.4%). Two patients demonstrated radiological deterioration; 1 patient underwent OATS at one year due to persistent symptoms and one patient required knee arthroplasty for disease progression.
Nine patients had the OATS procedure (1 patient was included in both groups after poor result with decompression); KSS improved from 57.9 to 80.2 post-operatively. Seven out of 9 cases were successful (77.8%) and one patient demonstrated radiological progression. One patient required a repeat arthroscopy for mensical tear and the other underwent knee arthroplasty for disease progression. The OATS group was therefore very slightly more sucessful with a lower rate of disease progression compared to the core decompression group.

Forst et al (1998) described outcomes of extra-articular core decompression in 16 patients, all of whom had failed a course of non-operative mangement. Mean KSS improved from 74±38.2 to 187.2± 52.1 post-operatively. One patient had a post-operative pulmonary embolus; this was the only complication reported. Radiologically, there was complete normalisation of bone marrow signal on repeat MRI in all but one patient at 6 months; the remaining patient had progression of disease with desctruction of the femoral condyle, but it is not reported whether further intervention was needed.

Autogenous bone grafting, Osteochondral Autograft (OATS) and Osteochondral Allograft

Johnson et al (2014) reported the outcomes of 25 patients (26 knees) following autogenous bone grafting; 15 of the 26 knees also had high tibial osteotomy (HTO). Nine patients were available for long-term clinical follow-up and their outcomes were reported as improved (7), worse (1) or no response (1). Seven patients in the HTO with grafting group and 3 patients in the grafting only group went on to have a total knee replacement; 1 patient required a second arthroscopy and 1 patient adhesiolysis giving

an overall reoperation rate of 48%.

The outcomes of 16 patients treated with osteochondral autografting were presented by Kotani et al (2003); 4 patients in this group also had HTO. The Japanese Orthopedic Association (JOA) clinical scores improved from a mean of 68.1 (60-75) to 88.8 (80-100) post-operatively. All patients had planned repeat arthroscopy at 18-21 months following index procedure. Both repeat arthroscopy and post-operative radiographs demonstrated graft acceptance in all cases. No adverse outcomes or failures were reported in this series.

McDermott et al (1985) presented the long-term results of fresh osteochondral allografts for different knee pathologies. There were 11 patients with SONK. Patients also had realignment surgery if necessary but the authors do not state how many, if any of the SONK group required this. The procedure was deemed to be successful in the absence of re-operation and if the fresh osteochondral allograft clinical scoring tool was ≥75 (appendix 5). Using these parameters, 3 out of 11 (27%) were sucessful, but the number of re-operations is not presented.

Tanaka et al (2008) reported outcomes of 6 patients undergoing autogenous osteochondral grafting; 5 out of 6 patients also had an arthroscopic mensicectomy. Lysholme scores improved from a mean of 54.7 (47-70) to 92.3 (85-100) at final follow-up. No radiological outcomes, complications or failures were reported.

Failures of Arthroscopic treatments, drilling and grafting

Table 2.15 gives an overall summary of the re-operation rate and failures requiring arthroplasty. Eight out of eleven studies described complications and failures; rates were widely variable ranging from zero to 40% for both further joint-preserving surgery and arthroplasty. The highest failure rate was 73% described my McDermott et al (1985), but the authors did not define what constituted failure and it is unclear how many of these patients had further interventions. In total, 22 out of the 112 patients with complications described required further intervention, giving an overall failure rate of 19.7% for this group.

Summary of arthroscopic interventions, drilling and grafting

Over half of the studies included in the systematic review are described in this section, with widely variable techniques. Aside from the outcomes described by Johnson et al (2014), who reported a re-operation rate of 48% and the failure rate of 73% described by McDermott et al (1985), the majority of the arthroscopic techniques and grafting procedures provided reasonably promising results, with overall improvements in clinical outcomes. It is important to note, however, that despite this section including the

highest number of included studies, they are limited to case series only without any higher level evidence to support the results.

Author, *study design*	**N=**	**Treatment**	**Need for further surgery (native joint) (%)**	**Need for TKR (%)**
Akgun *Case series*	26	Microfracture	0	0
Aglietti *Case series*	11	Arthrotomy and curettage	None described	
Deie *Case series*	12	Decompression & bone grafting	2 (16.7%) repeat arthroscopy	0
Duany *Case series*	7	Core decompression	1 (14.3%) OATS	1 (14.3%)
	9	OATS	1 (11.1%) arthroscopy and meniscal debridement	1 (11.1%)
Forst *Case series*	16	Extra-articular drilling	Not described	
Johnson *Case series*	25	Autogenous bone grafting	3 (12%): 2 arthroscopy± debridement, 1 manipulation & adhesiolysis	10 (40%)
Kotani *Case series*	16	Osteochondral autograft	0	0
McDermott *Case series*	11	Osteochondral allograft	8 (73%) overall failure, not specific to re-operations	
Miller *Case series*	5	Arthroscopic debridement	2 (40%): 1 repeat arthroscopy, 1 HTO	0
Tanaka *Case series*	6	Osteochondral autograft	Not described	
Valentí Nín *Case series*	4	Arthroscopic washout	0	0
	8	Arthroscopy and drilling	1 (12.5%) HTO	0

Table 2.15: Summary of failure rates of arthroscopic interventions, drilling and grafting of lesions

2.5.5.3 Clinical outcomes by treatment type: Realignment surgery (high tibial osteotomy)

Aglietti et al (1983) described the outcomes of 31 patients undergoing HTO; 21 also had an arthrotomy, with either fragment removal and drilling (n=18) or drilling alone (n=3). Hospital for Special surgery scores significantly improved ($p<0.001$, table 2.16). Radiologically, the lesion disappeared in 3, improved in 15, remained unchanged in 11 and worsened in 2. Arthritis was present pre-operatively in 22 patients; it remained unchanged in 17, worsened in 5 and developed in 4 patients, giving a deterioration in 29%. Radiographs were also analysed to determine alignment correction using the femorotibial angle (FTA). Knees with a mean correction of 170 degrees (range 165-

174º) had statistically significant improved outcomes compared to those whose FTA was either greater than 174 or less than 165 degrees ($p<0.01$). Two patients in this group had failure of treatment requiring knee arthroplasty.

First author, study design	Comparator	N =	Main clinical outcome	Pre-op value (mean)	Post-op value (mean)	Total re-operations
Aglietti *Case series*	N/A	31	HSS	58	79	2 (6.5%)
Koshino *Case series*	HTO vs HTO with grafting ± drilling	36	Ranawat score	HTO: 53 Graft: 58 Drilling: 56	HTO 87 Graft: 96 Drilling: 88	4 (11.1%)
Marti *Non-randomised comparative study*	HTO vs PWB	10	KSS	HTO:132 PWB:139	HTO:163 PWB:140	Not reported
Takeuchi *Case series*	N/A	30	KSS	51	93	0
Valentí Nín *Case series*	Various treatments	2	Ordoñez	N/A	Both excellent	0

Table 2.16: Study design, clinical outcomes and failure rates of studies describing outcomes of HTO. *Abbreviations: HTO: high tibial osteotomy; HSS= Hospital for special surgery score; KSS= American knee society score; PWB=partial weight-bearing.*

Koshino (1982) presented 36 patients (37 knees) undergoing HTO alone (n=14), HTO with drilling (n=17) or HTO with bone grafting (n=6). There was a statistically significant difference between pre- and post-operative scores for each type of surgical procedure and for each stage of osteonecrosis (table 2.16). The scores for those treated with HTO and bone grafting were significantly higher than the other groups. Radiologically, the lesion disappeared in 13, improved in 17 and remained unchanged in 7. There was a statistically significant increased score in patients who had a FTA between 164 and 173 degrees, compared to those outside this range ($p<0.05$). Three patients required additional procedures on their native knee and one patient underwent knee arthroplasty.

Marti et al (2000) conducted a non-randomised comparative study evaluating outcomes of HTO versus partial-weight bearing and analgesia for 3 months. Patients were given the option of which treatment modality they would prefer; 6 opted for HTO and 4 for conservative treatment. There was a statistically significant increase in KSS in the HTO

group (p=0.031) compared to the conservatively managed group (table 2.16). There was also a statistically significant difference in reduction of oedema, but not area of necrosis between the two groups on MRI post-treatment. No complications or failures were described for either group.

Takeuchi et al (2009) described the outcomes of 30 patients following HTO, combined with removal of damaged cartilage and drilling of the lesion. A bone substitute (Tomofix™) was used to fill the osteotomy defect to permit early weight-bearing. There was a statistically significant increase in KSS post-operatively ($p<0.01$). Radiologically, the FTA improved from 181±2.9º pre-operatively to 170±1.8º post-operatively. There was evidence of healing of the articular cartilage in 24 out of 30 patients during repeat arthroscopy. No patients required any additional surgery.

Valentí Nín (1998) described the outcomes of 2 patients undergoing HTO as part of a larger case series. Both patients were reported to have excellent clinical outcomes (Ordoñez classification), despite radiological progression in one of the patients.

Summary of overall failures of High Tibial Osteotomy

A summary of overall complication rates for HTO is given in table 2.17. Four out of 5 studies reported the number of patients requiring either additional surgery or knee arthroplasty, with a mean total re-operation rate of 6.1%, this ranged from zero to 8.1% for further native joint surgery and zero to 6.5% need for total knee replacement. These results represent some of the lowest complication rates of all the treatment modalities.

Summary of High Tibial Osteotomy

Overall, the included studies describing outcomes of HTO show positive results for disease of varying stages, with some of the lowest complication rates of all the treatment types. There is large variation in techniques, fixation methods and rehabilitation protocols between authors, along with the use of additional intra-articular procedures in some patients. Most authors, however, highlight the overall importance of adequate alignment correction, to sufficiently offload the affected compartment, aiming for a FTA of approximately 170º to achieve the best outcomes.

Author, *study design*	N=	Treatment	Need for further surgery (native joint) n=, (%)	Need for TKR n=, (%)
Aglietti *Case series*	31	HTO	0	2 (6.5%)
Koshino *Case series*	37	HTO ± drilling/ bone grafting	3 (8.1%); 1 arthrotomy for loose body, 2 metalwork removal	1 (2.7%)
Marti *Non-randomised comparative study*	6 vs 4	HTO vs PWB	None described	
Takeuchi *Case series*	30	HTO	0	0
Valentí Nín *Case series*	2	HTO	0	0

Table 2.17: Summary of overall failure rates described for high tibial osteotomy.
Abbreviations: HTO= high tibial osteotomy; PWB= partial weight-bearing; TKR= total knee replacement.

Summary of clinical outcomes for all treatment types

In summary, the 20 studies demonstrate a huge spectrum of techniques with variable outcomes. Eight studies presented outcomes of non-operative measures, either observation, bisphosphonate treatment, electromagnetic therapy or insoles, one of which was a randomised controlled trial (Uchio, et al., 2000). Five of these eight studies described the need for additional surgical treatment with a mean operation rate of 9.7% (range 0-16.7%). A further seven studies, all of which were case series, described washout of the knee, with either debridement, curettage with or without microfracture, drilling or core decompression; the mean re-operation rate in this group was 11.3% (range 0-40%). Various forms of grafting were described in 5 studies, 3 out of 5 described re-operation rates with a mean of 19.6% (range 0-73%). Finally, five studies demonstrated their outcomes of high tibial osteotomy, four of which presented their re-operation rates, which were the lowest of all the treatment groups with a mean of 6.1% (range 0-11.1%). Table 2.18 gives an overall summary of clinical, radiological outcomes and failure rates of the different treatment groups.

Intervention	**1st author, *study design***	**N=**	**Overall improvement in clinical scoring?**	**Overall improvement in radiological outcome?**	**Need for further surgery n=, (%)**
Bisphosphonates	Breer, *case series*	5	Yes	Remission of disease in all cases	Not reported
	Jureus, *case series*	17	Radiographic outcomes only	24% developed arthritis, further 18% arthritis and joint collapse	2 (11.8%)
	Kraenzlin *Observational study*	28	Yes	Resolution or improvement in all cases	2 (7.2%)
Pulsed EM therapy	Marcheggiani, *case series*	28	Yes	Overall improvement in WORMS scoring and size of lesion	4 (14.3%)
Lateral wedge insole	Uchio, *RCT*	18*	Yes	Overall improvement in lesion size	Not reported
Supportive measures: analgesia, physiotherapy	Aglietti*, case series*	22	Yes	Resolution/improvement in 41%, unchanged in 32%, worse in 27%	Not reported
	Valentí Nín*, case series*	6	67% good	No change in stage for 83%, remaining 17% progressed	1 (16.7%)
	Yates, *case series*	14	Resolution in all	Remission of disease in all cases	0
Arthroscopic Washout	Valentí Nín*, case series*	4	Excellent, good or fair outcome in all	No change in stage for 75%, remaining 23% progressed	0
Arthroscopic debridement	Miller*, case series*	5	Yes	No change in stage for any patient	2 (40%)
Arthrotomy & curettage	Aglietti*, case series*	11	Yes	Resolution/improvement in 18%, unchanged in 73%, worse in 9%	Not described
Arthroscopy & drilling	Valentí Nín*, case series*	8	Excellent 25%; good 50%; fair 12.5%; poor 12.5%	No change in stage for 75%, progression in 25%	1 (12.5%)

Table 2.18: Summary of clinical, radiological outcomes and failure rates of all included studies

Intervention	1st author, *study design*	N=	Overall improvement in clinical scoring?	Overall improvement in radiological outcome?	Need for further surgery n=, (%)
Arthroscopic microfracture	Akgun*, case series*	26	Yes	Improvement in 23%, unchanged in 62%, progression in 15%	0
Core decompression ± bone grafting	Deie*, case series*	12	Yes	Unchanged in 67%, progression in 33%	2 (16.7%)
	Duany*, case series*	7	Yes	Progression of disease in 29%	2 (28.6%)
	Forst*, case series*	16	Yes	Resolution in 94%, 6% progression	Not reported
Autogenous bone grafting	Johnson*, case series*	25	No	None described	13 (52%)
Osteochondral autograft transfer/Osteochondral Allograft	Duany*, case series*	9	Yes	Progression of disease in 11%	2 (22.2%)
	Kotani*, case series*	16	Yes	Graft acceptance in 100%,	0
	McDermott, c*ase series*	11	No	None described	8 (73%)
	Tanaka*, case series*	6	Yes	None described	Not reported
High Tibial Osteotomy	Aglietti, c*ase series*	31	Yes	Resolution/improvement in 58%, unchanged in 35.5%, progression in 6.5%	2 (6.5%)
	Koshino, *case series*	36	Yes	Resolution/improvement in 81%, unchanged in 19%	4 (11.1%)
	Marti *Non-randomised comparative study*	10	Yes	Reduction in necrotic area in 83%, reduction in oedema in 100%	Not reported
	Takeuchi, *case series*	30	Yes	Improvement in radiolucent area	0
	Valentí Nín, c*ase series*	2	Excellent in 100%	Improvement in 50%, progression in 50%	0

Table 2.18: Summary of clinical, radiological outcomes and failure rates of all included studies (ctd). **=number in treatment arm of study.*

2.5.6 Clinical results by stage

Although disease staging has been briefly discussed above, this section gives a further summary of the outcomes for early-stage disease with normal joint contour (equivalent to Koshino 1 and 2) and late-stage disease with altered joint architecture and collapse (equivalent to Koshino stage 3 and 4). Table 2.19 summarises the method of staging used, the number of patients in each stage and whether results were presented according to disease stage. Four studies are not included in the table as no staging was recorded for their patients (Johnson, et al., 2014; Jureus, et al., 2012; Kraenzlin, et al., 2010; McDermott, et al., 1985). Outcomes according to stage could only be extracted for 9 of the 16 studies with staging included: 3 studies were restricted to one disease stage (Breer S, et al 2013; Marcheggiani Muccioli, et al 2013; Yates, et al., 2007)) and 6 presented outcome data for each disease stage (Duany, et al., 2010; Forst, et al., 1998; Koshino, 1982; Tanaka, et al., 2009; Uchio, et al., 2000; Valentí Nín, et al., 1998).

Early stage with normal joint contour (Koshino Stages 1 & 2)

Five studies exclusively described outcomes of patients with early-stage SONK (i.e. normal joint contour and no collapse of the involved femoral condyle). As shown in table 2.20, all treatment modalities resulted in clinical and/or radiological improvement.

			Number of Patients					
1st Author and year	**Method of Staging**		**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**	**Outcomes described per stage?**
Akgun, 2005	Koshino		0	13	10	3		No
Breer, 2013			5	0	0	0		Yes
Deie, 2008			0	5	7	0		No
Koshino, 1982			0	10	16	11		Yes
Marcheggiani, 2013			28	0	0	0		Yes
Miller, 1986			0	2	3	0		No
Takeuchi, 2009			0	5	10	15		No
Tanaka, 2009			0	0	3	3		Yes
Forst, 1998			15	1	0	0		Change in stage recorded
Yates, 2007			14	0	0	0		Yes
Uchio, 2000	Koshino	Treatment	3	6	7	2		Change in stage recorded
		Control	2	7	1	3		
Valentí Nín, 1998	Koshino		7	8	1	5		Yes
Aglietti, 1983	Insall modification of Koshino		0	12	40	31	18	No
Marti, 2000	Insall modification of Koshino	HTO	2	2	0	2	0	No
		Control	2	0	1	0	1	No
Duany, 2010	Ficat & Arlet	Core Decompression	1	5	1	0		Yes
		OATS	0	0	8	0		
Kotani, 2003	Lotke		1b=12 1c=4	0	0	0	0	Partially

Table 2.19: Method of disease staging and number of patients in each stage for included research.
Abbreviations: HTO= high tibial osteotomy, OATS= osteochondral autograft transfer system.

1st Author, year	Intervention	N=	Results
Yates, 2007	Supportive measures	14	▪ Complete resolution of symptoms and MRI changes
Marcheggiani Muccioli, 2013	Pulsed EM therapy	28	▪ Significant improvement in KSS, EQ-5D & Tegner activity scale ▪ Pain reduction in 75% ▪ Significant reduction in WORMS score at 6 months
Breer, 2013	Bisphosphonates & vitamin D	5	▪ All patients' symptom free at 4 weeks ▪ Remission of bone marrow oedema in all cases
Forst, 1998	Extra-articular drilling	16	▪ Pain resolved in all patients ▪ Normalisation of bone marrow signal at a mean of 35.8 months ▪ KSS improved from 74 to 187.2
Kotani, 2003	OATS ± HTO	16	▪ JOA improved from 68.1 to 88.8 ▪ Radiological and arthroscopic confirmation of graft acceptance in all cases

Table 2.20: Summary of included studies specifically evaluating early-stage disease.
Abbreviations: EM=electromagnetic, KSS= American Knee Society score; OATS= osteochondral autograft transfer system, HTO=high tibial osteotomy, JOA= Japanese orthopaedic association score, WORMS=whole organ MRI score.

Three further studies described outcomes for a mixed population, with their results and outcome measures separated for early and late-stage disease (Duany, et al., 2010; Koshino, 1982; Valentí Nín, et al., 1998):

Duany et al (2010) described arthroscopy and decompression for 6 patients with early-disease. The patient with stage 1 disease had radiological progression and underwent an OATS procedure at 13 months following the initial surgery, with an improvement in KSS from 62 to 100 at final follow-up. The 5 patients with stage 2 disease demonstrated an increase in KSS from 59 (range 50-70) to 74 (range 45-100) post-operatively. One patient had radiological progression, requiring total knee arthroplasty 4 months after the index procedure, giving a total re-operation rate of 33% in this group. One patient with stage 2 disease underwent OATS as their primary procedure; their KSS increased from 52 to 80 post-operatively. (Duany, et al., 2010).

Valentí Nín et al (1998) published outcomes of 7 patients with Koshino stage 1 disease and 8 patients with stage 2 disease, treated with various modalities, depending on their symptom severity. Although 4 patients had evidence of radiological progression

following intervention, 75% still had an excellent clinical outcome despite worsening radiological features and did not require any further intervention (table 2.21). Only one patient with a poor clinical outcome (but no radiological progression) following arthroscopy and drilling required further treatment in the form of HTO.

Koshino Stage	N=	Treatment modality	Clinical outcome (Ordoñez)	Change in radiological stage	Further treatment
1	3	Weight-bearing relief, analgesia, physiotherapy	Good n=2 Fair n=1	No change: n=2 Progressed to stage 2: n=1	-
1	2	Arthroscopic washout	Excellent n=2	No change: n=1 Progressed to stage 4: n=1	-
1	2	Arthroscopy & drilling	Excellent n=2	No change: n=1 Progressed to stage 2: n=1	-
2	1	Weight-bearing relief, analgesia, physiotherapy	Good n=1	No change: n=1	-
2	1	Arthroscopic washout	Fair n=1	No change	-
2	5	Arthroscopy & drilling	Good n=4 Poor n=1	No change	HTO n=1 (poor outcome)
2	1	HTO	Excellent n=1	Progressed to stage 4: n=1	-

Table 2.21: Outcomes of treatment for early disease described by Valentí Nín et al (1998).
Abbreviations: HTO= high tibial osteotomy

Koshino described 37 patients with varying stages of disease who had been treated with HTO. He found that treatment of stage 2 disease had a higher statistically significant improvement in clinical outcomes compared to stage 3 ($p < 0.05$) and stage 4 disease ($p<0.01$). There was also a statistically significant improvement in those who had stage 3 disease, compared to stage four disease ($p < 0.05$) (table 2.22).

Koshino Stage	Number of Patients	Pre-op knee score	Post-op knee score
II	10	56±9	95±2
III	16	56±6	90±7
IV	11	54±6	81±11

Table 2.22: Outcomes as described by Koshino following HTO (Koshino, 1982)

Late disease with abnormal joint contour (Koshino stage III & IV)

Four studies isolated and presented their results for late-stage disease (Duany, et al., 2010; Koshino, 1982; Tanaka, et al., 2009; Valentí Nín, et al., 1998). The results of Koshino (1982) are shown above in table 2.22, suggesting that the clinical outcomes of HTO are better with earlier disease.

Tanaka et al (2009) evaluated the short-term effects of osteochondral autografting in 3 patients with Koshino stage 3 disease. The Lysholme score increased from 54.7 (range 47-69) to 95.3 (90-100) post-operatively. Three patients with stage 4 disease also demonstrated an increase in their Lysholme score, but to a lesser extent, increasing from 54.7 (range 47-69) to 89.3 (85-94) post-operatively.

Duany et al (2010) described the results of one patient with Ficat and Arlet stage III disease undergoing arthroscopy and decompression; their KSS increased from 75 to 90 post-operatively with no change in disease stage. There were 8 patients with stage III disease treated with OATS; their mean KSS increased from 58 (range 39-75) to 80 (range 43-80) post-operatively. One patient progressed to stage IV disease and required knee arthroplasty 11 months after their index procedure, giving an overall failure rate of 12.5% (Duany, et al., 2010).

Valentí Nín et al (1998) described one patient with stage 3 disease managed non-operatively, with a good outcome and no change in radiological stage. There were 5 patients with stage 4 disease treated with different modalities; 1 was managed with conservative measures and had a poor outcome. There were 3 treated with arthroscopy, HTO, or total knee replacement; all had excellent outcomes at final follow-up. One patient was treated with arthroscopy and drilling had a fair outcome. (Valentí Nín, et al., 1998).

Summary of results according to disease stage

Several studies exist evaluating conservative treatment, decompression, grafting or high tibial osteotomy for intermediate to late-stage disease. Although outcomes mostly improved, it appears, as stated by Koshino (1982) that treatments may lead to a better clinical outcome if intervention is employed earlier, before joint-collapse.

Despite there being twenty studies eligible for inclusion in this systematic review, less than half detailed their results in such a way as to be able to differentiate the results of the proposed treatment according to stage of disease. For the studies that did, there were often several different interventions described in the cohort, leaving individual numbers of patients in each treatment group small.

2.6 Systematic review: Discussion

This section summarises the main findings from the systematic review evaluating joint preserving treatments for SONK. The strengths and limitations of the methodology are then discussed followed by the clinical implications and conclusions of the review.

Summary of Main Findings

The systematic review identified numerous different treatment modalities for SONK, both non-operative and operative joint-preserving measures, with widely varying techniques. There was one randomised controlled trial, but this had high a risk of bias (Uchio, et al., 2000). The remaining included evidence consisted of multiple case series limited by relatively small numbers, inherently increasing the risk of possible selection, reporting and publication bias (O'Neil, et al., 2014).

Non-operative joint-preserving treatments

Supportive measures included a period of rest, analgesia and physiotherapy, the use of insoles, electromagnetic therapy and medical intervention with bisphosphonates. All case series demonstrated promising results in their small patient groups.

The randomised controlled trial describing a lateral wedge insole versus placebo showed positive results, but a power calculation was not included, patient numbers were relatively small and given the nature of the intervention, participants could not be blinded, questioning the overall strength of evidence (Uchio, et al., 2000).
The study describing the effect of pulsed electromagnetic therapy showed beneficial outcomes in stage 1 disease. However, patients in this study also received regular anti-inflammatory medication and recommendations on restricted weight-bearing; it is possible that these additional measures may influence outcomes (Marcheggiani Muccioli, et al., 2013). Studies evaluating analgesia with or without a period of weight-bearing restriction and physiotherapy alone have also shown similar improvements in results, making it difficult to formally conclude that electromagnetic therapy alone results in additional beneficial effects in early-stage disease (Aglietti, et al., 1983; Valentí Nín, et al., 1998; Yates, et al., 2007).

The role of bisphosphonates in the treatment of SONK is limited to evidence presented in small case series only, which have shown a beneficial effect (Breer, et al., 2013; Jureus, et al., 2012; Kraenzlin, et al., 2010). A double-blind randomised controlled trial evaluating bisphosphonates compared to placebo was excluded from this systematic review as it had a population with mixed pathologies (Meier, et al., 2014). This trial

provided conflicting evidence to the included studies and failed to demonstrate any additional benefit of ibandronate over placebo. A recent systematic review including 8 studies, specifically focussing on the use of bisphosphonates for SONK has been published following the conclusion of the review for this thesis. Despite several additional studies being included, the review comes to similar conclusions; bisphosphonates may have a role, but as their efficacy has not been validated by a randomised controlled trial (Meier, et al., 2014) further research is needed to identify whether they should continue to be a treatment option for SONK (Jordan, et al., 2016).

Several studies describing joint-preserving surgical interventions reported that their included patients had failed a period of non-operative treatments, usually for a period of up to 3 months (Akgun, et al., 2005; Duany, et al., 2010; Forst, et al., 1998; Miller, et al., 1986; Takeuchi, et al., 2009). It would suggest that conservative measures are therefore an acceptable first-line treatment, but without knowing the ratio of patients who were successfully treated by these means compared to those who went on to require further intervention it is impossible to evaluate the true effectiveness. Only one of these studies stated that 80 patients had symptomatic improvement following a period of analgesia and protected weight-bearing compared to 18 requiring further surgical intervention, suggesting a possible overall success rate of 82% for supportive treatment (Duany, et al., 2010). The efficacy, as well as the duration of treatment using these measures is an area that requires further research.

Joint-preserving surgery

Although this group of treatments makes up most of the included research, it consists of a selection of low level evidence, with high risk of bias.

Aside from earliest included studies by McDermott et al (published in 1985), who reported a failure rate of 73%, and the small study by Miller et al from 1986, where 2 of 5 patients (40%) required further intervention, the majority of the arthroscopic techniques and grafting procedures have provided reasonably promising results, with overall improvements in clinical outcomes. However, these from relatively small case series, for patients with widely variable disease presentations, and were often performed concominantly with realignment procedures. For those with positive outcomes, it is impossible to state whether this was due to the realignment or the grafting alone, or due to the combination of interventions. Larger scale studies or trials with more standardised techniques and the use of control groups to provide comparison would provide a useful contribution to this area of treatment.

The studies describing outcomes of high tibial osteotomy for SONK also show positive results for disease of varying stages. There is large variation in techniques, fixation

methods and rehabilitation protocols between authors, along with the use of additional intra-articular procedures in some patients. Most authors, however, highlight the overall importance of adequate alignment correction, to sufficiently offload the affected compartment, aiming for a femorotibial angle of approximately 170º to achieve the best outcomes.

Following on from the planning and completion of this systematic review, two systematic reviews have since been published evaluating the use of bisphosphonates for SONK (Jordan, et al., 2016) and joint-preserving surgical procedures (Lieberman, et al., 2014) for the treatment of both SONK and secondary ON. Lieberman et al (2014) found that core decompression was successful for small pre-collapse lesions and bone grafting is effective for pre- and post-collapse lesions. Osteochondral grafting was also found to be effective. Jordan et al (2016) concluded that bisphosphonates may have a role in the treatment of SONK, but this has not been supported by a single randomised controlled trial (Meier, et al., 2014). The results both systematic reviews present similar conclusions and support the results of this review, that further larger trials are needed to determine the true efficacy and make recommendations for treatment.

Complication rates and overall failure

The systematic review set out to review failure of treatment with need to progress to additional surgery or joint arthroplasty. Fourteen of the included studies (70%) provided information on patients needing further surgical intervention. Rates were highly variable, ranging from zero to 40% of patients needing further joint-preserving intervention, as well as zero to 40% of patients requiring total knee arthroplasty after their initial joint-preserving treatment. The varying follow-up periods described in the included research ranging from a few months to many years, makes a definitive comparison of overall failure rates inaccurate. It could be argued that the complication rate is relatively high for the various techniques, with one in ten patients in the included studies requiring further joint preserving surgery and 11% of patients ultimately requiring total knee arthroplasty. However, the small numbers involved and the uncertainty regarding complications in the studies excluded from this calculation make it difficult to fully appreciate the true success of the described interventions.

Efficacy of treatments according to disease stage.

Overall, less than half of the included studies detailed their results in such a way as to be able to differentiate the results of the proposed treatment per stage of disease. For the 45% of included studies which did provide some information regarding this, there were often several different interventions described in the cohort, leaving individual numbers of patients in each treatment group small. This, along with the numerous

different outcome measures used across the included research makes it difficult to provide comparison and come to any firm conclusions regarding the efficacy of specific treatments for each stage of disease. Presenting results across the spectrum of disease may also result in inaccuracies; individual treatments may successful for early disease, for example, but if the patient cohort is presented together, rather than specific to stage of disease, it may reduce the apparent effectiveness. This highlights the need for future research to be sub-grouped according to disease stage.

Strengths and Limitations

Despite the weaknesses in available evidence, there are several strengths to the methodology used to undertake this systematic review. Both the Cochrane handbook and PRISMA checklists were used for guidance throughout the development and execution of the review, results were presented according to the PRISMA flowchart to minimise bias while conducting the review and ensure clear and transparent reporting of results (Higgins & Green, 2011; Liberati, et al., 2009; Moher, et al., 2009). Numerous databases were utilised, followed by a search of the references of included studies to identify and include as much relevant research as possible. Two reviewers were involved throughout the process to try and avoid introducing selection and reporting bias; studies were independently reviewed and selected for inclusion by two reviewers (MC Killen and CP Charalambous), data was then extracted from included research using a standardised proforma, by two reviewers (MC Killen and MP Dey), ensuring the same information was obtained, or any deficits in methodology or results were identified (Moher, et al., 2009). All included studies were screened using a risk of bias checklist included within the data extraction proforma (appendix 2).

Potential weaknesses of the methodology used include the decision to exclude any papers not available in English, potentially introducing an element of selection bias and risking missing important studies which may impact the overall results. However, a systematic review evaluating the effect of English language restriction has failed to show evidence of this, with none of the included studies finding major differences between summary treatment effects in English-language restricted meta-analyses (Morrison, et al., 2012) . In addition, there were several conference proceedings identified in the initial search which were relevant to the review, but no full texts were published in the literature for formal inclusion and analysis, the decision to exclude such literature may have introduced a degree of publication bias (Blackhall & Ker, 2007), but it is unclear whether inclusion of such data would influence overall results and may in fact result in overestimation of treatment effectiveness (McAuley, et al., 2000). There may be further limitations, present with all systematic reviews in terms of an element of both publication and reporting bias of the included studies, whereby only

series with positive results are written up and selected for publications (Dwan, et al., 2008); the availability of further higher-level evidence would hopefully limit such factors, by reporting outcomes of either randomised trials or comparative studies showing whether one treatment is superior to another.

Overall, the body of evidence describing joint preserving treatments for SONK is limited. The included randomised controlled trial had a high risk of bias, and the remaining evidence is limited to small studies, mostly in the form of case series. The nature of the evidence itself results in an introduction of possible reporting bias, and further analysis of the individual studies found that all but one scored as high risk of bias from deficiencies in their methodology and results.

Limitations in drawing conclusions from the studies has also arisen from the use of numerous different classification systems to stage disease (Ficat, 1985; Koshino, 1982; Lotke PA, 1982), as well as an even larger number of outcome measures used to quantify outcomes, making direct comparison of results almost impossible. There are currently no recommendations for the most appropriate method of staging for SONK, but it does appear from review of the literature that the Koshino classification remains the most commonly utilised (Koshino, 1982). Regarding clinical scoring systems, it is unclear from the literature whether any of these scoring tools are validated specifically for SONK, as most of the knee-specific scoring tools were initially designed for evaluating outcomes related to either osteoarthritis of the knee or ligamentous instability, which may affect the relevance and strength of the results (appendix 5). There is no existing research evaluating the ceiling effects of the scoring tools used; if maximum scores are easily attained, it may give an overestimation of the efficacy of the treatment described, affecting the validity of the results (Wang, et al., 2008). Evaluation whether a ceiling effect exists for each scoring system would be worthwhile when deciding on the best score to use for measurement of clinical outcomes for SONK.

There is very little in the way of ‘new evidence’ included in this systematic review, with publication dates of included research ranging from 1982 to 2014; only 35% of studies have been published in the last 10 years. Giving the ever-advancing surgical techniques, particularly in arthroscopy, these results may not provide a true representation of treatments currently being performed, and the potentially improved outcomes that often come with developments in procedures (Carr, et al., 2015). At the time of writing, there were currently no ongoing trials related to SONK registered with either ISRCTN (ISRCTN, 2017) or Cochrane Central Register of Controlled Trials (Cochrane Library, 2017); although these resources are mostly limited to UK and

European trials, the lack of any ongoing research further emphasises the need for some more up to date evidence.

Implications for clinicians

At the time of writing this is the first available systematic review to evaluate both medical and surgical joint-preserving treatment for SONK. Although it has not been able to provide conclusive evidence, it has been able to present the outcomes and failure rates of 20 studies, which met the inclusion criteria. From these studies, it is difficult to come to any conclusion as to whether bisphosphonate treatment has a role in treatment of SONK, over and above the traditional conservative measures of rest, physiotherapy and analgesia, as these measures alone have also shown to be beneficial (Aglietti, et al., 1983; Valentí Nín, et al., 1998). Most studies reporting the numerous joint-preserving surgical measures have demonstrated relatively promising results, ranging from simple arthroscopic debridement to joint re-alignment with high tibial osteotomy, but they vary widely in overall study design and quality, along with differences in surgical techniques. The included research has also demonstrated widely variable in complication rates and ultimate need for joint replacement, with some research showing much higher failure rates than with non-operative measures alone (Miller, et al., 1986; Johnson, et al., 2014; McDermott, et al., 1985; Valentí Nín, et al., 1998). Although the results of the systematic review have provided some guidance on the success and failure rates of various treatments, both medical and surgical, the combined evidence is not strong enough to make formal recommendations to influence current practice.

Implications for further research

This review has identified the need for larger, well designed and appropriately powered randomised controlled trials with formal comparison of joint-preserving treatments with each other or placebo to determine the true effectiveness of the available treatment options. There is a need for comparison of the different drilling and grafting techniques with each other as this is an area with the most limited evidence. Given the uncommon nature of SONK it is likely that such trials would require multi-centre collaboration either on a national or international scale (McCulloch, et al., 2002; Solomona & McLeod, 1995). It may also be that high quality, non-randomised methods are needed as an alternative, due to small patient numbers; well-designed observational studies may provide a suitable alternative to give important information on differences between various interventions (Silverman, 2009). It is also imperative that future trials are set-up to analyse outcomes according to disease stage, along with standardisation of disease

grading and outcome scoring, to try and determine which treatment is best to use for each patient group.

A quarter of the included studies stated that their cohort had undertaken a period of non-operative management before proceeding to surgical intervention (Akgun, et al., 2005; Duany, et al., 2010; Forst, et al., 1998; Miller, et al., 1986; Takeuchi, et al., 2009). Additional important information to gather from future research would include whether all patients undergo a provisional trial of non-operative measures with analgesia and physiotherapy and if so, in what proportion of patients is this successful. Complication rates and failures should be clearly defined and stated to aid in evaluating treatment effectiveness compared to non-operative measures.

One of the main difficulties in synthesising the results for this review was the huge variation in measures used to assess outcomes. It is unclear from the literature whether any of these outcomes used have been validated for use in SONK, and most tools employed were initially developed for other knee conditions, particularly knee osteoarthritis and ligamentous instability (appendix 5). In addition to this, there is no evidence evaluating ceiling effects of the scores used, further questioning the overall validity of results. There is therefore a need to either develop or validate an existing tool for use in SONK to provide some standardisation and aid in future interpretation of clinical results.

2.7 Conclusion and recommendations of the Systematic Review

The systematic review has identified 20 studies describing treatments ranging from analgesia and physiotherapy to realignment surgery using high tibial osteotomy. Although the evidence to support the overall efficacy of a period of analgesia and physiotherapy is limited, 25% of included studies stated that their entire patient population underwent a trial of such measures prior to proceeding with further intervention, suggesting that this may be a commonly employed initial treatment (Akgun, et al., 2005; Duany, et al., 2010; Forst, et al., 1998; Miller, et al., 1986; Takeuchi, et al., 2009). One study suggested that 82% of their entire cohort were successfully treated with non-operative measures alone (Duany, et al., 2010). In the event of failure of non-operative treatment, there is no good evidence to advise on which is the best treatment to consider next; currently available research is limited to case series and small randomised trials, the majority of which have a high risk of bias.

There is no doubt that further, up-to-date research evaluating the treatment of SONK would be worthwhile, to reflect evolving technology and surgical practice. Recommendations from the outcome of this systematic review are as follows:

1. Non-operative treatment with rest, analgesia and physiotherapy appears to be an acceptable initial strategy for treatment. For authors presenting a cohort of patients who have failed non-operative measures, it would be worthwhile to know the proportion of patients who have been treated overall, to gain better knowledge of the overall success rates of this treatment modality.
2. A minimum follow-up period should be employed for studies, to determine the true success of interventions. Limiting overall follow-up to 8 weeks, as utilised in one study (Breer, et al., 2013), is insufficient to determine whether a treatment is effective in the long-term.
3. Where possible, studies should utilise a control group, particularly for those where interventions are being used concomitantly with analgesia and physiotherapy, to give a better understanding of treatment efficacy.
4. An effort should be made to minimise bias in future research, using appropriate study designs and guidance for the reporting of studies, for example, CONSORT or STROBE, alongside risk of bias tools while planning and developing studies (Moher, et al., 2010; (von Elm, et al., 2008).
5. There should be clear and transparent reporting of failure rates and complications experienced with reported treatments. It is often unclear whether there were no complications experienced, or whether this has simply not been reported.
6. There should be a standardised disease staging used for studies relating to SONK, and results should be presented per disease stage.
7. Outcome reporting also needs to be standardised, with a view to validation of either an existing clinical scoring tool, or formulation of a new score with a low ceiling effect to improve overall validity of outcomes reporting.

Given the inconclusive nature of the results of the systematic review, further methods were considered to provide additional evidence and work towards understanding which treatments are considered most appropriate to use for different stages of disease. It was decided that the use of consensus methodology would be the most appropriate way to proceed; such techniques have been increasingly used and have demonstrated effectiveness in providing agreement on topics that do not yet have strong empirical evidence to support them. Following on from this review, a Delphi consensus study was therefore undertaken, involving an international group of knee experts to try and provide further information to reach the objectives that were not addressed from the systematic review.

CHAPTER THREE: DELPHI STUDY OF JOINT-PRESERVING TREATMENTS FOR SPONTANEOUS OSTEONECROSIS OF THE KNEE

3.1 Introduction

The systematic review was conducted as an initial phase in working towards the formulation of recommendations for the treatment of SONK, through evaluation of currently available evidence. Research has shown the success rates of various medical and surgical treatments for patient groups of differing sizes, but it has failed to demonstrate which treatment is most effective for patients overall or with different disease stages

In such situations where good quality evidence is lacking, consensus methods can be a helpful tool to provide further information and guide clinical practice (Jones & Hunter, 1995). A Delphi consensus method was therefore undertaken to gather opinions on best practice from an international group of experts. Various scenarios were presented, relating to different disease stages, to try and establish which treatment is best for patients throughout the spectrum of SONK, as this was one of the main areas where the systematic review failed to provide any good quality evidence. A second area highlighted from the systematic review was that several studies stated that their cohort undergoing surgical intervention had failed a period of non-operative management (Akgun, et al., 2005; Duany, et al., 2010; Forst, et al., 1998; Miller, et al., 1986; Takeuchi, et al., 2009); this was explored further in the Delphi study to determine whether this is standard practice before proceeding with any surgical treatment. It is unclear from the evidence reviewed whether surgeons perform specific first-line, less invasive treatments, such as medical treatment or arthroscopic measures, to try and improve symptoms before proceeding with more major alternatives, such as high tibial osteotomy in the event of failure of initial treatment; this is also explored in the scenarios presented.

This chapter will give an overall introduction to why a Delphi study design was chosen and provide details on the aims, objectives and methods of the study. Following on from this, the two rounds of the Delphi study will be described in detail along with the results, a discussion and conclusion.

3.2 Aims & Objectives

The aim of this Delphi study was to identify commonly utilised treatment modalities for SONK and to reach an agreement on most appropriate first and second-line

management of different stages of disease. The specific objectives of this Delphi study are detailed below.

Delphi Objective 1:

To identify if specialists give a standard period of observation with adjuncts such as analgesia, physiotherapy and/or restricted weight-bearing before proceeding with surgical intervention.

Delphi Objective 2:

To establish whether experts consider that there is a role for medical treatment of SONK with bisphosphonates.

Delphi Objective 3:

To establish whether specialists regularly perform arthroscopic drilling or microfracture, or grafting procedures, and, if so, establish a consensus on what stage in the disease process it should be used.

Delphi Objective 4:

To establish if experts agree on whether high tibial osteotomy has a role as either a primary treatment or secondary intervention after failure of less invasive methods.

Delphi Objective 5:

To achieve a consensus on first-line treatment of patients with SONK but normal joint architecture (no collapse of the femoral condyle or tibial plateau) and preferred second-line treatment in the event of persisting symptoms following intervention.

Delphi Objective 6:

To achieve consensus on both first and second-line treatment of patients with SONK with collapse of the femoral condyle and knee malalignment.

The combination of outcomes from the systematic review and Delphi study will aim to provide a foundation for evidence-based guidance for treatment of patients with different stages of disease, as well as assessing ongoing deficits in evidence and the value of further research into the management of SONK. This will be discussed in the final chapter of the thesis.

3.3 Delphi Study Methodology

A two-round Delphi study was chosen to gather evidence from an international group of knee specialists regarding commonly utilised joint-preserving treatments for patients with various stages of SONK. The Delphi technique was initially developed for the military in 1948 to aid in forecasting events (Dalkley & Helmer, 1962). Since then, Delphi studies have long been used in the setting of healthcare and medical related research (Fearon, et al. 2011; McKenna, 1994; Powell, 2003; Rayens & Hahn, 2000). The Delphi method has been defined as a structured process for collecting knowledge and opinion from a group of experts using a series of questionnaires, in order to determine commonly used treatments to aid in the development of clinical assessments or guidelines and provide recommendations for future research (Hutchings, et al., 2006; Jordan, et al., 2003; Ziglio, 1996).

Using a Delphi technique has the advantage of being open to a wide range of potential participants, is not limited by location and has a potentially low time commitment for those involved. It permits anonymous responses, eliminating the possibility for the group to become dominated by individuals, which can sometimes occur in face-to-face groups (Jairath & Weinstein, 1994; Critcher & Gladstone, 1998). The Delphi method also allows participants to refine their opinions in response to the views of the group between rounds (Skulmoski, et al., 2007). It does, however, rely on an adequate number of willing participants and carries a possibility that consensus may never be reached.

There are three main consensus techniques that are used in the field of medicine; a consensus development panel, the nominal group technique and a Delphi consensus (Waggoner, et al., 2016). A consensus development panel is commonly used to aid formulation of healthcare policies, whereas, a nominal group process is often used to evaluate appropriateness of interventions in healthcare; both techniques can ultimately result in changes to the decision-making process involved in treating patients (Waggoner, et al., 2016; Jones & Hunter, 1995). Although both these techniques have their advantages, they involve face-to-face meetings with the involved participants. Given the planned international nature of the consensus in this thesis, this would have been logistically very difficult, costly and would have involved relatively large time commitments, potentially reducing the number of interested and available experts. For this reason, it was decided that a Delphi consensus would be the most appropriate method to use for this study.

There are wide variations in the description of the Delphi technique in the literature (Boulkedid, et al., 2011; Dalkley & Helmer, 1962; Diamond, et al., 2014). In its traditional form, three rounds are used. The first round begins with an initial questionnaire or brainstorming session to generate ideas and form a basis for the issues that need to be raised in future rounds (Fearon, et al., 2011). Feedback from round one is presented in the form of a second-round questionnaire, which aims to gather opinions on the issues raised. Subsequent rounds usually consist of the presentation of the opinions of the panel, with members being asked to reconsider their opinions considering the information presented from other members until a consensus is reached (Hsu & Sandford, 2007; Keeneya, et al., 2001; Sumsion, 1998).

3.4 Delphi Study Method

For this thesis, the systematic review had already provided a basis for the issues that needed to be raised in questionnaires. For this reason, a modified two-round Delphi technique was used, an adaptation which has already been described in the literature (Mullen, 2003). It was also proposed that reducing the number of rounds from three to two would hopefully lead to increased response rates from the chosen panel. An overview of the Delphi process used is shown in figure 3.1.

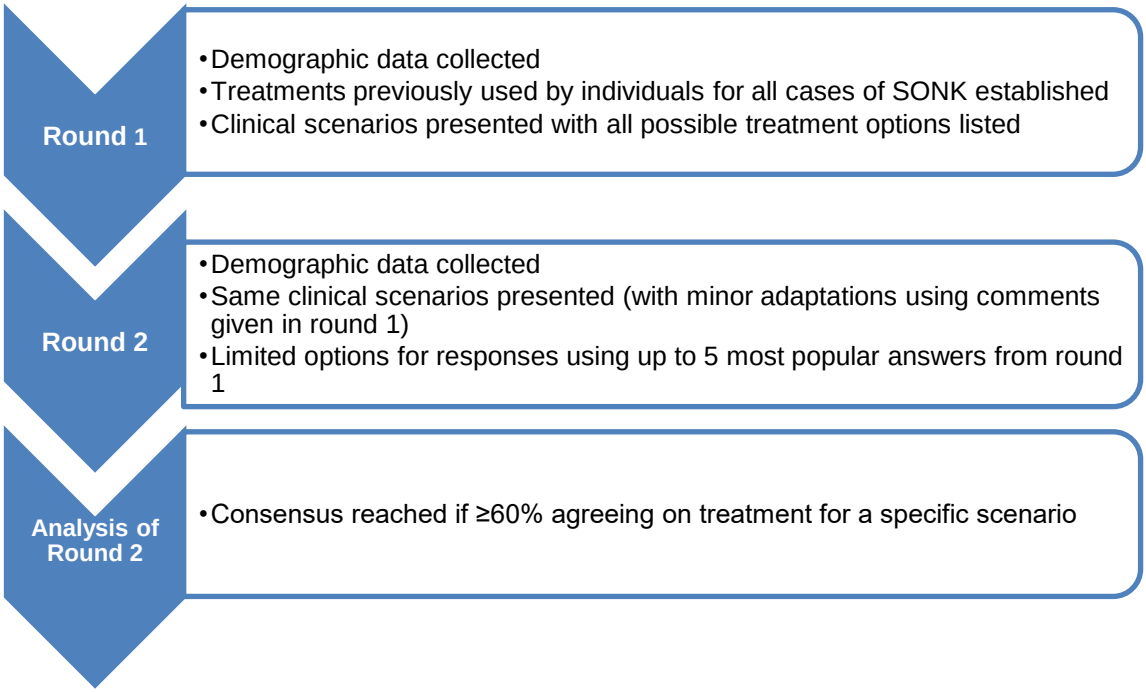

Figure 3-1: A diagrammatic representation of the Delphi process used

3.4.1 The Panel & Sample Size

Before undertaking the first round of the Delphi study, panel members were identified. To be eligible to take part and contribute to the study, participants were required to have 'expert' knowledge of SONK. There are no established set criteria for 'experts' but is largely dependent on the subject area (Keeney, et al., 2006). It has been stated that invited participants should have sufficient knowledge and experience of the area under investigation, capacity and willingness to participate, sufficient time to permit participation and have effective communication skills (Adler & Ziglio, 1996). Selection of panel members does have the theoretical risk of introducing bias, as those agreeing to participate often have a particular interest in the field being examined and may have a vested interest in a specifc treatment related to personal involvement in research (Murry & Hammons, 1995; Sandrey & Bulger, 2008). It is therefore important to select individuals that can be relatively impartial so that the results of the study reflect a true representation of current opinion and knowledge (Goodman, 1987). A group of practicing clinicians who regularly manage cases of SONK were selected as well as a group of authors, to try and minimise any bias towards the treatments published by the author group.

The first group of experts contacted were members of the "20/20 knee group", a special interest group of 21 fellowship-trained knee surgeons working in different centres throughout England. Members of this group have experience in managing patients with SONK and may have a higher than average case load of this condition compared to other practicing knee surgeons. Contact with this group was made through one of its members, who was willing to aid in facilitation and distribution of emails, in the absence of contact details being available in the public domain.

The second group in the Delphi panel were selected using a PubMed search to identify those who have recently published on the topic of SONK and are working as a knee surgeon, with no limit on country of practice, provided they have published in English. The keywords 'spontaneous, osteonecrosis and knee' were used to search for relevant publications. Consecutive publications, ordered from most recent first, including a reasonable population of SONK (no case reports) were reviewed to identify surgeons who were most likely to still be practicing. This process was continued, until sufficient authors were identified. One author per article was invited to take part in the study, in keeping with the publication of contact details for a single author in the publication. Usually, this was the most senior author of these publications, when possible, as it was presumed that this author would have the most experience in treating patients with SONK and would therefore be most suited to being involved in the study; if there was any uncertainty, a further search was performed of the authors' other publications to

establish that the person to be contacted was a practicing clinician. Although initially 20 authors were sought, further authors were identified following dissemination of initial round 1 emails due to several of the listed email addresses being undeliverable and a lower than expected response from the first group contacted. In total, 40 authors were identified and contacted to take part in the study.

3.4.2 Defining consensus

There is no absolute figure on what constitutes consensus in a Delphi study; the gold standard would be 100% agreement in all statements (Keeney, et al., 2006). However, when presenting clinical scenarios where the best option is not known, this is often not achievable and differing opinions will almost always be present between experts. It is therefore accepted in the literature that agreement anywhere between 50% to 80% of cases can be used as an acceptable consensus end-point (KG & Moore, 1979; Green, et al., 1999). For this study, a value of 60% was used to define consensus; this is above the minimum described in the literature, but any higher percentage was thought to be difficult to achieve given the possible large variation in clinical practice between surgeons.

3.4.3 Ethical Approval, Data Protection & Confidentiality

Prior to the onset of the study, the proposal was submitted, reviewed and approved by the STEM research ethics committee at the University of Central Lancashire (appendix 10). Issues detailed in the submission for ethical approval included participant information leaflets, consent to participate, withdrawal procedure, anonymity of respondents as well as storage of contact details and responses to the study.

The email addresses obtained from the author group were available online publicly, unlike those of the 20/20 knee group. It was therefore agreed that a single member of this second group would co-ordinate dissemination of the questionnaire to overcome confidentiality and consent issues; at no point were the email addresses of the group disclosed. Only authors with publications in English were contacted to overcome any communication problems. The participant information leaflet distributed with the initial contact email is given in appendices 6 and 7. The initial invitation was sent out to all participants, with the purpose of the study and the anticipated timetable, at least one week prior to the distribution of the first-round of questionnaires to give participants sufficient time to decide whether to take part. Implied informed consent was judged to be enacted on completion and return of the questionnaires and participants were made aware that they were free to withdraw from the study prior to its onset or at any point throughout by email request. Participants were made aware of these facts from the initial email and information leaflet (appendices 6 and 7); this information was also re-

emphasised in the email when the link to round 1 of the study was distributed. Feedback was given in the form of amended answer options or minor changes to question stems if necessary, and participants were made aware that the multiple-choice answer selection in round 2 was made up of the most popular answers from round 1.

To ensure anonymity was upheld, an online survey was chosen (SmartSurvey), with no request for any personal details and automatic anonymisation of the responses by the software used. More specifically, the survey website had UK-based servers in keeping with data protection regulations. The data involved in this Delphi study was stored in keeping with university policy, in password protected files, which were only accessed by the researcher, and supervisory team when necessary. Emails and email addresses were deleted following completion of the study. Data will be kept for 5 years following completion of the study, then destroyed.

3.4.4 Development of Questionnaire

A two-round Delphi process was designed for this study. Each round was separated into two parts; the first section aimed to capture demographic data of the participants regarding their level of experience and the treatments they use in their current practice. The second section involved the presentation of several descriptive scenarios of patients presenting with different stages of SONK. The development of scenarios and potential answers were put together using information highlighted in the systematic review; the survey development did not involve the participants.

The first section of the questionnaire was used as a tool to capture the demographic data of those responding to the survey. This was composed of four questions to gauge their level of experience as a knee surgeon, as well as their previous experience with the different treatments, using an extensive list of modalities described in the literature. The questions used to capture this information are shown in table 3.1.

Question	**Answer modality**
Where is your country of practice?	Free text
Approximately how many years have you been practicing as a knee specialist?	Free text
On average, how many cases of Spontaneous Osteonecrosis of the Knee do you treat per year?	Free text
Please indicate which of the following treatments for Spontaneous Osteonecrosis of the Knee you have personally performed	Multiple choice (select all that apply)

Table 3.1: Questions used to capture demographic data in Round 1.

The second section of round 1 presented patient scenarios. The systematic review demonstrated that there was a significant lack of existing evidence regarding treatment outcomes for disease stages, therefore, patient scenarios were presented to establish opinion, and work towards developing consensus on which treatment to use for different disease stages and presentations. Most, but not all, research included in the systematic review used the Koshino classification to grade the severity of SONK (Koshino, 1982). For this Delphi study, descriptive terms were used instead of specific classifications to limit the ambiguity of the scenario being presented and to avoid the possibility of participants not being immediately familiar with the staging system used.

Three separate patient scenarios were developed using descriptive terms used to broadly describe different stages of disease in keeping with the Koshino classification:

1. A patient with normal radiographs but MRI changes in keeping with SONK (equivalent to Koshino stage 1);
2. A patient with sclerotic changes on plain radiographs, but normal knee alignment (equivalent to Koshino stage 2/3);
3. A patient with collapse of the femoral condyle and associated knee malalignment (Koshino stage 4).

Each patient scenario was further broken down into two sections. Participants were firstly asked to specify what their likely initial treatment would be for each case, then identify which second-line treatment they would use, should their initial management fail (with treatment failure being defined as ongoing symptoms, but no radiological progression). The scenarios were structured in this way to aid clinicians in deciding which treatment to use for patients at first presentation, as well as those patients returning who did not respond to their initial treatment, but who radiologically had remained at the same disease stage. For all scenarios, participants were given a list of treatment modalities described in included research and asked to choose their most likely treatment but were permitted to select more than one if they felt necessary. There was also the option to state ‘other’ with free text to describe an alternative treatment choice, which may not be covered. The answer options for each scenario are shown in table 3.2. A full copy of the questionnaire is included in appendix 8.

A period of rest, analgesia and full weight-bearing (please state duration)
A period of rest, analgesia and partial weight-bearing (please state duration)
A period of rest, analgesia and non-weight bearing (please state duration)
Arthroscopic Debridement
Arthroscopic drilling/microfracture: trans-chondral
Arthroscopic drilling/microfracture: extra-articular
Osteochondral transplantation: allograft
Osteochondral transplantation: autograft
High tibial osteotomy
Metal button resurfacing of the lesion
Unicompartmental knee replacement
Total knee replacement
Other (please specify)

Table 3.2: Treatment options given as possible answers for round 1 of the survey.

Prior to widespread email dissemination to selected participants, several colleagues with knowledge of the condition, were asked to pilot the study to ensure there were no areas of ambiguity in the questions, or difficulty understanding certain statements. This also provided an opportunity to trial the software on the website to ensure there were no technical issues. Following this initial pilot, no issues with the software or questionnaire layout were raised, but several minor changes were made to the question structure and the possible answers listed for each scenario. A treatment not described in the included research from the systematic review, but raised from the pilot was the option of metal button resurfacing, which was added in as an additional answer option, as it was thought that this may be a more recent treatment option without published data (Hobbs, et al., 2013). Aside from these amendments, the remaining aspects of round 1 were unchanged.

3.4.5 Dissemination of Questionnaire

An initial invitation was sent out via email to all participants with a brief overview of the purpose and anticipated timeline (appendix 6). Attached to this email, a participant information sheet was included containing more detailed information of the purpose of

the study, confidentiality, data protection along with the process of opting out of the study either from the outset or at any time during the process (appendix 7). Following on from this initial contact email, as no requests were received to be excluded from the study, all participants were sent an invitation to complete the first round of the Delphi study. Contained in this email, the purpose of the study was again detailed, the expected time taken to fill out the first round and the hyperlink to the survey website was given (appendix 6). A full version of round 1 of the study is shown in appendix 8. Emails were sent out to several participants at a time over a period of 48 hours, to ensure no technical problems were encountered with the software.

Each round of survey was initially available for two weeks. Timely response to each round was important as it was required to adapt the content for the following round. To facilitate this, all participants were contacted well in advance of the first round with personalised emails sent from a university email account with the anticipated time required to complete the survey and planned deadline detailed in each email. One reminder email was sent to participants at a week interval, to maximise the number of respondents.

All responses to round 1 were collected using the survey website and were subsequently entered into an Excel spreadsheet. Any additional comments put forward by participants were also used to develop and amend the round 2 questionnaire, particularly if it was expressed that certain areas of the scenarios require re-phrasing or further explanation to improve the clarity. At the end of round 1, all comments had been addressed and included in the round 2 questionnaire if necessary.

3.4.6 Development of Round 2

Round 2 was developed using feedback and results from round one and sent out to all potential participants, regardless of whether they had responded to the initial round. Given the anonymous nature of the responses from round 1, demographic data was collected at the beginning of round 2, to ensure a similar group of participants were involved. This was composed of three questions regarding their experience as a knee surgeon, but with multiple choice answers, instead of free text responses using the most common answers from round 1, to try and reduce the time taken to complete this section.

The same questionnaire format was used for round 2 and the statements were mostly unchanged. Participants were informed in the round 2 invitation email that only up to five of the most popular answers from round 1 were possible answers to the scenarios. This gave participants the opportunity to understand the most popular treatment

modalities chosen in round 1 and use this information to aid in their decision making while answering the round 2 scenarios. Instead of being able to select as many answers as possible, participants were asked to only select one treatment modality that they would be most likely to use in each scenario, with a final option included as 'none of the above' should they not agree with any of the options listed. A full copy of the round 2 questionnaire is shown in appendix 9. At the end of this round, responses were entered onto a second excel spreadsheet and the percentage of respondents selecting each treatment modality was calculated. If the final percentage of agreement for one treatment per clinical scenario reached 60%, then it was established that a consensus had been reached.

3.5 Analysis

A percentage agreement was calculated for each scenario and was used to evaluate the level of consensus for each round. The data captured was then presented using a series of tables, graphs and descriptive text to demonstrate the results. Any additional free text comments or suggestions gathered from round 1 participants were used to amend round 2 questions and responses where necessary.

In this section, the methodology has been outlined and the reasoning behind the choice of a Delphi study over other consensus methods. The rationale behind the scenarios used has been described, with the overall emphasis on achieving consensus from research participants on the content of the best treatment for patients with various stages of SONK.

Delphi Study Results

3.5.1 Round 1 participant demographics

Initially, round 1 was distributed to all members of the 20/20 group and the group of 20 authors simultaneously. Of the 21 members of the 20/20 group contacted, 8 responded (38%). Out of the 20 authors contacted using email addresses publicly available in the published literature, 4 emails were invalid and were returned undelivered. One potential participant contacted to state they did not wish to be involved but supplied an email address of a suitable colleague. Of the 16 delivered email invitations, 4 responses were received following the initial email and one reminder (25% response rate). Given this lower than expected response rate, the decision was taken to gather a further group of authors using the same search techniques and restart round one. A further 20 authors were identified and contacted. Again, 3 of the published emails were returned undelivered. Of the 17 emails delivered, 7 responses were received to round 1 from the second group of authors contacted. This gives an overall response rate of 33% for the author group. Overall, there were 19 responses to round 1 between the two groups and a total response rate of 35%.

Demographic data from round 1 participants is summarised in figures 3.2, 3.3 and 3.4. Most participants were from the UK or USA, with the remaining being practicing surgeons in other European countries. The majority (n=18, 95%) had at least 10 years' experience practicing as a knee surgeon. When it came to the number of cases of SONK treated per year, the results were more varied, with participants treating from two, up to 30 cases per year (mean 9.8 cases/year, SD 9.06).

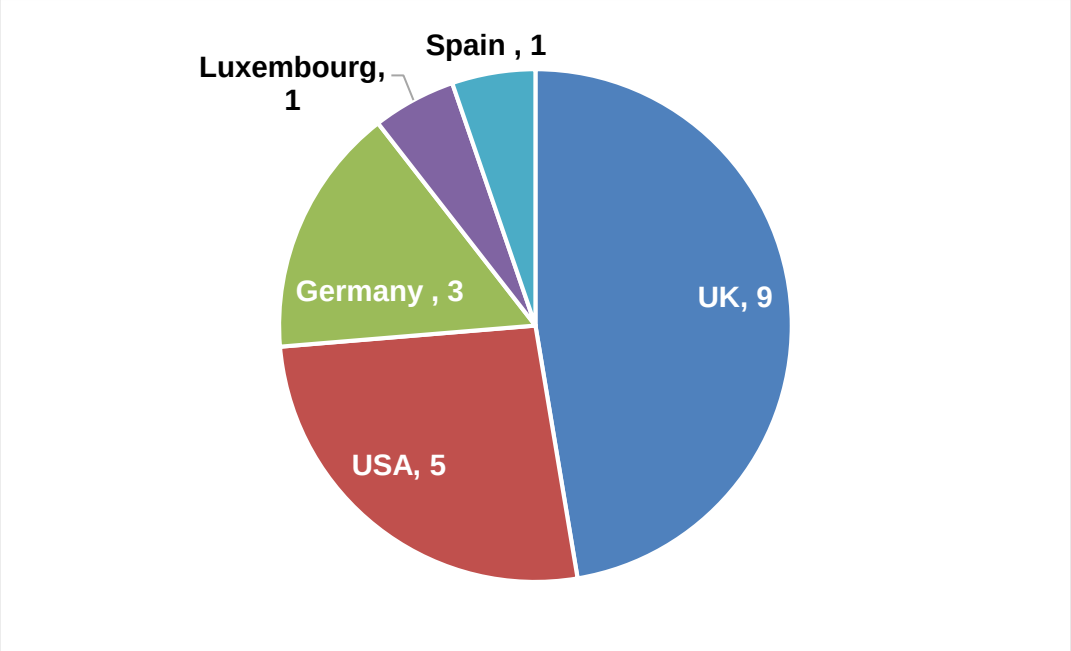

Figure 3-2: Chart summarising country of practice for all round 1 participants N=19

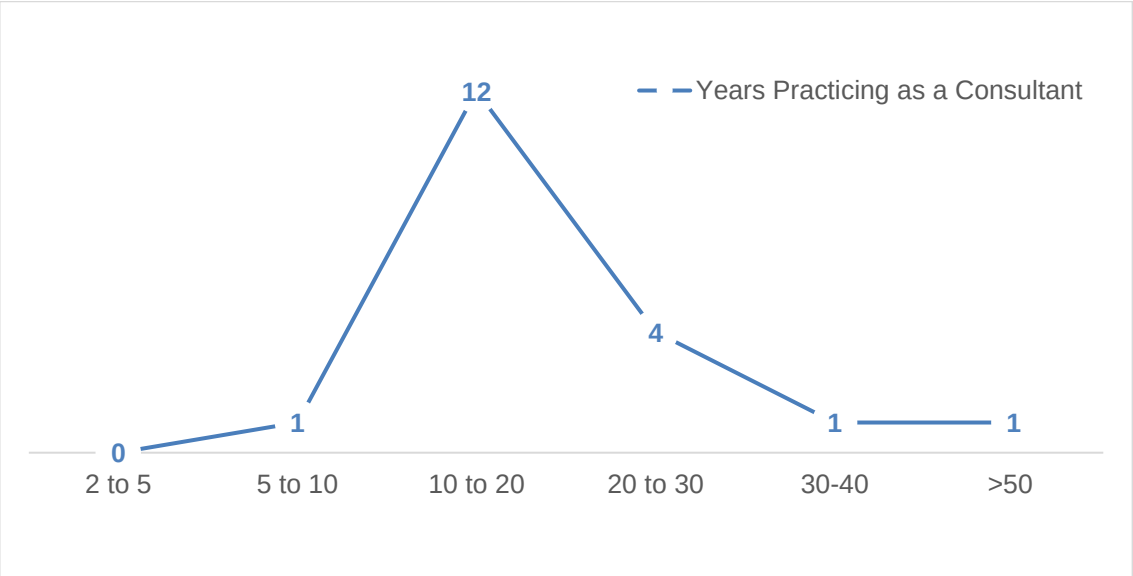

Figure 3-3: Graph summarising the number of years of experience, n= 19

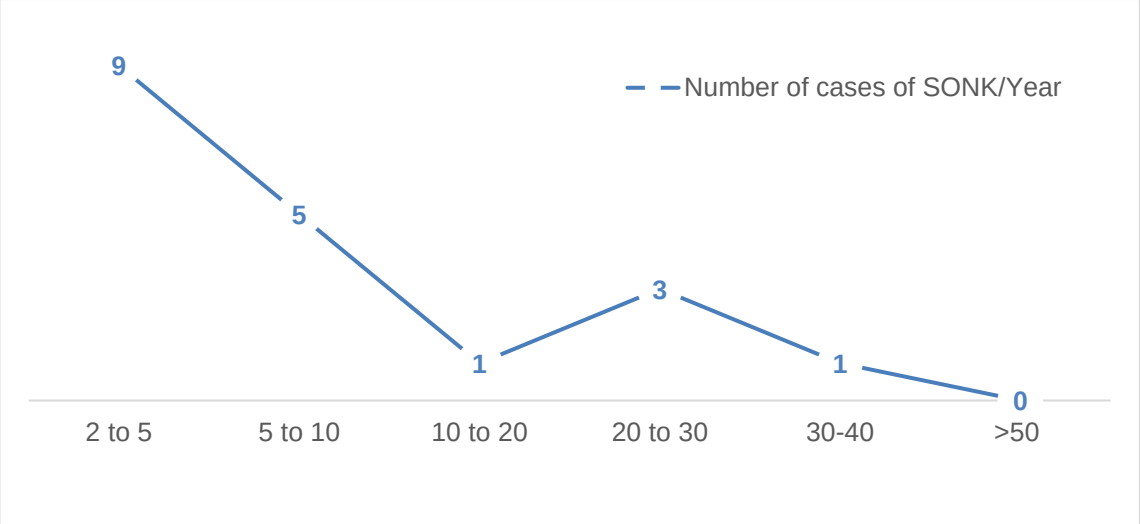

Figure 3-4: Graph summarising average case load of SONK treated per year, n=19

3.5.2 Round 1 range of treatments

Following collection of the round 1 demographic data, participants were then asked to indicate which, out of a list of treatments they have used at any time in their practice for the treatment or SONK. If a treatment was not listed in the multiple-choice list, a free text option was available; the results are summarised in table 3.3. By far the most commonly utilised treatments were knee arthroplasty, followed by high tibial osteotomy. The remaining arthroscopic treatments, along with grafting and decompression methods were utilised less frequently.

Treatment used	No. of respondents
Uni-compartmental knee replacement	14
Total knee replacement	12
High tibial osteotomy	9
Arthroscopic debridement	6
Arthroscopic drilling/microfracture: extra-articular	4
Arthroscopic drilling/microfracture: trans-chondral	3
Osteochondral transplantation: allograft	2
Osteochondral transplantation: autograft	1
Coagulation studies and anticoagulation	*1*
Conservative non-weight bearing	*1*
Antiresorptive Medication	*1*
Unloader brace	*1*
Conservative partial weight bearing and NSAIDs for 6 weeks	*1*
BioPoly after bony issue improved	*1*
Fine wire drilling	*1*
Extra-articular bone grafting when chondral surface intact	*1*

***Table 3.3: A summary of different treatment modalities used by respondents at any stage of their practice for the treatment of* SONK** *(treatments shown in italics were not in the multiple-choice list and were given as free text answers).*

3.5.3 Round 2 Participant Demographics

Round 2 was distributed to all members of the 20/20 group and the whole cohort of authors contacted in round 1 (excluding those with undeliverable email addresses), regardless of whether a response was received to the initial round. A total of 14 out of 54 (26%) responses were received, lower than the 19 (35%) received in round 1. In terms of country of practice, both rounds had a majority of over 70% from the UK and USA, with the remaining minority practicing throughout Europe. Experience and annual SONK case load also showed similar spread between rounds, with most participants having at least 10 years' experience as a knee surgeon, but mostly treating 2 to 10 cases of SONK per year. A comparison of demographics of participants in round 1 and 2 is shown in table 3.4.

Demographic		Round 1 (n)	%	Round 2 (n)	%
County of practice	UK	9	47	7	50
	USA	5	26	3	21
	Germany	3	16	2	14
	Switzerland	0	0	1	7
	Spain	1	5	1	7
	Luxembourg	1	5	0	0
	Total	**19**		**14**	
Years practicing as a knee specialist	5 to 10	1	5	1	7
	10 to 20	12	63	7	50
	20 to 30	4	21	4	29
	30-40	1	5	2	14
	>50	1	5	0	0
	Total	**19**		**14**	
Number of cases of SONK treated per year	2 to 5	9	47	6	43
	5 to 10	5	26	5	36
	10 to 20	1	5	1	7
	20 to 30	3	16	0	0
	30-40	1	5	1	7
	>40	0	0	1	7
	Total	**19**		**14**	

Table 3.4: Comparison of demographics of participants involved in round 1 and 2.

3.5.4 Scenario 1 (Koshino Stage 1 disease)

The first scenario, representative of early-stage disease (Koshino 1) is shown in table 3.5, there were no changes to the wording of the question stem between rounds 1 and 2. The results of round 1, scenario 1a are shown in figure 3.5 and 1b in figure 3.6.

A 60-year-old, active patient, with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee are normal, but MRI changes are in keeping with isolated spontaneous osteonecrosis of the weight bearing portion of the medial femoral condyle (no other degenerative changes or pathology)
Scenario 1a: What would be your first-line treatment?
Scenario 1b: Following failure of your first-line treatment, with ongoing pain but no radiological progression, what would be your usual second-line management?

Table 3.5: First scenario presented to participants, representative of early disease (equivalent to Koshino stage 1).

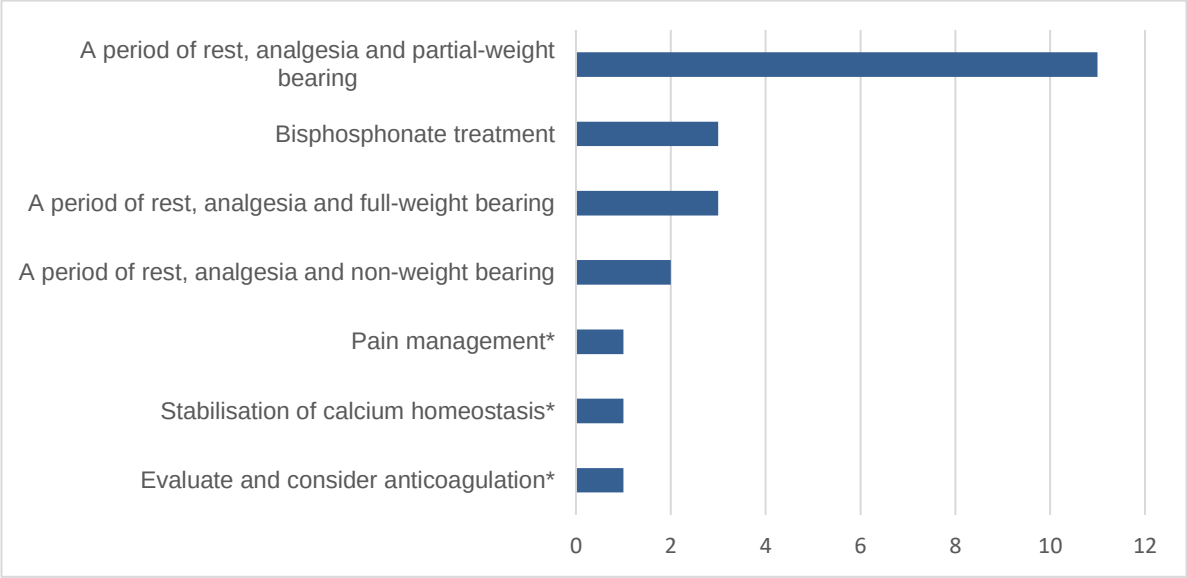

Figure 3-5: Bar chart demonstrating the number of participants selecting their preferred <u>first-line</u> treatment options for <u>round 1</u>, <u>scenario 1</u> equivalent to early-stage disease (Koshino 1), n=19
(= answers given as a free text option and not listed in the multiple choice). Participants permitted to select more than one answer.*

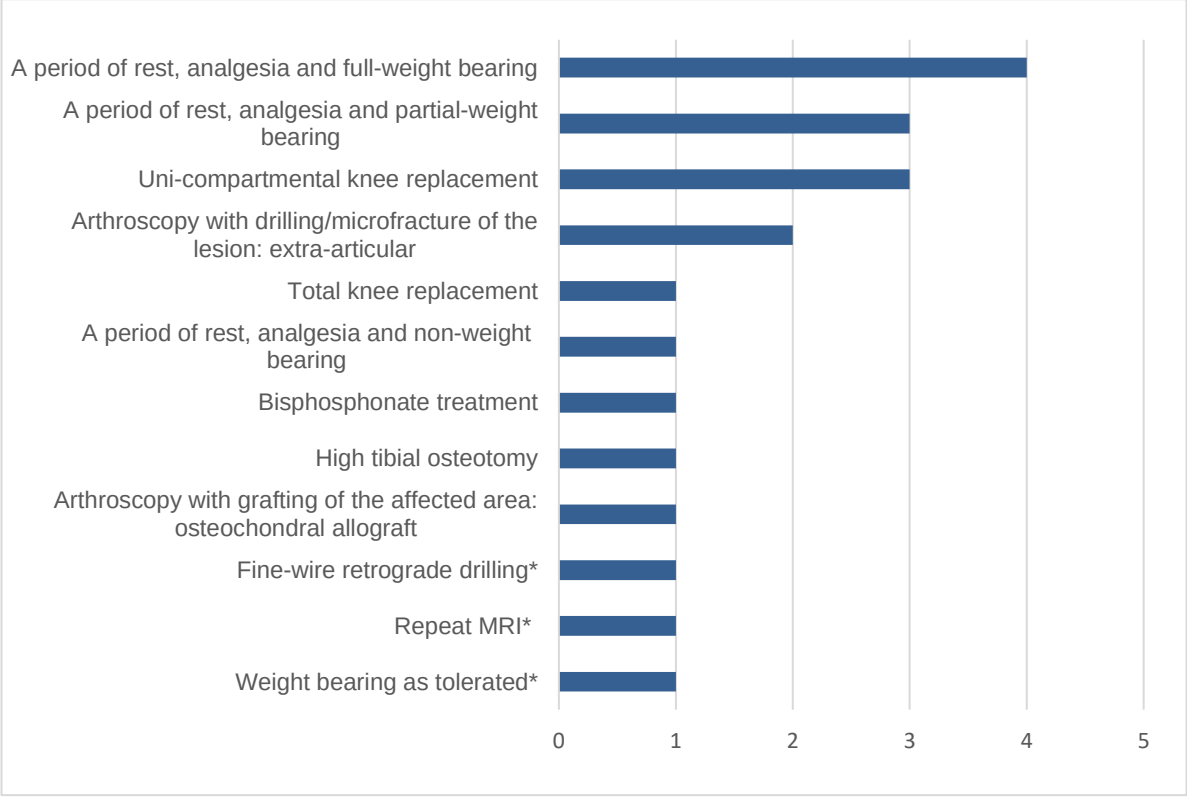

Figure 3-6: Bar chart demonstrating the number of participants selecting their preferred <u>second-line</u> treatment options for <u>round 1, scenario 1</u>, equivalent to early-stage disease (Koshino 1), n=19
(= answers given as a free text option and not listed in multiple choice), participants permitted to select more than one answer.*

For participants indicating that their treatment would entail non-operative measures, with analgesia with or without restricted weight-bearing, the intended duration of such treatment was requested; the mean duration was 11.5 weeks (range 6-24 weeks).

Analysis of the duration of such non-operative measures from round 1 clearly demonstrated three specific time periods (up to 6 weeks, up to 3 months, more than 3 months), so this was given as a separate question with a multiple-choice answer option, rather than a free text. Additional comments had also raised the treatment of functional bracing during a period of non-operative treatment, so this was added in as an additional yes/no answer as part of scenario 1.

Following review of the free text comments, the wording of the options for conservative treatment were adjusted. For round 2, the options were given as either ‘a period of rest, analgesia and full-weight bearing/weight bearing as tolerated’ or ‘a period of rest, analgesia and partial or non-weight bearing’ to limit the number of answer options.

Table 3.6 shows the most popular responses and percentage agreement from round 1, scenario 1; up to 5 of the top answers were used as possible multiple-choice options for scenario 1 in round 2 with the final option being ‘none of the above’. For scenario 1b, several answers scored equally, bisphosphonates therapy was carried forward to round 2 as it was most popular in scenario 1 from both scenarios combined. The results from round 2, scenario 1 are shown in figures 3.7 and 3.8.

Scenario	Treatment Option	Percentage agreement	n
1a	A period of rest, analgesia & partial-weight bearing	57.8%	9
	A period of rest, analgesia and full-weight bearing	15.8%	3
	Bisphosphonate treatment	15.8%	3
	A period of rest, analgesia and non-weight bearing	10.5%	2
1b	A period of rest, analgesia and full-weight bearing	21%	4
	A period of rest, analgesia and partial-weight bearing	15.8%	3
	Uni-compartmental knee replacement	15.8%	3
	Arthroscopy with drilling/microfracture of the lesion: extra-articular	10.5%	2
	Bisphosphonate treatment	5%	1

Table 3.6: Most popular answers from round 1, carried forward into round 2 (Scenario 1).

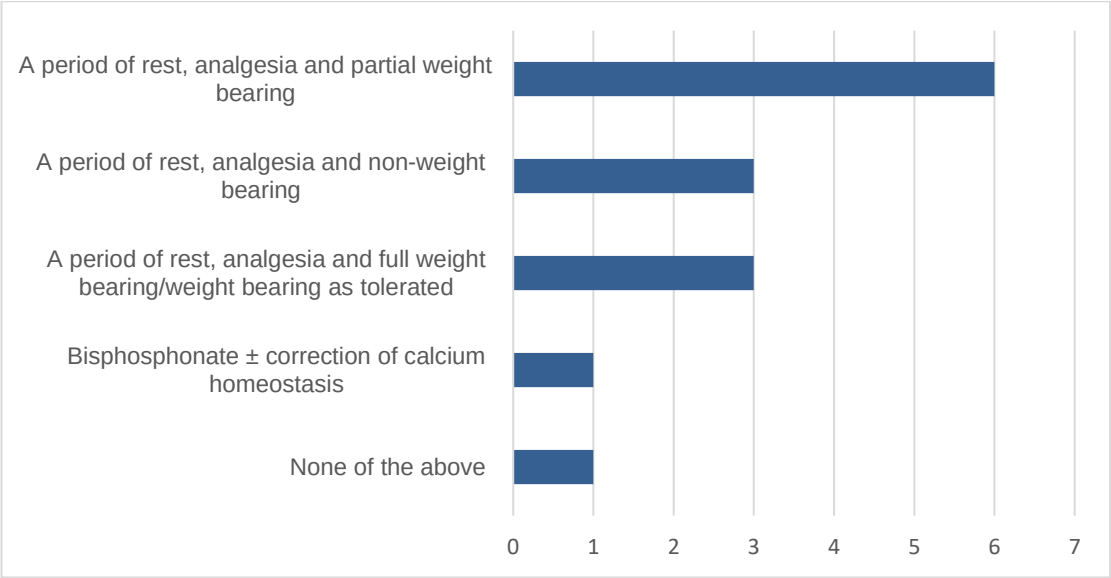

Figure 3-7: Bar chart demonstrating the number of participants selecting their preferred first-line treatment options for round 2, scenario 1, equivalent to early-stage disease (Koshino 1), n=14.

Out of the 14 responses to round 2, scenario 1a, 12 participants (86%) stated they would consider a period of rest and analgesia as their preferred first-line treatment; 50% would restrict the patients to partial-weight bearing, 25% would initiate a period of non-weight bearing, and the remaining 25% would allow their patients to fully weight-bear or weight-bear as tolerated. In terms of duration of such measures, the majority (n=8, 66.7%) would continue this treatment for a period of up to 3 months, 16.7% would treat for over 3 months and 16.7% for a period of up to 6 weeks. All 12 of the participants who selected a period of observation stated that they would not consider bracing of the knee during this time.

It was therefore determined that a consensus had been reached for first-line treatment in early-stage disease and the duration of such treatment; 86% of participants would treat with a period of rest and analgesia, with 66.7% of this group persisting with this treatment modality for a period of up to 3 months; 75% of participants selecting this treatment would restrict their patients to either partial or non-weight bearing during this time.

Scenario 1b presented the same information and asked for a preferred second-line treatment for early-stage disease following failure of initial treatment, with persisting symptoms but no radiological deterioration; the results are shown in figure 3.8.

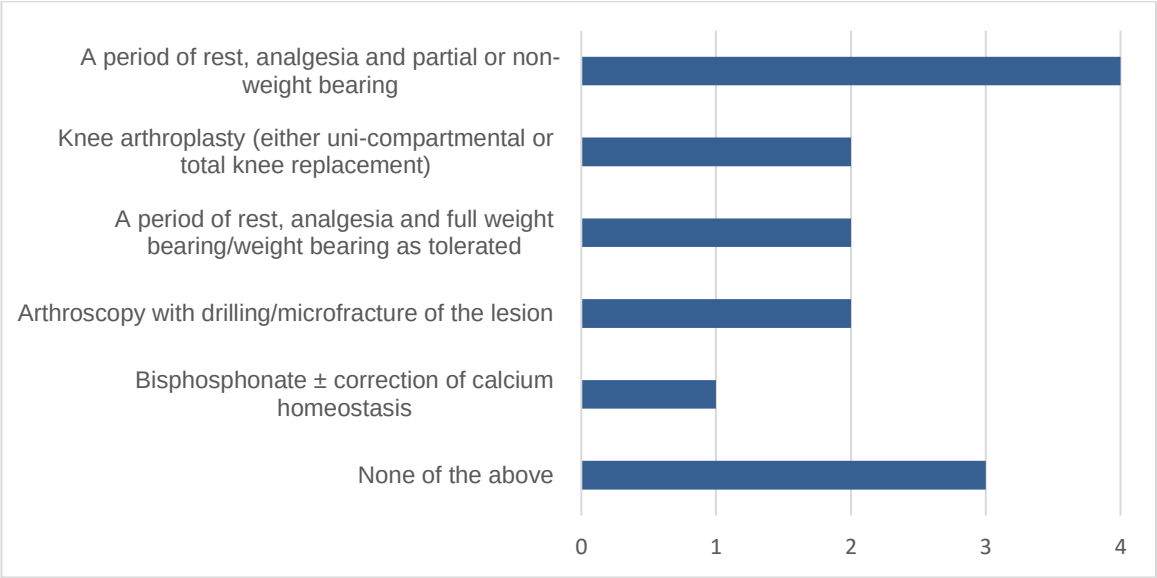

Figure 3-8: Bar chart summarising preferred second-line treatment for round 2, scenario 1, equivalent to early-stage disease (Koshino 1) n= 14.

In contrast to scenario 1a, there was a wider spread of answers for preferred second-line management following failure of initial measures; no single option reached a consensus of more than 60%. Non-operative treatment (with a period of rest and analgesia), regardless of weight bearing status reached a percentage of agreement of 43%.

From this scenario, representing early disease (Koshino stage 1) it can clearly be stated that a period of non-operative measures with analgesia and restriction in weight-bearing is an appropriate first line-treatment for a duration of up to 3 months. In terms of second-line treatment following failure of initial measures, a consensus has not been reached, with several different treatments options scoring almost equally (figure 3.8).

3.5.5 Scenario 2 (Koshino stage 2/3 disease)

Scenario 2 was then presented to represent intermediate-stage disease (Koshino 2/3) and is shown in table 3.7. This was also split into two sections, asking participants for their preferred first-line treatment (scenario 2a) and their second-line management (scenario 2b) should their initial measures fail; responses from round 1 are shown in figure 3.9 and 3.10 respectively.

A 60-year-old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion in the weight-bearing portion of the medial femoral condyle. MRI scan demonstrates a lesion with appearances consistent of spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology). Scenario 2a: What would be your first line treatment? Scenario 2b: Following failure of your first line treatment, with ongoing pain but no radiological progression, what would be your usual second line management?

Table 3.7: Scenario 2 presented to participants, representative of intermediate-stage disease (equivalent to Koshino 2/3).

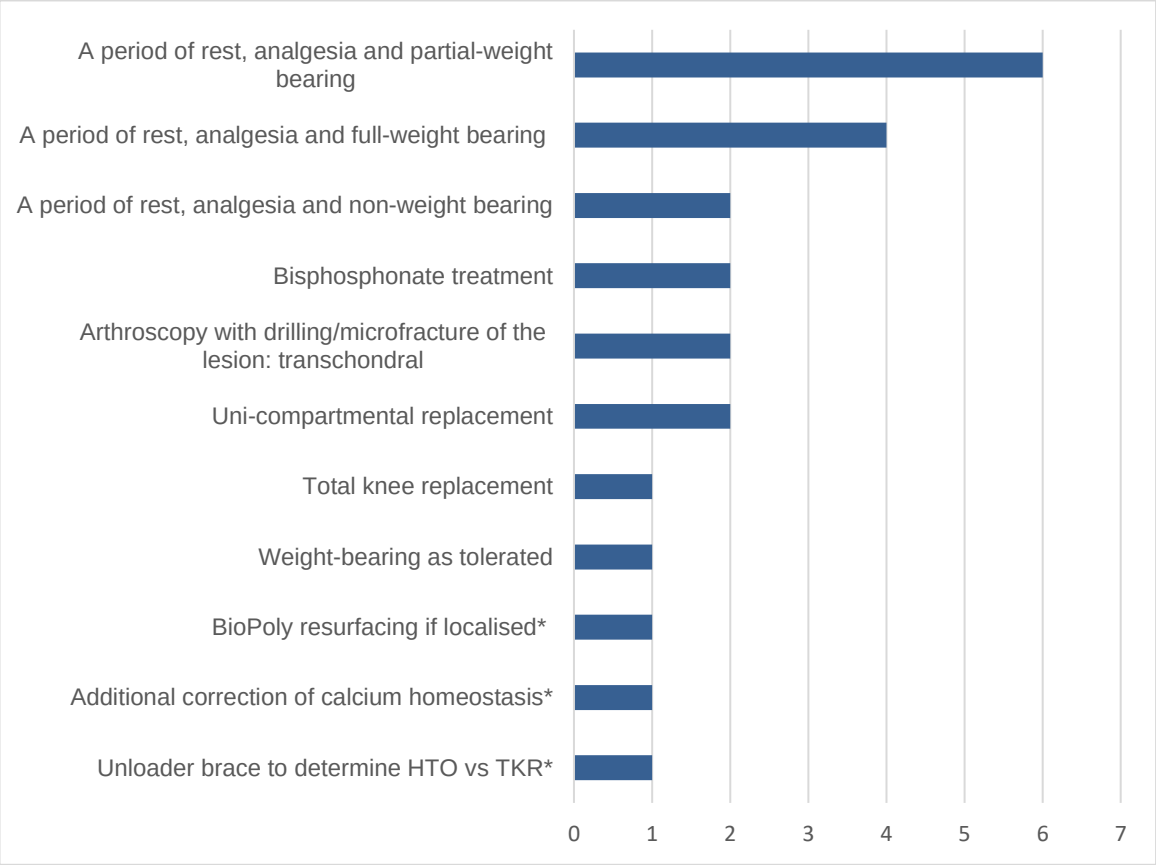

Figure 3-9: Bar chart demonstrating the number of participants selecting their preferred first-line treatment for round 1, scenario 2, equivalent to intermediate-stage disease (Koshino 2/3). n=19. *Participants permitted to select more than one answer (*= answers given as a free text option and not listed in the multiple choice). Abbreviations: HTO= high tibial osteotomy, TKR= total knee replacement.*

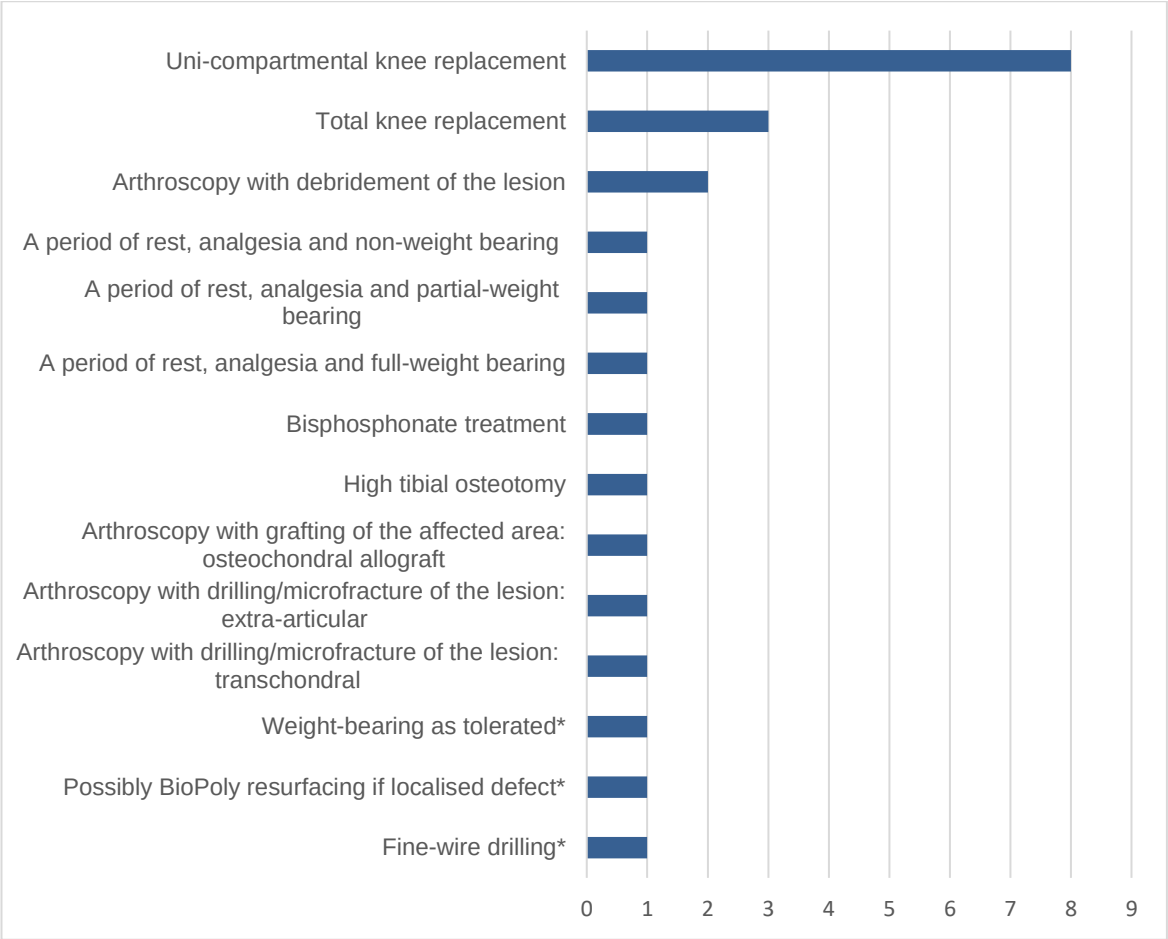

Figure 3-10: Bar chart demonstrating the number of participants selecting their preferred second-line treatment for round 1, scenario 2, equivalent to intermediate-stage disease (Koshino 2/3) n=19. *Participants permitted to select more than one answer (*= answers given as a free text option and not listed in the multiple choice).*

As with scenario 1, participants indicating that their treatment would entail non-operative measures were asked to state the intended duration of such treatment; the mean duration was 12.9 weeks (range 6-24 weeks).

In round 1, several participants commented that they would need additional clinical information regarding knee alignment prior to reaching a decision on treatment options for this scenario; this information was therefore added into the scenario for round 2, stating that the patient had normal knee alignment, otherwise the question stem was kept the same. One comment that was not addressed from round 1 stated that the treatment chosen would partly depend on the size of the lesion; it was felt that this would require numerous additional question stems, so was not taken forward.

The most popular answers from round 1, scenario 2 are shown in table 3.8, these answers were taken forward to be used for the multiple choice in round 2. For scenario 2b, there were 2 popular answers, but the remaining options were equally unpopular. Where possible, the treatment options with the best combined popularity across the

scenario were chosen to take forward to round 2. The results for round 2, scenario 2a are shown in figure 3.11.

Scenario	Treatment Option	Percentage agreement	n
2a	A period of rest, analgesia and partial-weight bearing	31.5%	6
	A period of rest, analgesia and full-weight bearing	21%	4
	Arthroscopy with drilling/microfracture	10.5%	2
	Bisphosphonate treatment	10.5%	2
	Uni-compartmental knee replacement	10.5%	2
2b	Uni-compartmental knee replacement	42%	8
	Total knee replacement	15.8%	3
	Arthroscopy with debridement of the lesion	5%	1
	Arthroscopy with drilling/microfracture	5%	1
	High tibial osteotomy	5%	1

Table 3.8 Most popular answers from round 1, carried forward into round 2, scenario 2.

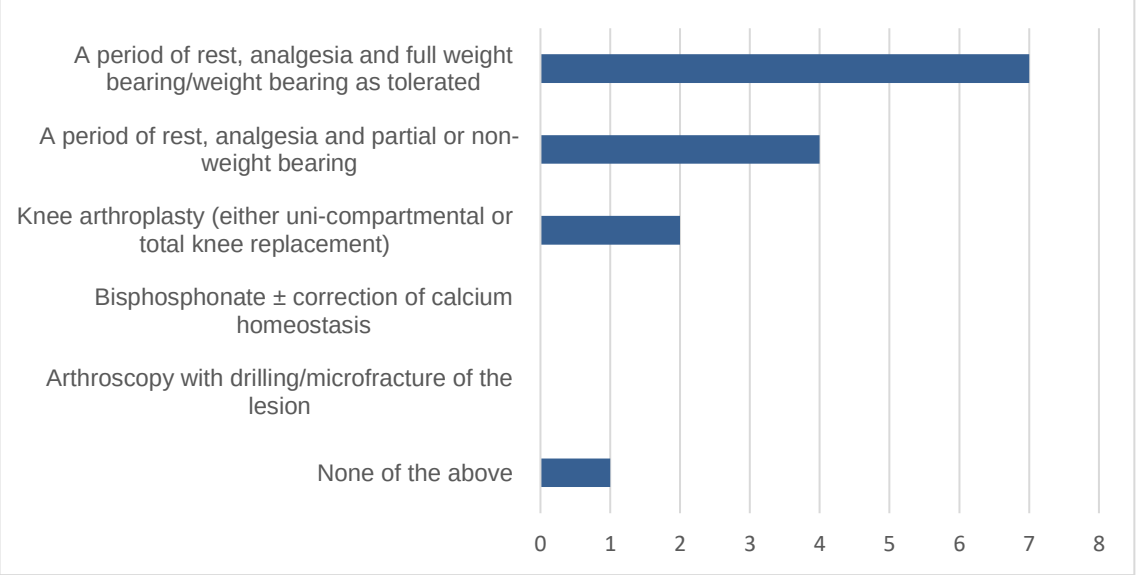

Figure 3-11: Bar chart demonstrating the number of participants selecting their preferred first-line treatment for round 2, scenario 2, equivalent to intermediate stage disease (Koshino 2/3) n=14.

Most participants stated that their first-line treatment for patients with intermediate-disease would be a period of rest, analgesia and either full weight-bearing, weight-bearing as tolerated or non-weight bearing; 78.6% of respondents selected one of these options. Out of the group selecting these measures, 63.6% would allow patients to fully weight-bear or weight-bear as tolerated, whereas the remaining 36.4% of the group would restrict the patients to partial or non-weight bearing. In terms of duration of

such measures, a consensus was reached, with 63.6% of participants stating that they would treat in this way for a period of up to 3 months (27.3% would treat for up to 6 weeks and 9.1% for a period of greater than 3 months). The remainder of participants stated they would treat with knee arthroplasty (14.3%) or would not treat with any of the available options (7.1%).

Scenario 2b was then presented, requesting a preferred second-line treatment, following failure of initial treatment for intermediate-disease, with persisting symptoms but no radiological deterioration; the results to this scenario are shown in figure 3.12. Seven participants (50%) would proceed with knee arthroplasty, the remaining group would either perform arthroscopy with drilling or microfracture (21.4%), undertake a period of rest, analgesia and partial or non-weight bearing (14.3%), or not use any of the possible options given (14.3%).

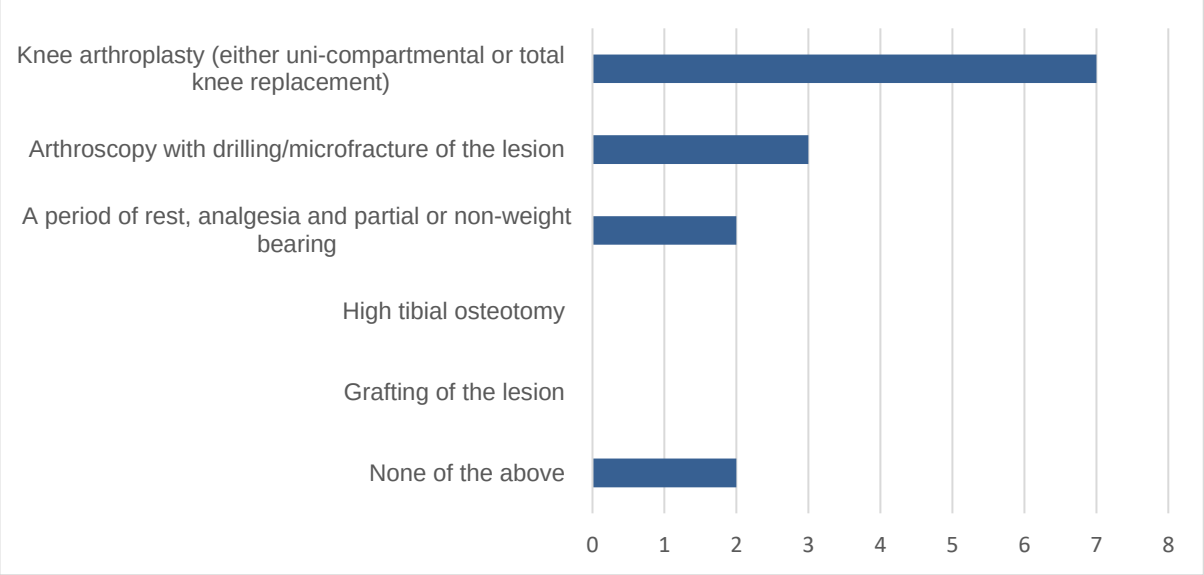

Figure 3-12: Bar chart demonstrating the number of participants selecting their preferred second-line treatment options for round 2, scenario 2, equivalent to intermediate stage disease (Koshino 2/3), n=14.

From this scenario, it can be concluded that a period of rest and analgesia for a period of up to 3 months is an acceptable first-line treatment for intermediate disease; 63.6% of participants selecting this option would allow their patients to either fully weight-bear or weight-bear as tolerated during this time. In terms of second-line treatment, knee arthroplasty was by far the most popular option, but with 50% of participants selecting this, it is not enough to reach consensus.

3.5.6 Scenario 3 (Koshino stage 4 disease)

The third and final scenario was presented to represent late-stage disease (Koshino 4) and formatted in the same way as the two previous scenarios. Scenario 3 is shown in table 3.9 and the results of round 1 in figures 3.13 and 3.14.

A 60-year-old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion with associated collapse of the weight-bearing portion of the medial femoral condyle. MRI confirms appearances in keeping with spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology) with associated collapse of the weight bearing portion.
Scenario 3a: What would be your first line treatment?
Scenario 3b: Following failure of your first line treatment, with ongoing pain but no radiological progression, what would be your usual second line management?

Table 3.9: Third and final scenario presented to participants, representative of late-stage disease (equivalent to Koshino stage 4).

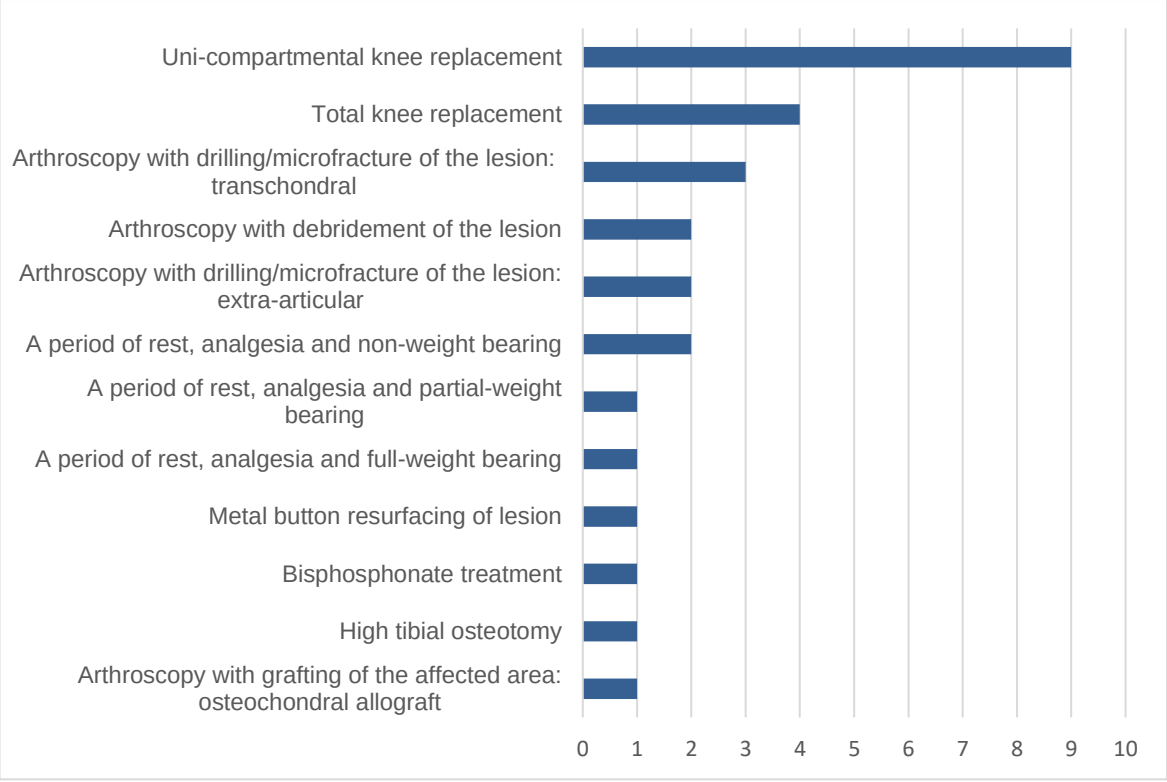

Figure 3-13: Bar chart demonstrating the number of participants selecting their preferred first-line treatment options for round 1, scenario 3, equivalent to late-stage disease (Koshino 4), n=19. *Participants permitted to select more than one answer (*= answers given as a free text option and not listed in the multiple choice).*

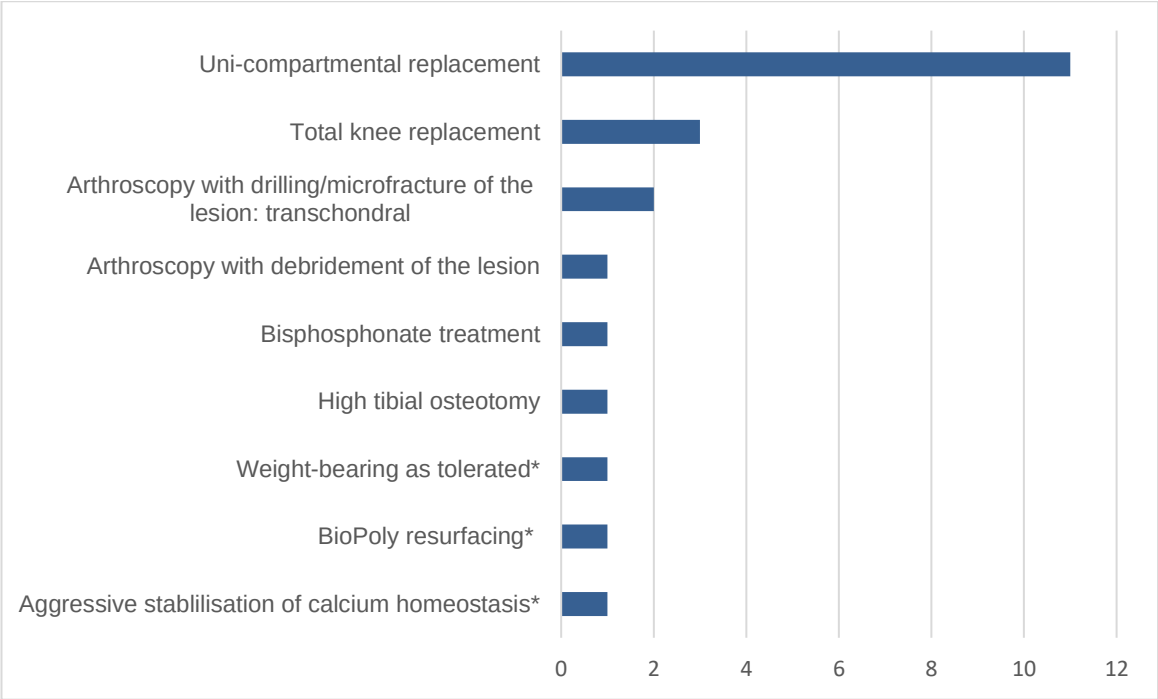

Figure 3-14: Bar chart demonstrating the number of participants selecting their preferred second-line treatment options for round 1, scenario 3, equivalent to late-stage disease (Koshino 4), n=19. *Participants permitted to select more than one answer (*= answers given as a free text option and not listed in the multiple choice).*

The percentage agreement for each treatment option was calculated and the top 4 or 5 answers were selected from each scenario to use as the multiple-choice answers for round 2; the percentage agreements for each scenario are shown in table 3.10.

Scenario	Treatment Option	Percentage agreement	n
3a	Uni-compartmental knee replacement	47.3%	9
	Arthroscopy with drilling/microfracture (extra-articular or transchondral)	26.3%	5
	Total knee replacement	21.1%	4
	Arthroscopy with debridement	10.5%	2
	A period of rest, analgesia and non-weight bearing	10.5%	2
3b	Uni-compartmental knee replacement	57.8%	11
	Total knee replacement	15.8%	3
	Arthroscopy with drilling/microfracture of the lesion	10.5%	2
	High tibial osteotomy	5.2%	1

Table 3.10: Most popular answers from round 1, carried forward into round 2 (scenario 3)

As in scenario 2, several participants commented in round 1 that they would need additional clinical information regarding knee alignment prior to reaching a decision on

treatment options for this scenario; this information was therefore added for round 2, stating that the patient had varus malalignment of the knee associated with condylar collapse. Otherwise, the scenario was kept the same as in round 1. The results to round 2 with the preferred first and second-line treatments for late disease are shown in figure 3.15 and 3.16 respectively.

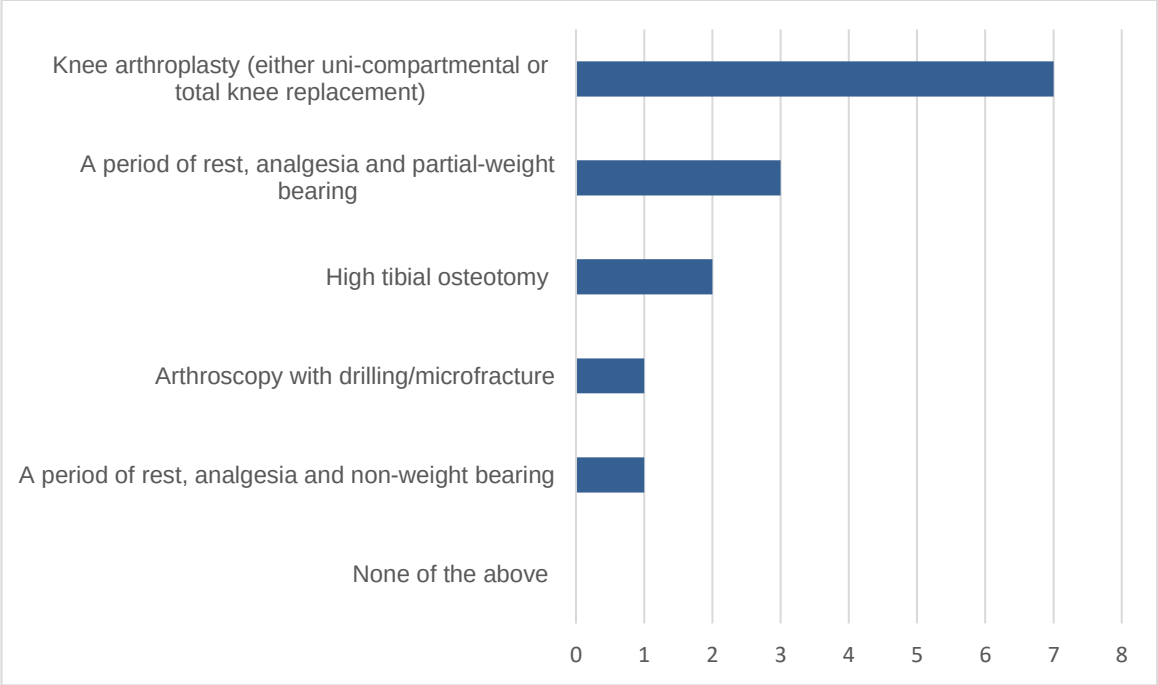

Figure 3-15: Bar chart demonstrating the number of participants selecting their preferred <u>first-line</u> treatment options for <u>round 2, scenario 3</u>, equivalent to late-stage disease (Koshino 4) n=14

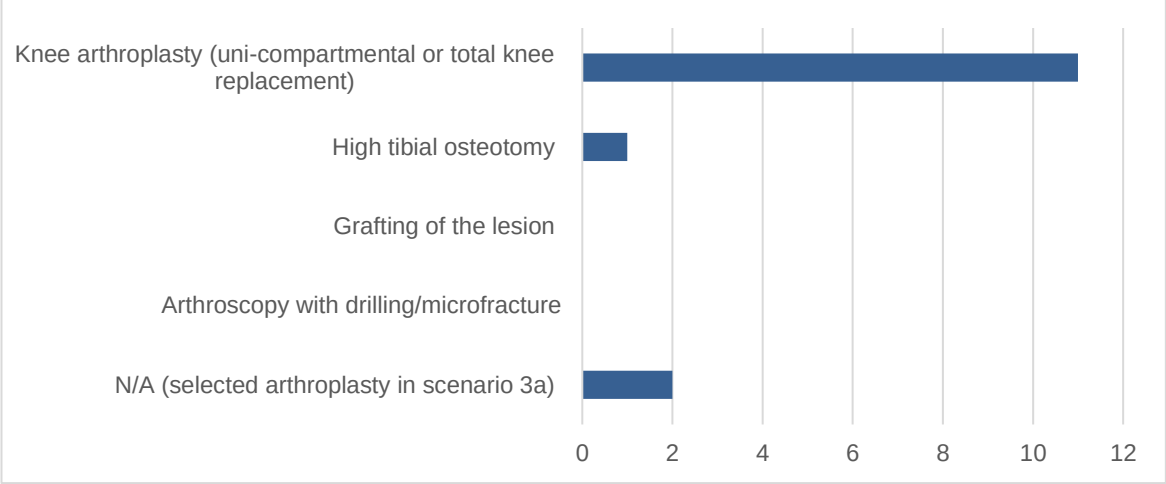

Figure 3-16: Bar chart demonstrating the number of participants selecting their preferred <u>second-line</u> treatment options for <u>round 2, scenario 3</u>, equivalent to late-stage disease (Koshino 4) n=14

For scenario 3a, representing first-line treatment for late disease, the treatment option of arthroplasty (either uni-compartmental or total knee replacement) was by far the most popular first line treatment option, but with 50% of participant selecting this modality is insufficient to achieve consensus. For scenario 3b, representing second-line

treatment, 78.6% of participants selected arthroplasty as their preferred treatment option, with 1 selecting high tibial osteotomy and the remaining 2 selecting the 'not applicable' option as they had chosen arthroplasty as first-line treatment.

From this scenario, it is appropriate to state that arthroplasty is considered a preferable treatment modality for both first and second-line treatment for patients with SONK and associated joint collapse. However, a consensus regarding the use of such surgery has only been reached for second-line treatment in this scenario.

3.5.7 Summary of Delphi Results

A summary of round 2 results and whether consensus has been reached for each scenario is shown in table 3.11. This 2-round Delphi study has reached a consensus for first-line treatment of early and intermediate-stage disease, with a period of rest and analgesia, with or without restriction in weight bearing being deemed appropriate for a period of up to 3 months. Consensus was also reached for treatment of patients with osteonecrosis and collapse of the medial femoral condyle, when initial measures have failed; 78.6% would proceed with knee arthroplasty. For the remaining scenarios, with the exclusion of scenario 1b, describing second line-treatment for early stage disease, a percentage agreement for a single treatment has reached 50%, which would be accepted as consensus in some literature, but did not reach the 60% that was set as the value for consensus in this study.

Scenario	**Most popular choice (percentage agreement)**	**Consensus reached?**
1a: early disease, first-line treatment	A period of rest, analgesia ± restriction of weight-bearing (85.7%)	Yes
1b: early disease, second-line treatment	A period of rest, analgesia ± restriction of weight-bearing (42.9%)	No
2a: intermediate disease, first-line treatment	A period of rest, analgesia ± restriction of weight-bearing (78.6%)	Yes
2b: intermediate disease, second-line treatment	Knee arthroplasty (50%)	No
3a: late disease, first-line treatment	Knee arthroplasty (50%)	No
3b: late disease, second-line treatment	Knee arthroplasty (78.6%)	Yes

Table 3.11: Summary of answers and percentage agreement to round 2 scenarios.

3.6 Delphi Study Discussion & Conclusion

This section summarises the main findings from the Delphi study evaluating joint preserving treatments for SONK. The strengths and limitations of the methodology are then discussed followed by the implications for both clinical practice and further research and conclusions of the review.

Summary of main findings

The main aim of the Delphi study was to engage orthopaedic knee experts in a formal consensus exercise to hopefully reach an agreement on the commonly utilised, and most appropriate treatments for different stages of SONK. An international group of surgeons have been involved throughout the study, with experience varying from 5 to over 50 years practicing as a consultant or international equivalent. From the collection of initial data in round 1, it became clear than numerous treatments, both operative and non-operative had been used at some stage in the practice of the respondents, with 17 different modalities being identified during initial data collection.

This study also set out to establish whether there is a role for non-operative management in the treatment of SONK. From the responses to the study, it has been demonstrated that a period of rest analgesia, with or without restriction of weight-bearing status has a role, throughout the spectrum of disease, but is most often utilised for patients in the early or intermediate-stages. A standard period of up to 3 months was the consensus for duration of this form of treatment. It is less clear from the results whether weight-bearing during this time should be restricted, with participants being more likely to enforce restriction in earlier disease.

Despite the supporting evidence of a randomised controlled trial evaluating the use of lateral wedge insoles for early stage disease (Uchio, et al., 2000), this is not a modality that was used by participants. Alternative medical management, particularly bisphosphonates, was rarely selected as a treatment modality for any disease stage; this response may reflect the very limited published evidence for their success (Breer, et al., 2013; Jureus, et al., 2012; Kraenzlin, et al., 2010). Additionally, bisphosphonate therapy may often be initiated and monitored by physicians, not surgeons, therefore by only including surgeons in this study, it may not fully relfect their overall usage in SONK.

A further objective was to establish whether specialists regularly perform arthroscopic interventions, or high tibial osteotomy, and at what stage in the disease process were these techniques most appropriate. Arthroscopy with drilling and microfracture was uncommonly chosen by participants throughout the spectrum of disease. Although

there are various small case series documenting success with the various arthroscopic techniques, combined with drilling and grafting (Akgun, et al., 2005; Deie, et al., 2008; Forst, et al., 1998; Kotani, et al., 2003), the Delphi results have concluded that arthroscopic interventions are uncommonly used. Whether this is due to personal experience or lack of evidence to support use of such techniques is unclear and further studies may be needed to be able to appreciate the efficacy and role of different techniques.

High tibial osteotomy (HTO) was also uncommonly selected, and its role was shown to be limited to late-stage disease with joint collapse and knee malalignment. This is not completely in keeping with the published evidence, which describes the use of HTO for intermediate as well as late-stage disease with mostly good results in moderately sized case series (Aglietti, et al., 1983; Koshino, 1982; Marti, et al., 2000; Takeuchi, et al., 2009; Valentí Nín, et al., 1998). It appears from the Delphi results that HTO is less frequently employed that the published literature would suggest. This may reflect the limited guidance regarding when to use such techniques and whether it should be limited to certain stages of disease, for example, in the presence of malalignment. Currently the best available research describing the technique for SONK is limited to case series only.

This study set out to achieve consensus on the treatment of patients with SONK and normal joint architecture. For patients with normal radiographic findings (Koshino stage 1), a consensus has been reached on preferred first-line treatment, with rest, analgesia and a period of restricted weight-bearing being the management of choice. This result supports the findings of the systematic review to a certain degree; several authors stated their patients undergoing surgery had failed such interventions, suggesting that all patients (at least in the early stages) have had a trial of non-operative management (Duany, et al., 2010; Miller, et al., 1986; Takeuchi, et al., 2009). It is less clear from the results, which is the best treatment for early disease when initial measures fail and this is an area which would warrant further research.

For intermediate-stage disease (Koshino stage 2/3), with normal joint architecture but radiographic evidence of SONK, by far the most popular first-line treatment was a period of rest and analgesia, without restriction in weight-bearing. For second-line treatment of this group of patients, knee arthroplasty was the most popular choice, but the percentage agreement of 50% was insufficient to establish consensus. This reflects the existing discussions in the literature emphasising that intermediate-stage disease is often the most difficult to deal with, particularly when patients have not improved from non-operative measures (Akgun, et al., 2005), but evidence from this Delphi shows that

arthroplasty may be an acceptable option in some of these patients, in whom first-line treatment measures have failed.

A consensus for treatment of patients with joint-collapse and knee malalignment following failure of initial measures has been reached, with more than three quarters of participants in agreement that knee arthroplasty would be the preferred method of treatment. For first-line treatment of this group of patients however, a consensus was not reached, with 50% of the group selecting knee arthroplasty, and the remainder selecting a period of rest, analgesia and partial weight-bearing (21.4%), high tibial osteotomy (14.3%), arthroscopy with drilling or microfracture (7.1%), or a period of rest, analgesia and non-weight bearing (7.1%). These findings are in keeping with the general agreement in the literature that knee arthroplasty is commonly the only option for patients with late-stage SONK (Karim, et al., 2015; Bruni, et al., 2012; Mont, et al., 2000).

Strengths and Limitations

At the time of writing, this is the first of any type of consensus study evaluating treatment of SONK, involving an international group of surgeons and has provided new evidence to support the use of different treatment modalities depending on disease stage, an area which is significantly lacking in currently available literature.

The response rate to both rounds of the study, particularly round 2 was lower than anticipated. Round 1 achieved an overall response rate of 35% compared to 26% in round 2. However, it is recognised than online-based Delphi studies often have lower response rates to traditional paper-based methods, particularly with subsequent rounds (Kwak & Radler, 2002). Although this is a challenge with the Delphi method, other consensus options were considered prior to the onset of the study and decided not to be logistically feasible given the international nature of the participants.

Although a lower number of participants were involved than planned, there are no clear guidelines on the ideal or minimum number for consensus studies; one study has suggested that Delphi studies with less than 6 participants have limited reliability, whereas any more than 12 results in an insignificant increase in reliability and have recommended an ideal panel size of 6-11 (Nair, et al., 2011).

A third round to the study may have resulted in consensus being achieved for all scenarios but given the reducing participant numbers between rounds 1 and 2, a third round would likely have had even fewer respondents with limited value of the results.

The lower than expected responses from the author group in round 1 led to an unexpected delay between the first and second rounds, while a second group of authors were contacted to take part; this is likely to have contributed to an additional

reduction in numbers between the two rounds. It is recognised that a lower than expected response rate can have an impact on the validity and overall quality of evidence and can risk introducing non-response bias (Hsu & Sandford, 2007). In hindsight, it may have been beneficial to ask potential participants to reply to the initial invitation, to gauge level of interest and identify a larger group of potential participants prior to the start of round 1.

Although an international group of participants were recruited from 6 different countries, this did not fully represent the author group. A large proportion of the publications were from Asia; 29.4% of authors contacted were based in Japan, China and South Korea, but no responses were received from any of these countries. This may have represented a language barrier, or, along with other non-respondents, may be due to a failure of receipt of the email requests; it is possible that unknown emails are automatically put into a junk mail folder. Involving participants from the UK, USA and Europe only may not fully reflect current practice as treatments may have varying popularity and differ according to country or continent.

A further limitation involves the definition of 'expert'; the annual case load of SONK was widely variable, ranging from 2 to 30 cases per year. The lower end of the spectrum may represent similar numbers to most orthopaedic knee surgeons. For future studies, it would be helpful to know each surgeon's overall experience (how many cases of SONK they have treated in total) as well as their annual case load as an initial information finding exercise, with only those treating a higher than average number of cases per year being selected for involvement in the final study. This would require many potential participants to be contacted in the initial stages and could lead to a limited population being eligible for inclusion.

In terms of limitations of the scenarios presented, there were some comments given in the free text area about lesion size. It was felt that this was beyond the scope of this study but would be an area for future research to determine whether lesion size, in addition to disease stage influences treatment. For the later scenarios, weight-bearing status was grouped into partial or non-weight-bearing as a single answer. The intention was to limit the number of answer options, but this may influence outcomes and would have been better kept as separate answers.

Implications for Clinical Practice

The results of the Delphi study have established that a period of non-operative treatment with analgesia, physiotherapy with or without restriction in weight-bearing is an acceptable first-line treatment, often regardless of the stage of disease, for a period of up to 3 months. This information can be used to guide future decision making for

clinicians, and highlights that surgical intervention is not always necessary as a first-line measure.

Although knee arthroplasty for SONK was beyond the scope of the systematic review, the Delphi study has confirmed that this is often the treatment of choice for patients with advanced disease, but more specifically in such patients where other treatment has failed, with 78.6% of participants selecting this as their preferred option.

Implications for future research

Although the Delphi has determined that a 3-month period of analgesia and physiotherapy is often used as a first-line treatment, it is less clear when it is appropriate to restrict weight-bearing; participants were most likely to enforce restriction in earlier disease. A comparative study evaluating whether weight-bearing status has any influence on disease progression and/or joint collapse would provide useful guidance for clinicians. There are numerous other areas where further research would be beneficial, particularly in providing further evidence on which treatments to use when initial measures fail, as this is where most of the uncertainty remains. Despite most research in the systematic review describing various arthroscopic interventions with drilling and grafting, the Delphi responses have not reflected the described techniques, with interventions being uncommonly selected. Further work is needed to determine whether such treatments have any role in management of SONK.

Conclusion and recommendations

Despite the limitations and smaller than anticipated numbers, this Delphi study has involved an international group of surgeons, who, when combined have a significant case load and years of experience in treating SONK. It has provided new evidence, which, following dissemination, may help to influence decision making for patients with different stages of disease and either support or change current practice, depending on clinicians' usual treatment methods. The recommendations from the results of this Delphi study are as follows:

1. A period of rest, analgesia with or without a period of restricted weight-bearing has an established role in the first-line treatment of early and intermediate stage disease in patients with SONK and normal joint architecture.
2. The use of knee arthroplasty for patients with SONK and joint collapse is an appropriate modality following failure of other measures.
3. The benefits of using bisphosphonate therapy at any disease stage is unclear.
4. Arthroscopic techniques, including microfracture, debridement and open grafting techniques are uncommonly used.

5. High tibial osteotomy appears to be reserved for cases of late-disease with malalignment.

This is the first study of its kind and will hopefully provide a basis for further work and potentially larger studies to clarify the best practice for stage-specific treatment of SONK. The overall combined implications of this study along with the systematic review will be discussed further in the following chapter.

CHAPTER FOUR: THESIS CONCLUSIONS

This chapter will summarise the overall major findings of the systematic review and Delphi study, a discussion of the implications for current practice will then follow, along with the need and priorities for future research. Finally, the conclusions to the thesis will be presented. The objectives of the thesis were divided into specific areas to evaluate effectiveness of non-operative measures, joint-preserving surgical treatment and review the various treatment modalities according to stage of disease; the findings related to these areas are discussed below.

Non-Operative Measures

The combined results of the systematic review and Delphi study have highlighted that a period of non-operative management with analgesia and physiotherapy is an appropriate first-line treatment for patients with early and intermediate-stage disease and can be trialled for a period of approximately 3 months before deciding whether additional intervention is required. Although only 3 included studies in the systematic review specifically evaluated a period of rest, analgesia and physiotherapy with improvement in overall clinical outcomes (Aglietti, et al., 1983; Valentí Nín, et al., 1998; Yates, et al., 2007), several additional studies have also implied that their entire population were treated with such measures, and it is only those who continued to have symptoms proceeded to alternative treatments (Akgun, et al., 2005; Duany, et al., 2010; (Forst, et al., 1998) Miller, et al., 1986; Takeuchi, et al., 2009). Whether to restrict weight-bearing during this time remains debated, as does the most appropriate second-line treatment for patients with persisting significant symptoms. The limited amount of published research regarding non-operative treatment does not seem to reflect specialists' willingness to trial a period of conservative treatment, with this being a popular choice throughout the spectrum of disease, but further research evaluating outcomes following these non-operative measures, and an assessment of whether weight-bearing status adversely effects outcomes would aid in clarifying the most appropriate treatment protocol for these patients.

Whether bisphosphonate therapy has a role for any disease stage in SONK is unclear. Although the small included case series demonstrated improvements in clinical and radiological outcomes (Breer, et al., 2013; Jureus, et al., 2012; Kraenzlin, et al., 2010), these were non-comparative . A recent systematic review specifically assessing the role of bisphosphonates in SONK has come to similar conclusions; more research is needed to ascertain whether they should have a continued role in management (Jordan, et al., 2016). This limited evidence has been reflected in the responses to the delphi study; bisphosphonate therapy was rarely selected by participants as a

treatment modality for early and intermediate-stage disease. This may either reflect the perceived lack of ineffectiveness or the fact that orthopaedic surgeons would only be involved in consideration and onward referral for treatment to another specialist, but not directly involved in administration and monitoring. This highlights the potential need to involve a more multi-disciplinary group of participants in any future consensus studies or workshops to guage a true overview of the frequency of bisphosphonate use in SONK.

Joint-Preserving Surgical Measures

Numerous joint-preserving surgical interventions have been described in the systematic review, both arthroscopic and open techniques; a similar range of modalities were identified as potential treatments in the Delphi study during collection of demographic information. They range from simple arthroscopic debridement to various drilling and grafting techniques and more invasive realignment surgery in the form of high tibial osteotomy. Although this is the area that had by far the most included research in terms of study numbers, it is limited to low level evidence only, with variable patient numbers, ranging from 6 to 36. This, along with hugely differing techniques and the numerous outcome measures used to quantify results makes it difficult to support the benefits of one type of joint-preserving surgical intervention over another. This lack of clarity is reflected in the Delphi study results; only drilling/microfracture and high tibial osteotomy were selected and carried forward to be possible answers in round 2, but even then they were rarely chosen by participants as preferred treatment options. Some joint-preserving surgical methods not described in the included research were also identified as preferred treatment modalities for patients in the initial rounds of the Delphi study; fine wire retrograde drilling was a technique identified by one participant as a preferred second-line treatment for early and intermediate disease. Another participant stated that they would consider BioPoly® resurfacing for small lesions, this is a resurfacing device made of up ultra-high molecular weight polyethylene and hyaluronic acid and has limited evidence to describe its use for various cartilage defects in the knee (Jeuken, et al., 2016; Nathwani, et al., 2017). Neither additional technique identified in the Delphi study has published evidence specific to treatment of SONK. Overall, this category of joint-preserving surgical treatments is vast, with numerous existing and emerging techniques. The roles of such treatment remain unclear from both the systematic review and Delphi study; this reflects the need for further up-to-date research to clarify which of the treatments are effective, and at what stage of disease is their use most beneficial.

Implications for Clinical Practice

The results of both the systematic review and Delphi study have established that a period of non-operative management with analgesia, physiotherapy with or without weight-bearing restriction for up to 3 months is an acceptable first-line treatment, often regardless of the stage of disease. A quarter of included studies employed this management for patients prior to proceeding with any surgery (Akgun, et al., 2005; Duany, et al., 2010; Forst, et al., 1998; Miller, et al., 1986; Takeuchi, et al., 2009). Consensus was reached that this was the preferred treatment option for patients with early and intermediate SONK, but some participants still selected this as a first-line treatment for all disease stages. This information can be used to guide future decision making for clinicians, and highlights that surgical intervention is not always necessary as a first-line measure.

Although knee arthroplasty for SONK was beyond the scope of the systematic review, it has been established that this is often the preferred intervention for patients with late-stage disease and associated joint collapse (Radke, et al., 2005). The Delphi study has confirmed that this remains the case and is often the treatment of choice for patients with advanced disease, but more specifically in such patients where other treatment has failed, with 78.6% of participants selecting this as their preferred option, confirming the general opinion in the literature (Karim, et al., 2015; Mont, et al., 2000).

Implications for future research

The findings of both the systematic review and Delphi study suggest that further research would be worthwhile, to reduce the level of uncertainty still present and work towards eliminating the knowledge gap regarding stage-specific treatment for SONK. A significant proportion of the included studies in the systematic review are over ten years old; this further highlights the need for more up to date, good quality research to reflect advances in techniques and current trends of practice.

Although this thesis has determined that a 3-month period of analgesia and physiotherapy is often used as a first-line treatment, it has failed to clearly define during which stages of disease it is most appropriate to restrict weight-bearing. At the very least, a comparative study evaluating whether full weight-bearing versus partial or non-weight bearing has any influence on disease progression would provide useful guidance for clinicians. There are numerous other areas where further research would be beneficial, particularly in evaluating in more detail the efficacy of bisphosphonates, the various arthroscopic techniques, grafting and high tibial osteotomy. Despite

randomised controlled trials often being the gold-standard to determine true efficacy of treatments, they are not always feasible for less common conditions (Gagne, et al., 2014; Kesselheim, et al., 2011). For all treatments, well designed comparative studies may provide further information regarding effectiveness, especially with more of a focus on outcomes related to disease stage. It is however, difficult to fully appreciate whether such studies would be possible given the infrequent presentation of SONK and would likely need to be at the very least multi-centre trials over a significant time period, either on a national or international basis.

There is also a need to standardise outcome reporting, as the wide variety of measures used, which are often based on country of practice makes it difficult to compare clinical results. At present, most outcome measures used were developed for knee osteoarthritis and it is unclear if any have been validated specifically to assess SONK, this is an area which would also warrant further work to improve overall interpretation of results.

The uncommon nature of SONK also makes working towards further consensus studies difficult; most knee surgeons will see very few cases of SONK throughout their career, so finding alternative approaches to identify experts with more experience than the average orthopaedic knee surgeon, other than using the methods employed in this Delphi study would prove challenging.

Conclusion

The results of the systematic review and Delphi study have provided a foundation of evidence regarding the effectiveness of joint-preserving treatments for SONK but have also identified large gaps in current research and the need for larger, well-designed and up-to-date studies to be able to work towards developing treatment guidelines for different stages of disease. At present, although this study has concluded that certain treatments are commonly used and effective, there is insufficient evidence to definitively state which treatment to use during each stage of disease.

At the time of writing, this thesis is the first to describe the outcomes of both surgical and non-surgical joint-preserving treatment modalities for the management of SONK and is the first of any type of consensus study evaluating current practice and treatment according to disease stage. The results of the systematic review and Delphi study together are not fully conclusive; however, they do suggest that a period of non-operative measures with analgesia and physiotherapy are often appropriate and

effective for patients with early and intermediate-stage disease, with knee arthroplasty being warranted for patients with late-stage disease and joint collapse. The efficacy of other joint-preserving treatments remains debated, with only limited evidence to support their use. Further research is therefore needed before being able to state whether treatments such as bisphosphonate therapy, various arthroscopic techniques with lesion drilling and grafting or high tibial osteotomy should have a continued role in the routine management of patients.

Spontaneous osteonecrosis of the knee is a relatively uncommon disease, and this is likely to be one of the major limiting factors in the currently available research and reasons behind the small studies and lack of established treatment guidelines, with high-level evidence almost non-existent. Future research in this area would undoubtedly be beneficial; clinical trials and larger consensus studies would be justifiable and worthwhile. This thesis has contributed new knowledge to the treatment of SONK, but more work is needed prior to being able to formulate formal guidelines for treatment according stage of disease.

CHAPTER FIVE: REFERENCES

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Appendix 1: Results of AMED and Cochrane search

AMED Search		
Search ID	**Search Terms**	**Number of Results**
3	1 AND 2	18
2	TX osteonecrosis OR TX avascular necrosis OR TX bone necrosis OR TX aseptic necrosis	295
1	TX knee OR TX knee joint	9929
Cochrane Search		
3	1 and 2	26
2	Osteonecrosis	6
1	Knee	136

Appendix 2: Systematic Review Data Collection Form

Paper Details	
Title	
Study ID (surname, year)	
Name of review author	
Date Completed	
Notes (eg references to check)	
Database identified	MEDLINE (OVID); MEDLINE-in-Process (OVID); EMBASE (OVID); AMED (OVID); Cochrane (including CENTRAL, DARE and HTA)
Translated to English	Yes/No
Duplicate publication	Yes/No

Methodology	
Aim of study?	
Study design	
Level of evidence	
Recruitment method for participants	
Inclusion criteria	
Exclusion	
Informed consent	Yes/No/Unclear
Ethical approval?	Yes/No/Unclear
Funding	Yes/No If yes, source/amount:
Statistical methods Appropriateness	
Power Calculation?	Yes/No
Setting (eg specialist centre)	

Participants	
Number eligible and included	
Number excluded	
Number refused to take part	
Number randomised to intervention (if applicable)	
Number randomised to control (if applicable)	
Excluded post-randomisation (if applicable)	
Number withdrawn	
Number lost to follow-up	
Included in analysis (Included for each outcome if relevant)	
Age: Mean- Range-	
Gender distribution	
Ethnicity (if included)	

Spontaneous or secondary ON (if secondary- cause eg steroids)	
Stage of disease --& method of staging (eg MR/XR)	
Time from diagnosis to treatment	
Patient co-morbidities	

Intervention	
Details of intervention(s)	
Details of control (if applicable)	
Co-interventions (if relevant)	
Delivery of intervention Timing Frequency Duration	
Providers (consultant/level of experience)	
Integrity of intervention (delivered as intended/any assessment in article?)	

Outcomes	
Primary outcome measure	
Secondary outcome measures (if included)	
Methods of assessing outcomes (clinical/radiological and scoring system used)	
Validity/reliability of outcome measures	
Methods of f/u for non-respondents (if any)	
Timing of f/u: Frequency Length of overall f/u	
Adverse events & frequency	
Additional treatment needed/given?	

Results					
Outcome	Timing of outcome assessment	Intervention group		Control group (if applicable)	
		Observed (n)	Total (N)	Observed (n)	Total (N)

Notes on results/outcomes (and details if descriptive terms used only):

Quality Assessment:

MINORS	
	Score (0=not reported, 1=reported inadequately, 2=reported adequately)
Clearly stated aim?	
Inclusion of consecutive patients?	
Prospective data collection?	
Endpoints appropriate to study aim?	
Unbiased assessment of the study endpoint?	
F/u period appropriate?	
Loss to f/u >5%	
Prospective calculation of study size?	
For comparative studies:	
An adequate control group?	
Contemporary groups?	
Baseline equivalence of groups	
Adequate statistical analysis	
TOTAL SCORE=	
Global ideal score=16 for non-comparative and 24 for comparative studies	

Cochrane risk of bias (for RCTs)

Domain	**Review authors' judgement**	**Support for judgement**
Random sequence generation*	***High risk*** ***Unclear*** ***Low risk***	**Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.** *Quasi-RCTs and Controlled Before and After (CBA) studies must be rated as 'High Risk' for random sequence generation as the methods were not, by definition, truly random.*
Allocation concealment	***High risk*** ***Unclear*** ***Low risk***	**Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.** *CBA Studies should be rated 'High Risk. Quasi-RCTs are likely to be rated 'High Risk but there may be some exceptions.*
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	***High risk*** ***Unclear*** ***Low risk***	**Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.**

Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	***High risk*** ***Unclear*** ***Low risk***	**Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective**. If the outcome is objective (eg. length of hospital stay) the rating should be 'Low risk.
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	***High risk*** ***Unclear*** ***Low risk***	**Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.**
Selective reporting	***High risk*** ***Unclear*** ***Low risk***	**State how the possibility of selective outcome reporting was examined by the review authors, and what was found.**
Other sources of bias	***Note: all answers should follow the format:*** ***High risk*** ***Unclear*** ***Low risk***	**State any important concerns about bias not addressed in the other domains in the tool.** **If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.**

Appendix 3: List of Excluded Studies

1st Author	Year	Title	Reason for Exclusion
Beckmann	2012	Intravenously applied prostacycline and bisphosphonates in osteonecrosis and bone-marrow oedema	Full text not in English
Carpintero-Benitez	1998	Osteonecrosis of the tibial plateau	No clinical or radiological outcome measures
Convery	1991	Fresh osteochondral allografting of the femoral condyle	Steroid associated cases only
Feldkamp	1986	Arthroscopy of the spontaneous osteonecrosis of the knee joint.	Full text not in English
Flynn	1994	Osteoarticular Allografts to Treat distal femoral osteonecrosis	Mostly secondary ON (one patient with SONK)
Fukui	2002	Iliac bone graft for steroid-associated osteonecrosis of the femoral condyle	Steroid associated cases only
Gortz	2010	Fresh Osteochondral Allografting for Steroid-Associated Osteonecrosis of the Femoral Condyles	Steroid associated cases only
Gross	1983	Reconstruction of skeletal deficits at the knee: a comprehensive Osteochondral Transplant programme	No differentiation between SONK/secondary ON in results
Hsu	1989	The Study of Maquet Dome High Tibial Osteotomy	No differentiation between OA & SONK in results
Jacobs	1989	Core decompression of the distal femur for avascular necrosis of the knee	No differentiation between spontaneous/secondary ON
Jureus	2013	The natural course of Spontaneous Osteonecrosis of the Knee	Mostly arthroplasty (2 cases HTO)
Karataglis	2006	Autologous osteochondral transplantation for the treatment of chondral defects of the knee	Only 2 cases SONK
Koshino	2004	Fifteen to twenty-eight years' follow-up results of high tibial valgus osteotomy for osteoarthritic knee	No differentiation between OA & SONK in results
Lotke	1982	The treatment of osteonecrosis of the medial femoral condyle	No clinical or radiological outcome measures
Marulanda	2006	Percutaneous drilling for the treatment of secondary osteonecrosis of the knee	Secondary osteonecrosis only
Maynou	1998	Long-term results of autogenic osteochondral grafts in large articular defects of the knee	Full text not in English
Meier	2014	Effect of ibandronate on spontaneous osteonecrosis of the knee: a randomised, double blind, placebo controlled trial	No separation of patient populations
Meyers	1989	Resurfacing of the knee with fresh osteochondral allograft	Steroid associated cases only
Mont	2000	Atraumatic osteonecrosis of the knee	Secondary osteonecrosis only
Mont	1997	Core decompression for avascular necrosis of the distal femur	Steroid associated cases only
Motohashi	1989	Clinical course and roentographic changes of osteonecrosis in the femoral condyle under conservative treatment	No differentiation between SONK/secondary ON in results

1st Author	Year	Title	Reason for Exclusion
Ripoll	2009	Osteonecrosis of the knee. Iliac crest mesenchymal cell perfusion	Full text not in English
Saito	2014	Five- to ten-year outcome following medial opening-wedge high tibial osteotomy	No differentiation between OA & SONK in results
Shasha	2002	Long-term clinical experience with fresh osteochondral allografts for articular knee defects in high demand patients	No separation of patient populations
Soucacos	1997	Idiopathic osteonecrosis of the medial femoral condyle: classification & treatment	No clinical or radiological outcome measures
Valenti	2005	Idiopathic osteonecrosis of the medial tibial plateau	No clinical or radiological outcome measures
Wang	2002	Treatment of focal articular cartilage lesions of the knee	No separation of patient populations

Appendix 4: MINORS assessment for relevant included studies

MINORS criteria	Aglietti, 1983	Marti, 1999	Koshino, 1982	Akgun, 2005	Breer, 2012	Deie, 2008	Duany, 2009	Forst, 1998	Johnson, 2014	Jureus, 2012	Kotani, 2003	Kraenzlin, 2010	Marcheggiani Muccioli, 2012	McDermott, 1984	Miller, 1986	Takeuchi, 2009	Tanaka, 2009	Valentí Nín, 1998	Yates, 2007
Clearly stated aim?	2	2	2	2	2	1	1	1	2	2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients?	0	2	0	0	1	2	0	0	0	2	0	0	2	2	0	0	0	0	2
Prospective data collection?	2	2	0	0	0	0	0	0	2	2	0	2	2	2	2	0	0	0	0
Endpoints appropriate to study aim?	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	1	1
Unbiased assessment of the study endpoint?	0	0	0	2	2	0	1	1	0	0	0	1	2	0	0	0	1	0	0
F/u period appropriate?	2	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	0
Loss to f/u >5%	1	2	2	2	2	2	2	2	0	2	2	2	2	1	2	2	2	2	2
Prospective calculation of study size?	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
An adequate control group?	0	1	0																
Contemporary groups?	0	2	0																
Baseline equivalence of groups	0	1	0																
Adequate statistical analysis	0	2	2																
TOTAL SCORE=	9	18	10	10	9	9	7	7	8	12	8	11	16	11	10	8	9	7	7

Appendix 5: Description of Functional Scoring Tools

Score name, abbreviation	Domains assessed	Max score	Score breakdown	Developed for specific conditions?
Clinical Scoring Tools				
Activity level of Cincinnati (Mandelbaum, et al., 2000)	Pain, swelling, giving way, overall activity level, walking, stairs, running, jumping	100	<30 poor; 30-54 fair; 55-79 good; >80 excellent	Originally for ACL injuries
Euro-Qol (EQ-5D) (The EuroQol Group, 1990)	Mobility, self-care, usual activities, pain/discomfort, anxiety/depression & EQ-VAS	Each domain scored: 1=no problems, 2=some problems, 3=extreme problems, EQ-VAS scored from 0-100		Generic measure of health
Fresh small fragment osteochondral allograft score (McDermott, et al., 1985)	Pain, instability, walking aids, walking distance, knee range of motion, knee effusion	100	Higher scores indicate better outcomes; 100= normal knee, ≥75= successful outcome	Osteochondral allografts
Hospital for special surgery knee score (HSS)/Ranawat knee score (Ranawat, et al., 1976)	Pain, function, range of motion, muscle strength, flexion deformity, instability	100	Excellent 85-100; good 75-84; fair: 60-69; poor <60	Developed for knee arthroplasty
Japanese Orthopaedic Association score (JOA) (Japanese Orthopedic Association, 1988)	Pain on walking, pain on ascending or descending, range of motion, joint effusion	100	Higher scores indicate better outcomes	Validated for knee osteoarthritis
American Knee Society Score (KSS) (Insall, et al., 1989)	Pain, stability, range of motion; function: walking distance, stair climbing	100	Excellent 85-100; good 75-84; fair: 60-69; poor <60	Developed for knee osteoarthritis
Lysholme Score (Lysholm & Gillquist, 1982)	Pain, swelling, limp, squatting, instability, support, stair climbing, locking	100	Higher scores indicate better outcomes	Developed for ligamentous instability
Ordoñez (Ordóñez, et al., 1987)	Excellent: close to normal function, no pain & active life; Good: 90º flexion, and mild occasional pain; Fair: <90º flexion, mild pain, and limited gait; Poor: constant pain, limping, very limited function			Initial description for osteonecrosis
Summary of common complaints (Johnson, et al., 2014)	Reported status (same/improved/worse); persistent symptoms; activity limitations; walking; physical examination			Not stated

Score name, abbreviation	Domains assessed	Max score	Score breakdown	Developed for specific conditions?
Tegner score (Tegner & Lysholm, 1985)	Limp, support, locking, instability, pain, swelling, stair-climbing, squatting	100	Higher scores indicate better outcome	Introduced for knee ligament injuries
Visual analogue scale (VAS) (Huskisson, 1974)	Scale ranging from 'no pain' to 'worst pain imaginable', usually a numerical scale from 0-10 or 0-100		Lower numerical value indicates less pain	Generic pain scoring tool
Radiological Indices and Scoring Tools				
Femorotibial angle (FTA) (Moreland, et al., 1987)	The angle formed by the femur & the tibia, measured by drawing lines through the centre of tibial and femoral shafts	Normal alignment considered to be between 182-184 degrees		N/A
Whole Organ Magnetic Resonance Imaging Score (WORMS) (Peterfy, et al., 2004)	Articular cartilage integrity, subarticular bone marrow abnormality/cysts/bone attrition, meniscal integrity, cruciate and collateral ligament integrity, synovitis/effusion, intra-articular loose bodies, peri-articular cysts/abscesses	332	Lower scores correlate with improved radiological findings	Developed for osteoarthritis

Appendix 6: Delphi Invitation Email Templates

Initial Invitation:
Dear Doctor _____,

I am emailing to invite you to participate in an international Delphi study to support research into joint-preserving management of spontaneous osteonecrosis of the knee (SONK).

As an established knee expert who has recently published on the topic (or is a member of the 20/20 knee group) I am keen to gain your views and trends of practice to work towards a consensus for managing patients with SONK.

Each round of the survey is anticipated to take 15 minutes to complete and a total of three rounds are planned.

At present, there is no well-established evidence base for the treatment of SONK or recommendations for treatment depending on disease stage
Your expertise would be extremely beneficial in understanding current treatment trends and working towards the development of higher level evidence for the management of SONK.

Please find attached a participant information leaflet containing further information.
The first round of the survey will be distributed in the next 2 weeks via email and I would be grateful if you would consider participating.
Please find attached a participant information leaflet containing further information.

Yours Sincerely,

Maire-Clare Killen

Research Student, University of Central Lancashire
Orthopaedic Registrar, Northern Deanery, UK

Round 1 Invitation:

Further to my initial email, I am attaching the link for the first round of the Delphi study to support research into joint-preserving management of Spontaneous Osteonecrosis of the Knee.

This first round will remain open for two weeks; your timely response would be appreciated.

Here is a link to the survey:

http://www.smartsurvey.co.uk/s/T3LXJ/

Thank you in advance for your participation.

Yours Sincerely,

Maire-Clare Killen

Research Student, University of Central Lancashire
Orthopaedic Registrar, Northern Deanery, UK

Round 2 email:

I am emailing with regard to the second round of a Delphi study aiming to reach consensus in the management of spontaneous osteonecrosis of the knee. In the first round, we presented several clinical scenarios and asked participants to state their preferred treatment from a variety of options.

Following analysis of the responses from the first round, we are now presenting the clinical scenarios again, alongside the most commonly chosen treatment strategies obtained from round 1. We aim to work towards reaching a further treatment consensus using the limited treatment options presented.

We are asking you to participate in this second round by following the link below, regardless of whether or not you took part in the first round.

http://www.smartsurvey.co.uk/s/1K7BL/

This link will remain open for 2 weeks and a reminder will be sent at the one week stage. Thank you in advance for your continued participation.

Yours Sincerely,

Maire-Clare Killen

Research Student, University of Central Lancashire
Orthopaedic Registrar, Northern Deanery, UK

Appendix 7: Participant Information Leaflet

Spontaneous Osteonecrosis of the Knee

We would like to invite you to take part in a Delphi consensus study investigating treatment of spontaneous osteonecrosis of the knee.
This is being undertaken as part of an MSc in research alongside a systematic review of the condition at the University of Central Lancashire.

Before you decide whether or not you would like to take part, please take time to read this information sheet, detailing why this research is being done and what it will involve.

What is the purpose of the study?

At present, there is no well-established evidence base for the treatment of Spontaneous Osteonecrosis of the Knee (SONK) or recommendations for treatment depending on disease stage. The multitude of treatments available can make it difficult to decide which treatment options to use and when.
There is a clear indication for non-operative management in patients with mild symptoms who are in the early stage of osteonecrosis. In addition, there is some consensus in the literature on the indications and outcomes for patients with severe SONK requiring total knee arthroplasty. However, the difficulty lies with the group of patients with osteonecrosis without features of arthritis.

Overall, the Delphi study will hopefully provide information on whether there is consensus on primary, secondary, and, where necessary, tertiary treatment for patients with intermediate-stage SONK.

This will hopefully allow for clinicians, who often only see a few cases of SONK per year to make a more informed, evidence-based decision on which treatment is best for their patient.

Why have I been invited to take part?

As an established knee expert, who has recently published on the topic we are keen to gain your views and trends of practice to work towards a consensus of opinion for managing patients with SONK.

What will I be asked to do if I take part?

We are inviting you to participate as a Delphi panel member. This would involve completing a brief online questionnaire, regarding your current area of practice and the approximate number of cases of SONK you see and treat each year.
Following this, you will be asked to complete a short questionnaire regarding your most likely course of treatment for several patient scenarios.

Following your response to each round, you will receive feedback regarding the groups' response prior to the beginning of the next round.
Each round of the survey is anticipated to take 15 minutes to complete and a total of three rounds are planned.
In order to allow timely conclusion of the study we would respectfully request a response time of 2 weeks for completion of each round.

Reminder emails will be sent (via the survey website) to participants at weekly intervals.

You have the right to withdraw from the study at any time. However, we will be unable to withdraw data already submitted by you as this will have been anonymised.
Withdrawal will be assumed on non-response to the survey. If you would prefer to stop receiving any further emails, please email MKillen1@uclan.ac.uk.

Who is organising the research?
The Delphi study will be conducted by Maire-Clare Killen, as part of a research MSc under the supervision of the College of Clinical and Biomedical Sciences at the University of Central Lancashire.

Confidentiality
Your contact details will be held in a password-protected file on the UCLAN server and destroyed immediately following completion of the study; all submitted data will be anonymised upon receipt prior to analysis.
All responses received in the study will remain confidential, and your identity will not be divulged. Direct quotes to free-text answers may be used as part of the study report, but these will be anonymised so as not be traceable back to you.

Data protection
Survey responses will be collected online using a survey company, utilising an encrypted internet server, based in the United Kingdom.

Anonymised data will be downloaded to a password protected folder on the UCLAN server to allow analysis; data will be stored for the duration of the research project and for a maximum of 12 months following completion to allow write-up and publication then deleted.

Research ethics
The proposed Delphi study abides by the ethical requirements of the University of Central Lancashire and has been approved by the STEMH Ethics Committee at the University of Central Lancashire. Consent to take part will be assumed on completion and submission of the on-line questionnaires.

What will the data be used for?
Primarily, the data will be used in combination with the results of a systematic review and presented as part of an MSc thesis. Following this, the aim is to disseminate the results in either a conference presentation or a peer-reviewed journal.

What if I have any complaints?
If you have any complaints, concerns or issues about this study, please contact the University Officer for Ethics at OfficerForEthics@uclan.ac.uk. To help identify the study please include the study name or description and the researcher. Please also include information about the substance of the complaint.

What do I do now?
Thank you for reading this information sheet and for considering taking part in this research. Your expertise would be extremely beneficial in understanding current treatment trends and working towards the development of higher level evidence for the management of SONK.

The first round of the survey will be distributed in the next 2 weeks via email and I would be grateful if you would consider participating.
If you do not wish to be included from the onset, please inform me by email:
MKillen1@uclan.ac.uk

If you have any further questions or concerns, please do not hesitate to contact me on the email address below.

Maire-Clare Killen
MKillen1@uclan.ac.uk
Research Student, University of Central Lancashire
Orthopaedic Registrar, Northern Deanery, UK

Appendix 8: Round 1 Questionnaire as presented to participants

1. Where is your country of practice? *

2. Approximately how many years have you been practicing as a knee specialist? *

3. On average, how many cases of Spontaneous Osteonecrosis of the Knee do you treat per year? *

4. Please indicate which of the following treatments for Spontaneous Osteonecrosis of the Knee you have personally performed (select as appropriate): *

- [ ] Arthroscopic debridement,
- [ ] Arthroscopic drilling/microfracture: transchondral
- [ ] Arthroscopic drilling/microfracture: extra-articular
- [ ] Osteochondral transplantation: allograft
- [ ] Osteochondral transplantation: autograft
- [ ] High tibial osteotomy (to offload the affected compartment)
- [ ] Metal button resurfacing of lesion
- [ ] Uni-compartmental knee replacement
- [ ] Total knee replacement
- [ ] Other (please specify):

5. Scenario 1a.
A 60 year old, active patient, with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee are normal, but MRI changes are in keeping with isolated spontaneous osteonecrosis of the weight bearing portion of the medial femoral condyle (no other degenerative changes or pathology).

What would be your first line treatment (preferably state one, but if you use a combination of treatments please tick more than one)? *

- [ ] A period of rest, analgesia and full-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and partial-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and non-weight bearing (please state duration of this in comment box below)
- [ ] Arthroscopy with debridement of the lesion
- [ ] Arthroscopy with transchondral drilling/microfracture of the lesion
- [ ] Arthroscopy with extra-articular drilling/microfracture of the lesion
- [ ] Arthroscopy with grafting of the affected area (osteochondral autograft)
- [ ] Arthroscopy with grafting of the affected area (osteochondral allograft)
- [ ] High tibial osteotomy
- [ ] Bisphosphonate treatment
- [ ] Metal button resurfacing of lesion
- [ ] Uni-compartmental knee replacement
- [ ] Total knee replacement
- [ ] Other (please specify):

Comments: Please state duration of period of observation if selected above.

6. Scenario 1b.
A 60 year old, active patient, with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee are normal, but MRI changes are in keeping with isolated spontaneous osteonecrosis of the weight bearing portion of the medial femoral condyle (no other degenerative changes or pathology).

Following failure of your first line treatment, with ongoing pain but no radiological progression, what would be your usual second line management? (Preferably state one, but if you use a combination of treatments please tick more than one)? *

- [ ] A period of rest, analgesia and full-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and partial-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and non-weight bearing (please state duration of this in comment box below)
- [ ] Arthroscopy with debridement of the lesion
- [ ] Arthroscopy with transchondral drilling/microfracture of the lesion
- [ ] Arthroscopy with extra-articular drilling/microfracture of the lesion
- [ ] Arthroscopy with grafting of the affected area (osteochondral autograft)
- [ ] Arthroscopy with grafting of the affected area (osteochondral allograft)
- [ ] High tibial osteotomy
- [ ] Bisphosphonate treatment
- [ ] Metal button resurfacing of lesion
- [ ] Uni-compartmental knee replacement
- [ ] Total knee replacement
- [ ] Other (please specify):

Comments: Please state duration of period of observation if selected above.

7. Scenario 2a.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion in the weight-bearing portion of the medial femoral condyle. MRI scan demonstrates a lesion with appearances consistent of spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology).

What would be your first line treatment (Preferably state one, but if you use a combination of treatments please tick more than one)? *

- [ ] A period of rest, analgesia and full-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and partial-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and non-weight bearing (please state duration of this in comment box below)
- [ ] Arthroscopy with debridement of the lesion
- [ ] Arthroscopy with transchondral drilling/microfracture of the lesion
- [ ] Arthroscopy with extra-articular drilling/microfracture of the lesion
- [ ] Arthroscopy with grafting of the affected area (osteochondral autograft)
- [ ] Arthroscopy with grafting of the affected area (osteochondral allograft)
- [ ] High tibial osteotomy
- [ ] Bisphosphonate treatment
- [ ] Metal button resurfacing of lesion
- [ ] Uni-compartmental knee replacement
- [ ] Total knee replacement
- [ ] Other (please specify):

Comments: Please state duration of period of observation if selected above.

8. Scenario 2b.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion in the weight-bearing portion of the medial femoral condyle. MRI scan demonstrates a lesion with appearances consistent of spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology).

Following failure of your first line treatment, with ongoing pain but no radiological progression, what would be your usual second line management? (Preferably state one, but if you use a combination of treatments please tick more than one)? *

- [ ] A period of rest, analgesia and full-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and partial-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and non-weight bearing (please state duration of this in comment box below)
- [ ] Arthroscopy with debridement of the lesion
- [ ] Arthroscopy with transchondral drilling/microfracture of the lesion
- [ ] Arthroscopy with extra-articular drilling/microfracture of the lesion
- [ ] Arthroscopy with grafting of the affected area (osteochondral autograft)
- [ ] Arthroscopy with grafting of the affected area (osteochondral allograft)
- [ ] High tibial osteotomy
- [ ] Bisphosphonate treatment
- [ ] Metal button resurfacing of lesion
- [ ] Uni-compartmental knee replacement
- [ ] Total knee replacement
- [ ] Other (please specify):

Comments: Please state duration of period of observation if selected above.

9. Scenario 3a.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion with associated collapse of the weight-bearing portion of the medial femoral condyle. MRI confirms appearances in keeping with spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology) with associated collapse of the weight bearing portion.

What would be your first line treatment (Preferably state one, but if you use a combination of treatments please tick more than one)?
*

- [ ] A period of rest, analgesia and full-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and partial-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and non-weight bearing (please state duration of this in comment box below)
- [ ] Arthroscopy with debridement of the lesion
- [ ] Arthroscopy with transchondral drilling/microfracture of the lesion
- [ ] Arthroscopy with extra-articular drilling/microfracture of the lesion
- [ ] Arthroscopy with grafting of the affected area (osteochondral autograft)
- [ ] Arthroscopy with grafting of the affected area (osteochondral allograft)
- [ ] High tibial osteotomy
- [ ] Bisphosphonate treatment
- [ ] Metal button resurfacing of lesion
- [ ] Uni-compartmental knee replacement
- [ ] Total knee replacement
- [ ] Other (please specify):

Comments: Please state duration of period of observation if selected above.

10. Scenario 3b.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion with associated collapse of the weight-bearing portion of the medial femoral condyle. MRI confirms appearances in keeping with SONK, isolated to the medial femoral condyle (no other degenerative changes or pathology) with associated collapse of the weight bearing portion.

Following failure of your first line treatment, with ongoing pain but no radiological progression, what would be your usual second line management? (Preferably state one, but if you use a combination of treatments please tick more than one)? *

- [ ] A period of rest, analgesia and full-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and partial-weight bearing (please state duration of this in comment box below)
- [ ] A period of rest, analgesia and non-weight bearing (please state duration of this in comment box below)
- [ ] Arthroscopy with debridement of the lesion
- [ ] Arthroscopy with transchondral drilling/microfracture of the lesion
- [ ] Arthroscopy with extra-articular drilling/microfracture of the lesion
- [ ] Arthroscopy with grafting of the affected area (osteochondral autograft)
- [ ] Arthroscopy with grafting of the affected area (osteochondral allograft)
- [ ] High tibial osteotomy
- [ ] Bisphosphonate treatment
- [ ] Metal button resurfacing of lesion
- [ ] Uni-compartmental knee replacement
- [ ] Total knee replacement
- [ ] Other (please specify):

Comments: Please state duration of period of observation if selected above

Appendix 9: Round 2 Questionnaire as presented to participants

1. Where is your country of practice? *****

- UK
- USA
- Germany
- Spain
- Luxembourg
- Other (please specify):

2. Approximately how many years have you been practicing as a knee specialist? *****

- 1-5
- 5-10
- 10-20
- 20-30
- 30-40
- >50

3. On average, how many cases of Spontaneous Osteonecrosis of the Knee do you treat per year? *****

- 1-5
- 5-10
- 10-20
- 20-30
- 30-40

- [ ] >40

Scenario 1a.
A 60 year old, active patient, with no other medical problems presents with significant knee pain despite regular analgesia.
Plain radiographs of the knee are normal, but MRI changes are in keeping with isolated spontaneous osteonecrosis of the weight bearing portion of the medial femoral condyle (no other degenerative changes or pathology).

What would be your most likely first line treatment using the options listed below? *****

- [ ] A period of rest, analgesia and full weight bearing/weight bearing as tolerated
- [ ] A period of rest, analgesia and partial weight bearing
- [ ] A period of rest, analgesia and non-weight bearing
- [ ] Bisphosphonate treatment ± correction of calcium haemostasis
- [ ] None of the above

5. If you have selected a period of rest and observation for your preferred choice, what would be your recommended treatment duration? *****

- [ ] Up to 6 weeks
- [ ] Up to 3 months
- [ ] > 3 months
- [ ] N/A (other treatment modality chosen)

6. If you have selected a period of rest and observation for your preferred choice, would you routinely use adjuvant offloading knee bracing during this time? *****

- [ ] Yes
- [ ] No
- [ ] Not applicable

7. Scenario 1b.
A 60 year old, active patient, with no other medical problems presents with significant knee pain despite regular analgesia.
Plain radiographs of the knee are normal, but MRI changes are in keeping with isolated spontaneous osteonecrosis, limited to the weight bearing portion of the medial femoral condyle. There are no other degenerative changes or pathology, and normal joint alignment.

Following failure of your first line treatment, defined by ongoing significant pain but no radiological progression, what would be your most likely second line management from the options below? *****

- A period of rest, analgesia and full-weight bearing/weight bearing as tolerated
- A period of rest, analgesia and partial or non-weight bearing
- Arthroscopy with drilling/microfracture of the lesion
- Bisphosphonate treatment ± correction of calcium haemostasis
- Knee arthroplasty (either uni-compartmental or total knee replacement)
- None of the above

8. Scenario 2a.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion in the weight-bearing portion of the medial femoral condyle.
MRI scan demonstrates a lesion with appearances consistent of spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology, and normal joint alignment).

What would be your most likely first line treatment using the options listed below?
*****

- A period of rest, analgesia and full weight bearing/weight bearing as tolerated
- A period of rest, analgesia and partial or non-weight bearing
- Arthroscopy with drilling/microfracture
- Bisphosphonate treatment ± correction of calcium haemostasis
- Knee arthroplasty (uni-compartmental or total knee replacement)
- None of the above

9. If you have selected a period of rest and observation for your preferred management, what would be your recommended treatment duration? *****

- Up to 6 weeks
- Up to 3 months
- >3 months
- N/A (other treatment modality chosen)

10. Scenario 2b.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia. Plain radiographs of the knee show a sclerotic lesion in the weight-bearing portion of the medial femoral condyle.
MRI scan demonstrates a lesion with appearances consistent of spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology and normal joint alignment).

Following failure of your first line treatment, defined by ongoing pain but no radiological progression, what would be your most likely second line management using the options listed below? *****

- A period of rest, analgesia and partial or non-weight bearing
- Arthroscopy with drilling/microfracture
- Grafting of the lesion
- High tibial osteotomy
- Knee arthroplasty (either uni-compartmental or total knee replacement)
- None of the above

11. Scenario 3a.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia.
Plain radiographs of the knee show a sclerotic lesion with associated collapse of the weight-bearing portion of the medial femoral condyle and varus malalignment of the knee.
MRI confirms appearances in keeping with spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology).

What would be your most likely first line treatment using the options listed below? *****

- A period of rest, analgesia and partial weight bearing

- A period of rest, analgesia and non-weight bearing
- Arthroscopy with drilling/microfracture
- High tibial osteotomy
- Knee arthroplasty (uni-compartmental or total knee replacement)
- None of the above

12. Scenario 3b.
A 60 year old, active patient with no other medical problems presents with significant knee pain despite regular analgesia.
Plain radiographs of the knee show a sclerotic lesion with associated collapse of the weight-bearing portion of the medial femoral condyle and varus malalignment of the knee.
MRI confirms appearances in keeping with spontaneous osteonecrosis, isolated to the medial femoral condyle (no other degenerative changes or pathology).

Following failure of your first line treatment, defined by ongoing pain but no radiological progression, what would be your most likely second line management using the options listed below? *****

- Arthroscopy with drilling/microfracture
- Grafting of the lesion
- High tibial osteotomy
- Knee arthroplasty (uni-compartmental or total knee replacement)
- N/A (selected arthroplasty in scenario 3a)

13. Thank you for your participation in round 2 of this Delphi Study. We will be in touch soon with the results. Please leave any additional comments below.

Appendix 10: Copy of approval letters

uclan
University of Central Lancashire

27th September 2016

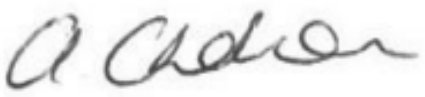
Waqar Ahmed/Maire-Clare Killen
School of Dentistry
University of Central Lancashire

Dear Waqar/Maire-Clare,

Re: STEMH Ethics Committee Application
Unique Reference Number: STEMH 448_amendment

The STEMH Ethics Committee has approved your proposed amendment to your application 'Spontaneous osteonecrosis of the knee: Delphi Study'.

Yours sincerely,



Ambreen Chohan
Deputy Vice-Chair
STEMH Ethics Committee

UNIVERSITY OF CENTRAL LANCASHIRE
GRADUATE RESEARCH SCHOOL
REFEREE'S REPORT ON APPLICATION FOR RESEARCH PROGRAMME APPROVAL

1. Proposal Details	
Important: If you feel you may have a **conflict of interest**, or if you have a **low level of confidence** in your ability to provide an assessment of this proposal, **please advise the Secretary before proceeding.** In the case of a strongly multi- or interdisciplinary proposal, please comment only on the elements of the proposal within your area of expertise (please state what this is in 2.4).	
Name of Student: Marie- Clare Killen	**Submitted for Degree of: MSc (by research)**
Name of Referee: Karen May	**Project Title:**
Name of Director of Studies: Paola Dey	**Management of Spontaneous Osteonecrosis of the Knee a Systematic Review & Delphi Study**

2. Referee's Assessment Please provide a short narrative assessment addressing the following criteria and **circle** the appropriate response. **Reports will be returned to the referee if no comments have been included.**		
2.1 The overall structure of the programme **I believe that the structure of this programme is suitable**	**Appropriate**	**Inappropriate**
2.2 The aims and objectives of the research **The student has set out clear aims and objectives that are suitable for the chosen method**	**Appropriate**	**Inappropriate**
2.3 The relationship of the research to previous work/brief literature review **This piece of research will add to previous work in this area and should provide a consensus view of current practice**	**Appropriate**	**Inappropriate**
2.4 **The proposed programme of work, in particular the methodology, experimental design, timescales, and underpinning activities (including the programme of related studies)** The chosen methodology and study design is suitable to answer the question set and should provide a clear overview of current practice developing this into a consensus view to help set clinical guidelines. The time scale is appropriate to the study	**Appropriate**	**Inappropriate**

2.5 The suitability of the programme for the target award **Suitable for this target award**	**Appropriate**	**Inappropriate**
2.6 If the application is for MPhil/PhD, is the point at which transfer is expected to occur clearly delineated and is it at an appropriate position in the programme N/A	**Appropriate**	**Inappropriate**
2.7 Its element of originality (MPhil/PhD, PhD, MD routes only) **N/A**	**Appropriate**	**Inappropriate**
2.8 The quality of the writing and presentation **The student presents the study in a well written and appropriate style**	**Appropriate**	**Inappropriate**
2.9 Are there any issues other than academic probity that come to your attention and which are of concern and may impact on the programme and have not been addressed during the review process eg research governance, financial resources, facilities, location, the supervisory team? **I believe this student will be well supported through the process by the team in place**	**YES**	**NO**

3. Your Conclusions

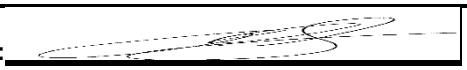
Please use the space below to make any comments relating to this proposal, not made elsewhere

I recommend *(delete as appropriate):*

A. Acceptance of the proposal as it stands

If <u>minor revisions</u> or <u>further work</u> are required, prior to formal submission to Committee, please return this form and the accompanying documentation to the student and DoS.

B. Revisions have been made to the proposal and I now recommend acceptance of the proposal

Referee's Signature: 	**Date:24/03/15**

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