Timing of Anterior Cruciate Ligament (ACL) Reconstruction

By

Apostolos D. Prodromidis

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ABSTRACT

Background: Anterior Cruciate Ligament (ACL) ruptures are common but the ideal timing for ACL reconstruction following injury is unclear.

Objectives: To determine if there is a relationship between timing from ACL rupture to surgery and clinical, functional and patient-reported outcomes. To explore the feasibility of collecting clinicians' views on ACL reconstruction timing.

Design and methods: A systematic review of five databases to identify studies investigating outcomes following different timing of reconstruction surgery and a pilot vignette study to identify variations in clinical decisions about timing of surgery in four different case scenarios.

Results: Systematic review: Ten studies were identified, only one was a randomised controlled trial. There appeared to be no difference in outcomes between early (< 3 months) and subacute (3 to 6 months) ACL reconstruction, but medial meniscal and chondral injuries were more common following delayed (> 6months) ACL reconstruction. The two studies on functional and/or patient reported outcomes had conflicting findings, with the trial suggesting no difference between early or delayed reconstruction. The studies had limited evidence about the relationship between timing of surgery and patient characteristics. Pilot Vignette study: The pilot vignette study had a response rate of 45% but a high question completion rate. There was clinical variation in timing between surgeons and across patient groups, but none recommended delayed surgery (>6 months).

Conclusions: Given the potential deleterious effects of meniscal and chondral injuries on knee function, delays of more than 6 months in patients deemed suitable for ACL surgery are not recommended, but there is some evidence that these delays are not common in practice. Further research on timing of ACL reconstruction should focus on shorter time-frames, functional and patient-reported outcomes, and the influence of patient characteristics, as available evidence is limited, inconsistent and of low quality. A vignette study seems feasible to provide insights on clinical decisions and guide current practice and future research.

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When someone works for a formal research degree along with a busy and demanding orthopaedic surgical training, time is never enough. Balancing research work and study with clinical duties has been challenging. Endless evenings in front of my desktop have been part of my life. However, this work could not be completed without the knowledge, skill, support and patience of all my supervisors. So, first, I would like to thank all my supervisors Professors Paola Dey, Charalambos Charalambous, Douglas Hammond and Waqar Ahmed for their understanding and support. Especially Professor Paola Dey who has been really supportive and patient enough all throughout to teach me the appropriate research methodology and thinking out of the box, making me a better researcher and a better writer. Second, Professor Charalambos Charalambous, Consultant Orthopaedic Surgeon at Blackpool Teaching Hospitals, my clinical supervisor, who transmitted the "bug" of research to me and matured my initial thoughts for the project. His experienced and balanced opinion on all clinical matters has been crucial in completion of a quality product. Also special thanks to Mr Nasri Zreik, the research student who kindly screened the outputs of my search and independently extracted data from the included studies as a second reviewer. Finally, I would like to thank my father Dimitrios Prodromidis who found my work interesting enough to do the nice drawings in Chapter 1.

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ACRONYMS AND ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACLR	Anterior cruciate ligament reconstruction
ICRS	International College Repair Society
KOOS	Knee injury and Osteoarthritis Outcome Score
LM	Lateral meniscus
MM	Medial meniscus
MRI	Magnetic Resonance Imaging
NHS	National Health Service
OA	Osteoarthritis
PCL	Posterior Cruciate Ligament
QoL	Quality of Life
RCT	Randomised Controlled Trial
ROM	Range of motion
ICC	Intraclass correlation coefficient
SF-36	36-Item Short-Form Health Survey
SFA	French Society of Arthroscopy
TAS	Tegner Activity Scale
TFI	Time from injury
UCLAN	University of Central Lancashire
UK	United Kingdom
US	United States

CHAPTER 1: INTRODUCTION

Anterior cruciate ligament (ACL) ruptures are common in adults, especially in younger populations (Gianotti et al. 2009). They can lead to knee instability, which can lead to meniscal tears and chondral damage, and consequently, may result in worse function and osteoarthritis (Caborn & Johnson 1993). This thesis examines the relationship between the timing of ACL surgery and clinical (meniscal tears and chondral injuries), functional and patient-reported outcomes.

The context and rationale for the thesis is outlined in this chapter. Firstly, the anatomy and the biomechanics of the normal knee are described, explaining also the stability of the knee and its contributors; then, the changes to these that happen when the ACL is injured (torn) are outlined, along with all concomitant injuries and the patients' symptoms in response to an injury (tear). Much of the work related to ACL anatomy and biomechanics was done two to three decades ago and more recent research does not add much to the introduction discussed in this chapter. Finally, the management of ACL injuries is discussed introducing the controversies over the timing of ACL reconstruction surgery.

1.1 Anatomy & Biomechanics

1.1.1 Normal Anatomy and Biomechanics – Stability of the knee

The normal basic anatomy and normal biomechanics of the knee joint needs to be understood before proceeding to describe the consequences of ACL injuries and their management. The knee is a big joint, which incorporates both gliding and rolling. It is composed of bones, cartilage, ligaments and tendons. The bones are the femur, the tibia and the patella. The articulating parts of these bones are lined with cartilage, which helps the smooth gliding of the bones over each other.

The cruciate ligaments are bands of connective tissue inside the knee joint that cross to form an "X" with the ACL in front and the posterior cruciate ligament (PCL) at the back (see Figures 1.1 and 1.2). The ACL extends from the posteromedial aspect of the lateral

condyle of the femur to the intercondylar notch of the tibia (Petersen & Zantop 2007; Kweon *et al.* 2013). The ACL and PCL each have two parts called "bundles", mainly composed of type I collagen (90%): an anteromedial and a posterolateral bundle for the ACL; an anterolateral and posteromedial bundle for the PCL (Miller & Thompson 2012). Other ligaments of the knee include: the collateral ligaments, medial and lateral, on the sides of the knee; the oblique popliteal ligament at the back of the knee; the arcuate ligaments which originate from the head of the fibula to pass into the joint capsule, and the coronary (or meniscotibial) ligaments, which connect the inferior edges of the menisci to the periphery of the tibial plateaus (Miller & Thompson 2012). This chapter will focus on ACL and the biomechanics and functions related to ACL.

The menisci are two wedge-shaped fibrocartilaginous structures inside the knee joint composed predominantly of collagen type I, which interpose between the condyles of the femur and the tibia. There is one medial and one lateral meniscus (see Figures 1.1 and 1.2); they are approximately 35 mm in diameter and triangular in cross-section (Woitys & Chan 2005). Only the peripheries (peripheral third) of both menisci are vascularised (Arnoczky & Warren 1982).

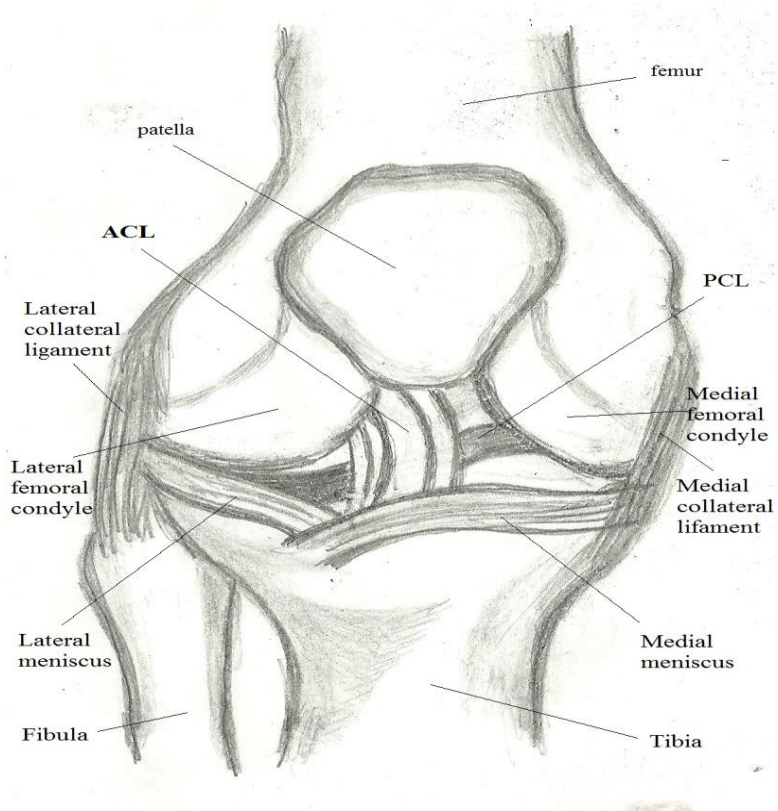


Figure 1.1 Knee joint anteroposterior view
(drawn by Dimitrios Prodromidis)

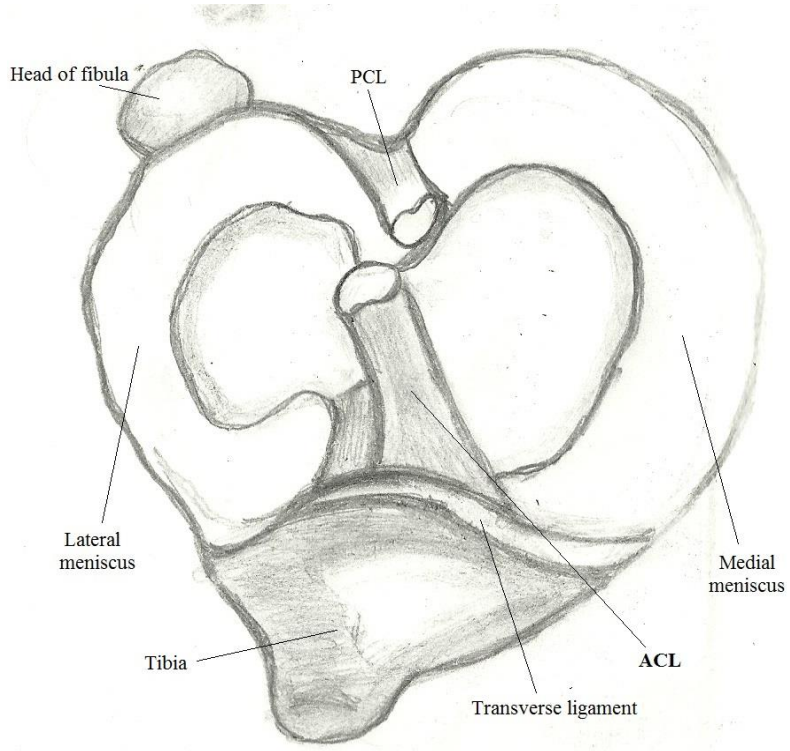


Figure 1.2 Knee joint axial view
(drawn by Dimitrios Prodromidis)

The primary function of the ACL is to limit anterior translation of the tibia on the femur and hyperextension, which is accomplished by its anteromedial bundle (Fu *et al*. 1993). The secondary function is to limit the internal rotation of the tibia and valgus displacement of the knee, which is accomplished by its posterolateral bundle (Sakane et al. 1997).

The menisci are also important for the structural integrity of the knee joint, performing the following functions:

(i) Acting as shock absorbers and load transmitters: This is achieved by enhancing the articular conformity between the femoral condyles and the upper tibia (Aagaard & Verdonk 1999). They increase the actual surface contact area, so the forces transmitted from femur to tibia are reduced and in that way the stresses on the tibial cartilage are reduced (Bryceland *et al*. 2017; Woitys & Chan 2005).

(ii) Contribute to joint lubrication: This is achieved by distributing the synovial fluid across the articular surface, which reduces friction (Bryceland *et al*. 2017).

(iii) Contribute to stability: This is achieved by the ligaments that are attached to the menisci, further exaggerating the stability provided by the ligaments (Woitys & Chan 2005).

The articular cartilage is the lining of the lower femur and the upper tibia inside the joint. Thick cartilage is necessary for smooth gliding of the bones over each other whilst moving the knee, spreading the load over a wider area.

Stability of the knee

Stability is essential for normal function of the knee joint. It is generally divided into static and dynamic. Static stabilisers include the following passive structures:

(i) Joint capsule.

(ii) Bony anatomy/geometry.

(iii) Ligaments: ACL, PCL, Medial Collateral Ligament, Lateral collateral ligament and oblique popliteal.

(iv) Other associated structures: menisci, coronary ligaments, menisco-patellar and patello-femoral ligaments.

Dynamic stabilisers are all the associated muscles and their aponeuroses (layers of flat broad tendons which join the muscles and body parts they act upon), like the quadriceps femoris, the popliteus, hamstrings, biceps femoris. They provide the knee joint with the ability to adjust to changing loads transmitted during activities and to maintain stability (Williams *et al*. 2001).

Stability of the knee can be further divided as follows:

(i) Anteroposterior stability: this is accomplished by both static and dynamic stabilisers. The main anteroposterior stabiliser is the ACL, which provides most of the resistance to anterior translation of the tibia on the femur; similarly, the PCL provides the major resistance to posterior tibia translation (Fu *et al*. 1993).

(ii) Medial/Lateral (Varus/Valgus) stability: this is accomplished by both static and dynamic stabilisers. The knee is reinforced medially and laterally by the

collateral ligaments (medial and lateral), which play the more crucial role in resisting varus/valgus stresses, especially with the knee in extension. When the knee bends, the musculature (especially the pes anserinus) contributes to medial/lateral stability. Both cruciate ligaments contribute to varus/valgus stability, but much less than the collateral ligaments and muscles.

(iii) Rotational stability: Static stabilisers are more crucial for rotational stability. ACL and PCL are the most important, especially in extension. ACL as rotational stabiliser is the main constraint of excessive anterior translation of the tibia on the femur, on either excessive lateral opening of the joint (anterolateral rotational stability) or on excessive medial opening of the joint (anteromedial rotational stability) (Miller & Thompson 2012).

1.1.2 The impact of Anterior Cruciate Ligament injury on anatomy and biomechanics of the knee

In an ACL deficient knee after an ACL rupture, the anatomy is changed, and this may alter the biomechanics and function of the knee. The many different stabilisers of the knee were described above. Amongst them, dynamic stabilisers (muscles) are more powerful, so even in the absence of static stabilisers, dynamic stabilisers may maintain stability of the knee. Therefore, in an ACL deficient knee, strengthening of the muscles (quadriceps and hamstrings), co-ordinated with training, can control instability to allow the patient to undertake low demand sports and control anteroposterior instability (Daniel *et al*. 1994). However, even with the best dynamic muscular strengthening and training with an absent ACL, full rotational stability cannot be achieved because muscles contribute to anteroposterior stability and cannot control rotational stability for which the main contributor is the ACL (as described above).

Amongst static stabilisers, ACL is the most powerful static stabiliser and crucial for anteroposterior and rotational stability of the knee. Consequently, in an ACL deficient knee there is anterior laxity and rotational instability and the knee will be prone to give way with twisting on the weight bearing knee. Anterior translation of the tibia, hyperextension and internal rotation of the tibia, and also valgus displacement will not be reduced. All these forces may increase the loads transmitted to menisci and cartilage

lining of femur and tibia leading to wear inside the joint, damaging the menisci and cartilage (Caborn & Johnson 1993). These ACL deficient patients may continue with episodes of instability (the knee "gives way") sustaining further injuries at their menisci and cartilage (Eckstein *et al*. 2015; Fithian *et al*. 2002).

As analysed above, menisci transmit loads and absorb shocks contributing to the stability of the knee. Consequently, when menisci are damaged and torn, high stress loading takes place, which may lead to "wear and tear" inside the joint which leads to osteoarthritis (OA). Menisci also contribute to joint lubrication as mentioned above. When menisci are damaged or torn, abnormal lubrication takes place, which leads to increased friction and so increased "wear and tear" inside the joint which may lead to OA (Englund *et al*. 2009a; Fithian *et al*. 2002). Hence, meniscal tears may be associated with the development of OA (Englund 2004; Englund *et al*. 2009b).

In an ACL-deficient knee, cartilage gets damaged and worn due to instability and gliding of the bones over each other whilst moving. Therefore, less cartilage in an ACL-deficient knee predisposes to pain, and loss of cartilage is the main feature of osteoarthritic knees. Consequently, with cartilage injuries in an ACL-deficient knee after an ACL injury, it is more likely that the knee will develop OA (Miller & Thompson 2012; Fithian *et al*. 2002).

1.2 Pathogenesis of Anterior Cruciate Ligament injury

1.2.1 General

ACL rupture is a common injury, with an estimated incidence of 36.9 per 100,000 0f the general population and 1 per 1,750 in younger populations (16 to 45 years old) (Garrick & Requa 2000; Gianotti *et al*. 2009;). Typically, an ACL injury occurs in a non-contact deceleration situation that causes a valgus twisting injury (prior to a change of direction or landing motion) (Boden *et al*. 2000). The knee twists (rotates) on the fixed ipsilateral foot and the ACL fails. This is what usually happens when an athlete lands on his leg and quickly pivots in the opposite direction. Less commonly, an ACL injury can also occur when someone stops suddenly or puts his/her foot hard onto the ground (cutting). Contact injury is a less common mechanism. With regards to sports,

ACL tears most often occur in rugby, soccer and basketball in younger patients, and in skiing amongst older patients (Prodromos *et al*. 2007; Pujol *et al*. 2007).

1.2.2 Natural progress of Anterior Cruciate Ligament injury

The natural progress of an ACL injured knee helps us understand the implications and the consequences of an untreated ACL injury. After an injury to the ACL, an acute inflammation of the knee takes place. It takes up to 12 weeks for this inflammation to settle down and motion to be restored (Mohtadi *et al*. 1991). Function and stability is impaired during this post-traumatic inflammation period.

Noyes *et al*. (1983a) investigated the disability caused to individuals by an ACL tear after the inflammation settles down (known as the "rule of thirds"). All patients included in the study (n=103) were active in sports, two-thirds of them in high-school or college athletics, representing a young, athletically active population. Part I of the study reported on all 103 patients and over a 5-year follow-up period, 35% were back in strenuous sports, 31% had overall disability with instability during walking activities and 33% had "giving-way" symptoms (instability) during recreational sports (Noyes *et al*. 1983a). In part II of the study, 84 of these patients with chronic ACL laxity were recruited into a rehabilitation program (Noyes *et al*. 1983b). All patients wanted to return to athletic or recreationally active lifestyles. Failure to complete this rehabilitation program was considered an indication for ACL reconstruction. More than one-third of the patients improved with no or minimum symptoms during daily activities or during recreational activities, but had some symptoms during strenuous sports activity. One-third of the patients became worse and failed the program, complaining of symptoms of pain, swelling or giving-way that prevented any recreational activities and were often present with daily activities. More than one-third of the patients (36%) did not benefit from the program and required ACL reconstruction.

These results show the different response and function of active patients with an ACL injury after the natural progress of the injury and shows that not every patient necessarily benefits from operative treatment with early ACL reconstruction surgery.

1.3 Outcomes of Anterior Cruciate Ligament injury

1.3.1 Meniscal injuries/tears

The most common concomitant event inside a knee after an ACL injury or even at the time of injury is a meniscal tear. There is enough evidence to suggest that, in an acute ACL tear, the lateral meniscus is most commonly injured, as opposed to the medial meniscus, which is more often involved, after some time, in chronic ACL tears (Bellabarba *et al*. 1997; Cipolla *et al*. 1995; Nikolic 1998). Therefore, acutely after an ACL tear, a lateral meniscal tear (LM) is most likely to be encountered, whereas, as time from injury elapses, a medial meniscal (MM) tear is expected. However, in a chronically ACL deficient and arthritic knee, it can be difficult to differentiate if the meniscal tear occurred as a result of the initial injury or as a result of the chronic arthritis inside the knee (Englund *et al*. 2008; Englund *et al*. 2009a). This thesis will focus on such post-traumatic meniscal tears within a specific time-frame after the acute ACL injury (which is defined in Chapter 2), as these tears may be reduced by early restoration of knee stability. Contrarily, chronic degenerative meniscal tears after this pre-defined time-frame, which may occur as part of a chronic arthritic or ageing process, are not of interest for this thesis.

Reducing meniscal tears by restoring knee stability is important, as meniscal damage is considered a potent risk factor for OA (Bryceland *et al*. 2017; Englund *et al*. 2009b; Fithian *et al*. 2002). A lot of biomechanical studies have shown that a torn non-functioning meniscus causes increased joint cartilage contact stress by altering load transmission, decreasing shock absorption and decreasing joint stability (Andrews *et al*. 2017; Fukuda *et al*. 2000; Walker *et al*. 2015; Wojtys & Chan 2005). These increased contact stresses inside the knee will lead to cartilage damage, which is the main feature of OA, predisposing the ACL deficient knee to pain and impaired function, increasing the risk of developing OA (Englund 2004; Englund *et al*. 2009a; Englund *et al*. 2009b; Fithian *et al*. 2002). This is reinforced by studies which have shown increased contact stresses in knees which had menisectomy as compared to knees with intact menisci or even knees which had a meniscal repair (Aagaard & Verdonk 1999; Englund & Lohmander 2004; Paletta *et a*l. 1997). Such knees after menisectomy have shown an increased risk of developing OA (Aagaard & Verdonk 1999; Englund & Lohmander 2004; Cicuttini & Forbes 2002; Hede *et al*. 1992). Total menisectomy has worse

outcome than partial menisectomy. These studies provide evidence for the importance of menisci and their protective effect against OA.

1.3.2 Chondral injuries

In an ACL injury, associated injuries to the articular cartilage occur inside the knee joint at the time of injury (Lahm *et al*. 1998; Noyes *et al*. 1980). These are known as chondral injuries. Apart from these chondral injuries that occur at the time of injury (acute chondral injuries), damage to articular cartilage can continue to occur inside an unstable knee due to the effects of instability as described above (Kullmer *et al*. 1994). So, if knee stability is restored early, then no further cartilage damage should be expected. The severity of the chondral injury can vary. The chondral injuries can be classified and graded. There are several types of classification systems for assessing chondral injuries. The most commonly reported are summarised in Table 1.1 and are the ones used in this thesis.

Table 1.1. Classification systems of chondral injuries

Classification of chondral injuries	**Outerbridge** (Outerbridge 1964; Cameon *et al*. 2003)	**SFA** (Dougados *et al*. 1994)	**ICRS** (Society 1998)	**Noyes** (Noyes & Stabler 1989)
Definition-Source	Originally designed for chondromalacia patellae to assess cartilage damage.	It assesses the severity of cartilage loss taking into account localization, size and depth of cartilage damage.	It assesses joint cartilage thickness.	It assesses cartilage abnormalities based on: description of articular surface, extent (depth) of involvement, diameter of the lesion, location of the lesion.
Grade 0	Normal	N/A	Normal	N/A
Grade I	Cartilage with softening and swelling	Softening	Intact surface but fibrillation and softening is present	Cartilage surface intact
Grade II	Partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5cm in diameter	Superficial fissure	Defects that involve 50% of the cartilage thickness	IIA: Cartilage surface damaged with less than half of cartilage thickness involved IIB: Depth of involvement greater than half of cartilage thickness but without exposed bone
Grade III	Fissuring to the level of subchondral bone in an area with a diameter >1.5cm in diameter	Deep fissure	Defects that extend through 50% of the cartilage thickness	Bone exposed
Grade IV	Exposed subchondral bone	Bone exposure	Cartilage defects that extend into the subchondral bone	N/A

SFA: French Society of Arthroscopy, **ICRS:** International Cartilage Repair Society, **N/A:** not applicable

1.3.3 Functional (objective) outcomes

Function is an important outcome after ACL surgery. Function may be measured objectively or may be reported subjectively by patients. For the purposes of this thesis, objectively measured function will be referred to as functional outcomes. Examples of functional outcomes include stability, laxity and range of motion of the knee. Subjective (patient-reported) outcomes are discussed in the next subchapter.

1.3.3.1 Stability of the knee

This can be assessed clinically by examining the patient with tests such as the Lachman test and the Pivot shift test (Gurtler & Stine 1987; van Eck *et al*. 2013).

The **Lachman test** is performed with the patient supine and the knee flexed at 20-30 degrees (Gurtler & Stine 1987). The clinician places one hand behind the patient's tibia and the other on the thigh. The tibia is pulled forward to assess the anterior translation of the tibia in relation to the femur. An intact ACL prevents anterior translation of the tibia, in contrast with an ACL-deficient knee, which shows increased anterior translation. More than 2 mm of anterior translation compared to the normal knee suggests a torn ACL ("soft endpoint"). An instrument called a "KT-1000 Arthrometer" can be used to determine this anterior movement in mm (described below).

The **Pivot shift test** assesses the degree of dysfunction in the ACL deficient knee by reproducing the event that occurs when the knee gives way because of a torn ACL, so it tests for knee instability (van Eck *et al*. 2013). It is the knee instability, and not just the ACL injury, that places the menisci at future risk, and gives rise to the feeling that "the knee may give away". The most commonly used method to perform this test is with the patient supine, the clinician holding the patient's leg with both hands and with the hip passively flexed to 20-30 degrees. The lower leg and ankle is gripped maintaining 20 degrees of internal tibial rotation. With the patient relaxed, the knee is placed in full extension. The opposite hand grasps the lateral part of the leg around the proximal tibiofibular joint. With the lower leg internally rotated, a valgus force is applied to the knee while it is slowly flexed. If the initially subluxed tibia reduces into place as the knee is flexed in the range of 30-40 degrees or if there is an anterior subluxation felt during extension, the test is positive for instability.

1.3.3.2 Instrumented measurement of knee laxity

The most commonly used instrument used for standardized measurements of knee laxity is the **KT1000 knee Arthrometer** (Daniel *et al*. 1985). The KT-1000 Arthrometer is an objective instrument which measures anterior tibial motion in relation to the femur. The instrument is strapped to the leg, pulling the tibia anteriorly, and measuring the amount of movement in millimeters (mm). It reports the extent of anteroposterior laxity of the knee in millimeters, as compared to the opposite normal knee. Mean values are estimated from the results of three tests. ACL laxity is measured with the knee slightly flexed (20-30 degrees) and with the application of standard force (15, 20 and 30 pounds). Difference of more than 3mm from the normal knee is considered clinically significant (Daniel *et al*. 1985; Arneja & Leith 2009).

1.3.3.3 Range of motion (ROM) of the knee

This includes measurement of the flexion and extension of the knee. It is typically measured with a tool called a goniometer. Normal ROM of the knee is 0 degrees extension (knee completely straight) to 135 degrees flexion (knee fully bent).

1.3.4 **Patient-reported (subjective) outcomes**

Another important aspect with regards to the success of ACL injury management is how much patient-reported (subjective) outcomes are also improved. These outcomes may incorporate subjective measures of pain, activity limitation and/or quality-of-life. A consensus amongst experts has been reached to define certain measurement properties to assess the performance of such patient-reported outcomes (COSMIN: Mokkink *et al*. 2010). These properties include reliability, internal consistency, validity and responsiveness. There are different types of reliability. *Test-retest reliability* is the extent to which the patient-reported outcome measure is free from measurement error, that is, it will consistently provide a similar score when repeated in the same patient (Mokkink *et al*. 2010). It is measured by the intraclass correlation coefficient (ICC), with an ICC > 0.70 being considered acceptable (Bland & Altman 1986). Patient-reported outcome measures are usually made up of a number of different questions or items. *Internal consistency* is the internal relationship of these items; it measures how

much these items are correlated between each other (Mokkink *et al*. 2010). It is usually measured with Cronbach's α, a statistic drawn from pairwise correlations between these items. Cronbachs's $\alpha > 0.60$ is considered acceptable (Cortina 1993; Cronbach 1951). *Validity* is how much patient-reported outcome measures actually measure what they are supposed to measure (Mokkink *et al*. 2010). There are distinct types of validity; content, face, construct, and criterion validity (Mokkink *et al*. 2010). *Content validity* is how much a measure appears to cover all the different aspects of the construct that is purporting to measure, for example, a knee specific quality-of-life measure might need to cover physical function, emotions, pain; this is often determined by those affected by the condition. *Face validity* is about how much the measure appears to be a good measure for those who are going to use it or be tested by it. Both content and face validity reflect the relevance and comprehensiveness of the items of the patient-reported outcome measure. *Construct validity* refers to the extent to which the scores of a patient-reported outcome instrument are consistent with known hypotheses about the construct, for example, if there is evidence that older people have worse quality of life than younger people, then a new measure should have worse scores for older people than younger people. *Criterion validity* refers to consistency between measure and a 'gold standard', for example, scores for a short form of an outcome measure might expect to highly correlate with the long form. There are different kinds of criterion validity; *concurrent validity* when, for example, the scores of two outcome measures, which measure similar constructs, correlate; and *predictive validity* when the outcome measure correlates with an outcome in the future, for example, quality of life measure may predict return to normal activities. Finally, responsiveness is how much the measurement tool or instrument can detect changes over time in the construct it purports to measure (Mokkink *et al*. 2010).

In the following subsections, commonly used patient-reported outcome instruments for ACL injury are discussed.

1.3.4.1 Knee scores

- **Lysholm knee score** (Tegner & Lysholm 1985)**:** This is a knee score, which is collected with a questionnaire distributed to patients asking them to assess how their knee pain has affected their ability to manage in everyday life over the last 24 hours. The Lysholm knee score has been in use for 25 years. There are questions

about 8 domains: limp, use of cane or crutches, locking sensation in the knee, giving way sensation from the knee (instability), pain, swelling, climbing stairs and squatting. There are 3 up to 6 possible answers for each item for the patient to select and each answer gets a certain score. Only one answer can be selected by the patient. The score can range between 0 to 100: 95 to 100 indicates an excellent result; 84 to 94 indicates a good result; 65 to 83 indicates a fair result; less than 65 indicates a poor result.

Briggs *et al*. in 2009 undertook a comprehensive assessment of measurement properties of the Lysholm score as a patient-reported outcome instrument for patients with ACL injuries when used to assess early return of knee function after ACL treatment. They reported that the test-retest reliability was acceptable, with ICC > 0.90 and there was also acceptable internal consistency for all 8 domains (Cronbach's $\alpha > 0.60$). Content validity was reportedly acceptable for the overall Lysholm score. Correlation of the overall Lysholm score with the physical score of the Short Form-12 (SF-12) health-related quality-of-life scale and the IKDC was performed to establish the criterion validity, and there was strong correlation of the Lysholm with IKDC (r = .8) and moderate with SF-12 (physical component) (r= .4). They also looked at floor (scale = lowest possible) and ceiling (scale = highest possible) effects which were acceptable at < 30% for the overall score. For the construct validity, all hypotheses (constructs) were found significant. Finally, they reported that the score was responsive to change at each of the time points (large overall effect size and large overall standardised response mean at all time periods).

- **Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)** (Bellamy 2009)**:** It is a widely used self-administered standardized questionnaire first developed in 1982, employed to evaluate the condition of patients with OA of the knee and hip. It evaluates pain, stiffness and physical functioning of the joints with 24 questions. Five questions for pain (score 0-20), seven for stiffness (score 0-8) and 17 questions for functional limitation/ disability (score 0-68). There has been a recent systematic review on WOMAC measurement properties (Gandek 2015). This systematic review included 76 studies from 22 countries and reported on internal consistency, construct validity and responsiveness of WOMAC. It has shown high internal consistency (Cronbach's $a \geq 0.90$) for the function scales and acceptable (Cronbach's $a \geq 0.70$) for the pain and stiffness scales. It has acceptable

test-retest reliability (ICC ≥ 0.70). Regarding construct validity, it has shown that 45 studies reported correlations among the three WOMAC scales (pain, stiffness, function) or between the WOMAC and 20 other measures. With regards to responsiveness, two studies reported that patients provided ratings of change over time (better, same, worse), with change scores being higher for patients who reported improvements.

- **Knee Injury and Osteoarthritis Outcome Score (KOOS)** (Roos *et al*. 1998): The KOOS was developed as an extension of the WOMAC Osteoarthritis Index aiming to evaluate the short-term and long-term symptoms and function in patients with knee injury and OA. Its advantage as compared to other similar instruments (like the Lysholm or WOMAC) is that it follows up both short-term (acute injury) consequences in physically active and younger patients and long-term (chronic) consequences in the older population (Roos & Lohmander 2003). The KOOS asks patients how they feel about their knee and how well they can do their usual activities during the last week. It asks about 6 domains: symptoms (5 questions), stiffness (2 questions), pain (9 questions), function in daily living (17 questions), function in sports and recreational activities (5 questions), knee-related quality of life (4 questions). The patient selects one of 5 options for each question which are none, mild, moderate, severe, extreme and scored from 0 to 4. Scores range from 0 to 100, with higher scores indicating better results. Occasionally, just one subscale of the KOOS is used in studies, such as the knee-related quality of life scale (Frobell *et al.* 2010).

  There has been a systematic review and meta-analysis on measurement properties of KOOS (Collins *et al.* 2016). This systematic review included 37 studies and reported on internal consistency, test-retest reliability, content and construct validity and responsiveness of the KOOS score. It reported acceptable internal consistency (Cronbach's $\alpha \geq 0.70$) for all sub-scales (domains). Pooled data from 26 studies showed that all sub-scales (domains) demonstrated acceptable test-retest reliability (ICC ≥ 0.70). There was evidence from four studies about acceptable content validity. With regards to construct validity, most studies conducted hypothesis testing of KOOS subscales against SF-36 subscales, and when all data were pooled it showed correlations supporting the known hypotheses and the

construct validity. They also reported high responsiveness with large effect sizes and standardized response means.

- **International Knee Documentation Committee (IKDC) score**: This is a patient-reported knee-specific outcome measure which uses a questionnaire with a subjective scale providing patients with an overall function score (Hefti *et al*. 1993). The questionnaire comprises 3 categories: symptoms, sports activity and knee function. Scores are obtained by summing the individual answers to questions in each category and then transforming the total to a scaled number, which ranges from 0 to 100. Higher scores represent higher levels of function. There has been a recent systematic review that evaluated the measurement properties IKDC score (Grevnerts et al. 2015). It included 26 studies and reported on internal consistency, test-retest reliability, validity and responsiveness of IKDC. It showed strong evidence for positive internal consistency and acceptable test-retest reliability (ICC > 0.70) overall. It reported moderate evidence that the IKDC score has good content and structural validity. With the SF-36 as a 'gold standard', the level of evidence was indeterminate for criterion validity. The responsiveness was reported as 'strong positive' level of evidence due to four studies with positive scores, two of 'good' and two of 'fair' methodological quality.

1.3.4.2 Activity related scales

Tegner-Activity Scale (TAS) (Tegner & Lysholm 1985): This scale assesses activity levels with specific emphasis on the knee. The TAS has been in use for 25 years as a patient-reported activity related score to assess early return of knee function after ACL treatment (Briggs *et al*. 2009). There are 10 levels of activity and the patient indicates the highest level of activity that he/she participated in before the injury and the highest level that he/she participates in currently (either after injury or after ACL reconstruction). Scores range from 1 (least strenuous activity; disability because of knee problems) to 10 (high knee-demanding activity on a professional/competitive level). Briggs *et al.* in 2009 undertook a comprehensive assessment of measurement properties of the TAS scale (along with the Lysholm score) as a patient-reported outcome instrument for patients with ACL injuries. They reported that the test-retest reliability was acceptable (ICC ≥ 0.80). Content validity was reportedly acceptable for the overall TAS scale. Correlation of

the overall TAS level with the physical score of the Short Form-12 (SF-12) health-related quality-of-life scale and the IKDC was performed to establish the criterion validity, and there was weak correlation of TAS scale with IKDC (r = .2) and SF-12 (physical component) (r = .2). They also looked at floor and ceiling effects which were acceptable < 30% for the overall TAS score. For the construct validity, all hypotheses (constructs) were found significant. Finally, they reported that the TAS score was responsive to change at each of the time points (large overall effect size and moderate overall standardised response mean at all time periods).

- **Return to pre-injury activity level**: This is assessed by comparing the Tegner-Activity Scale (TAS) at follow-up post ACL reconstruction with pre-injury TAS.

1.4 Management of Anterior Cruciate Ligament injuries

The management of an ACL deficient knee has been a controversial field and there is still no clear consensus regarding the ideal treatment of this injury. Current approaches can be classified into non-operative management and operative management depending on several patient-specific factors as described below.

1.4.1 Non-operative management

Non-operative management consists of a rehabilitation program with physiotherapy, functional bracing and activity modification and it has traditionally been recommended for patients with sedentary occupations and less active lifestyles (Bogunovic & Matava 2013; Herrington & Fowler 2006; Strehl & Eggi 2007). Physiotherapy programmes tend to be prolonged, initially focusing on reduction of swelling and pain and restoration of knee range of motion; then strengthening of the muscles around the knee (mainly quadriceps and hamstrings) to improve joint stability (Buss *et al*. 1995; Williams & Bach 1996).

Functional knee bracing can help by supporting the ACL-deficient knee during high levels of activity that may involve twisting, pivoting and/or cutting. Custom braces offer greater support, but the exact mechanism is not entirely understood (Vailas & Pink

1993). It has been shown that a brace can reduce anterior tibial translation by 30%-40%, but it cannot restore normal stability of the knee during weight-bearing activity (Beynnon *et al*. 2003; Wojtys *et al*. 1996). This is a disadvantage making the risk of re-injury and associated injuries to the menisci and cartilage high due to instability (as described above).

Activity modification is also important in successful non-operative management of ACL injuries, especially with regards to level of sports. Jumping, cutting and pivoting sports such as football and basketball, and heavy manual labour are more ACL-dependent and should be avoided and ideally discontinued. Only non-cutting sports (like running), light manual work or no sports could be continued in the long term to reduce the risk of re-injury and/or injury to the menisci and cartilage (Nebelung & Wuschech 2005). This is a disadvantage for young and active patients who would like to continue their level of activity and sports and it may have an impact on their employability if they are engaged in manual work.

The outcome of a non-operatively managed ACL injury is mainly dependent on patient activity levels and better results with good-to-excellent outcomes reported in those with low activity demands and less active lifestyle (Buss *et al*. 1995; Muaidi *et al*. 2007; Strehl & Eggli 2007). Most patients (95%) can return to usual work and daily activities without functional difficulty (Buss *et al*. 1995; Muaidi *et al*. 2007), but 60% experience knee pain with activity (Buss *et al*. 1995). However, only a few highly active patients can return to their pre-injury level of activity and most need to reduce their level of activity by an average of 20% (Andersson *et al*. 1991; Muaidi *et al*. 2007). As previously reported, Noyes et al. (1983a) found that almost one-third of young and active patients who were managed non-operatively for their ACL injury improved with no or minimum symptoms during daily activities or during recreational activities, but one third of these patients did not benefit from non-operative management ("rule of thirds"). There has been lot of research on these patients since then, reporting again that approximately one-third of patients with ACL injury do not experience impairment or disability and they have been referred to as 'copers' (Herrington & Fowler 2006; Kaplan 2011). New knee injuries, including meniscal and chondral injuries, have been reported with greater frequency in non-operatively managed athletes with ACL injury who chose to return to high-level activity (Waldén *et al*. 2006); and the trend is now to treat with ACL reconstruction surgery those patients who wish to return to pivoting

sports regardless of coping ability (Kaplan 2011). Higher rates of meniscal injuries requiring surgery have been reported also in patients who followed a long-term rehabilitation period with delayed ACL surgery (Frobell *et al*. 2010).

1.4.2 Operative management

Operative management of ACL rupture consists of ACL reconstruction surgery performed by arthroscopic (keyhole) surgery. ACL reconstruction involves reconstructing the ruptured ligament with a graft placed in an isometric location trying to restore the knee joint to near normal stability and function (Dye *et al*. 1999). The graft can either be a tendon (such as hamstring or patellar tendons) from another part of the body (autograft) or a synthetic-allograft tissue (cadaveric). The main grafts used are autografts, with the hamstrings becoming the most widely used by surgeons (Cerulli *et al*. 2013). The surgery is supplemented by a rehabilitation physiotherapy program post-operatively.

Although good-to-excellent outcomes have been reported in the literature after ACL reconstruction surgery (Ardern *et al*. 2011; Marrale *et al*. 2007), evidence suggests mixed results with insufficient randomised evidence as to whether operative or non-operative treatment of ACL injuries is more effective overall in adults (Linko *et al*. 2005). ACL reconstruction is traditionally recommended for patients with a high-level of activity doing physically demanding jobs or who desire to return to jumping, pivoting or cutting sports (Bogunovic & Matava 2013; Daniel & Fithian 1994; Kaplan 2011). The possibility of returning to a high level of activity with no instability after ACL reconstruction is said to be the main advantage of undergoing operative management. Ardern *et al*. (2011) in their systematic review of 48 studies with 5770 patients report that most of the patients after ACL reconstruction can return to some form of sports participation (pooled rate 82%), with 63% returning to pre-injury sports level and 44% returning to competitive sport. The majority (90%) report normal or near normal knee function on patient-reported outcome scores after a mean follow-up of 41 months. The relatively low rate of return to pre-injury activity level and competitive sport, despite the high rates of successful functional outcomes, suggest that there are other factors after ACL surgery that contribute to these activity-related outcomes.

Age is an important factor to consider, but age alone should not be considered as the only reason for operative management. Any patient with very active lifestyle, for example, involving pivot-type movements would be impaired by an ACL deficiency, as ACL is the most important rotational stabiliser as explained above in section 1.1.1. Sometimes even low activity demand patients continue to experience instability with daily activities (non-copers) and then surgery is often recommended (Bogunovic & Matava 2013; Kaplan 2011). Also, both objective and subjective outcomes after ACL reconstruction do not seem to be impaired by age (Barber *et al*. 2012). Associated injuries to other ligaments, menisci or articular cartilage are also considered relative indications to proceed to operative management to achieve less instability and better outcomes (Bogunovic & Matava 2013; Daniel & Fithian 1994, Shirakura *et al*. 1995).

The challenge for the clinician is to identify which patients would tolerate non-operative management, with minimal risk of re-injury and associated injuries to menisci and cartilage due to instability, and which patients would or would not require operative management with ACL reconstruction to prevent instability, associated injuries and have their desired level of activity.

However, in patients suitable for surgical management, timing from ACL injury to ACL reconstruction remains a controversial issue and opinion varies a lot amongst surgeons and centres in different countries. Several studies have examined the effect of timing of ACL reconstruction after injury on outcomes and tried to identify the ideal timing. The question whether to perform an early or a delayed ACL reconstruction is still not clearly answered. The findings of available studies appear to be conflicting and there is no consensus among surgeons (Almekinders *et al*. 1995; Anstey *et al*. 2012; Frobell *et al*. 2010; Razi *et al*. 2013; Sri-Ram *et al*. 2013).

There is not enough randomised evidence on optimal management of ACL injuries and timing of ACL surgery in patients deemed suitable for such surgery. One randomised controlled trial tried to assess optimal management of an ACL rupture related to timing and did not find any difference in functional outcome between rehabilitation with early (within 10 weeks from injury) ACL reconstruction and rehabilitation with delayed (more than 10 weeks from injury) ACL reconstruction (Frobell *et al*. 2010). Similarly, in another retrospective study there was no difference in knee range of motion after 1 year, between patients who had ACL reconstruction within 4 weeks and patients who

had it after 4 weeks (Almekinders *et al*. 1995). However, there is still a theoretical risk of further meniscal and chondral injuries as a result of instability in an untreated ACL deficient knee, and the importance of early prevention of these meniscal tears is explained in section 1.3.1 as they could potentially lead to OA later. A large prospective study conducted in 2013 compared ACL reconstruction at different times from injury and concluded that younger patients who had early ACL reconstruction (before 5 months) developed fewer further meniscal and less chondral damage than those who had delayed ACL reconstruction (after 5 months) (Sri-Ram *et al*. 2013). Similar results are reported in other studies as well (Anstey *et al*. 2012; Razi *et al*. 2013).

Smith *et al*. (2010) in a systematic review and meta-analysis compared early (within 3 weeks from injury) and delayed (greater than 6 weeks from injury) ACL reconstruction and found no significant difference in clinical outcomes between the two groups. The review conclusion was limited by the poor methodological quality of the included studies. Also, in this review the delayed group included patients that had ACL surgery just over six weeks from injury, and it is unlikely that patients will have had opportunities to stress their knee and expose it to the possibility of new meniscal or chondral injuries. Hence, even though that review assessed issues like arthrofibrosis associated with early ACL reconstruction, it is not relevant to the issues examined in this thesis. There have been many studies before and since this review that compare early and delayed ACL surgery with timings that are more pertinent to this thesis and with regards to outcomes, especially clinical outcomes, relevant to trying to establish the benefits or drawbacks of early ACL reconstruction and rehabilitation.

As highlighted above, the definitions of early and delayed ACL reconstruction vary between studies, and analysis and interpretation of results is therefore difficult and challenging. Early ACL reconstruction has been defined as the surgery performed within 10 weeks from injury (Frobell *et al*. 2010); but also as surgery performed within 4 weeks (Almekinders *et al*. 1995); or even surgery performed within 6 months (Anstey *et al*. 2012). There are also studies that have used several (more than two) different time definitions for early or delayed intervention to assess the effect of timing of ACL reconstruction on outcomes (Razi *et al*. 2013; Sri-Ram *et al*. 2013).

Trying to define early ACL reconstruction is difficult, but for the purposes of this thesis I consider three periods. As it takes up to 12 weeks for the inflammation to settle down

and motion to be restored, this needs to be taken into consideration (as described above in section 1.2.2). So, this phase of up to 12 weeks with the inflammation inside the knee joint is the early phase post ACL injury, including the acute first 72 hours post injury. So, an ACL reconstruction surgery performed within 12 weeks post injury will be defined as **early** ACL reconstruction in this thesis. However, many patients may not have seen surgeons within this period. This may be because of delay in seeking medical attention, or delays waiting for surgery, or because of personal schedules or clinical decisions to allow for settling of the inflammation. Therefore, it may be 3-6 months before their treatment (when ACL reconstruction is usually arranged) (Fok & Yau 2013). In this thesis, any ACL reconstruction surgery performed between 3 months (12 weeks) and 6 months post injury will be defined as **subacute** ACL reconstruction in this thesis. Finally, any ACL reconstruction surgery performed after 6 months will be defined as **delayed** ACL reconstruction. Periods of delay beyond 36 months will not be considered in this thesis.

1.4.3 Management decision-making

Considering all the factors mentioned above, there are three timing options for further treatment of an ACL injury overall.

Option 1: Perform an ACL reconstruction in everyone after 12 weeks, once the knee has settled, the inflammation of the injury has subsided, and the knee has regained motion; but that would mean unnecessary surgeries in many patients in those who would benefit from non-operative management and this is evident in the above studies (Buss *et al*. 1995; Strehl & Eggli 2007; Frobell *et al*. 2010; Sri-Ram *et al*. 2013).

Option 2: Follow a "wait and watch" policy, waiting to see how the knee behaves and whether there is any residual symptomatic instability after rehabilitation with physiotherapy and an attempt to return to pre-injury activities, before deciding to proceed to a delayed ACL reconstruction (Smith *et al*. 2014). However, with this option there is a theoretical risk of residual instability, which can lead to further meniscal and chondral injuries as described above in section 1.2.2.

Option 3: Identify patients that would benefit from an early ACL reconstruction within 12 weeks, rather than a "wait and see" approach (Moknes & Risberg 2009; Wittenberg *et al*. 1998).

Bearing in mind the above time-frames and options, clear guidelines on the ideal timing for an ACL reconstruction, and on which patients could benefit from early, subacute or delayed ACL reconstruction surgery, would be of great value for all knee surgeons and patients. A systematic review may help identify and combine evidence, which could support clinical decision making to guide clinicians on the ideal timing of ACL reconstruction surgery and selection of patients. This thesis attempts to gather the information that may help to support the development of guidelines.

1.5 Research Aim & Objectives

1.5.1 Aim

The overall aim is to determine if there is a relationship between timing from ACL rupture to surgery and clinical, functional and/or patient-reported outcomes and to explore the feasibility of collecting clinicians' views on ACL reconstruction timing.

1.5.2 Objective 1

To determine if there is a relationship between the timing from ACL rupture to ACL reconstruction surgery and a) development of further meniscal tears and chondral injuries (clinical outcomes) and b) functional and patient-reported outcomes.

1.5.3 Objective 2

To determine if patient characteristics are related to the timing of ACL reconstruction and whether timing has an impact on outcomes in different patient groups

1.5.4 Objective 3

To explore the feasibility of collecting clinicians' views on appropriate timing of ACL reconstruction. To examine variations in practice and the factors influencing clinical decisions.

Objectives 1 and 2 are addressed through a systematic review of the literature on timing of ACL reconstruction. Objective 3 is addressed through the development and piloting of a vignette questionnaire exploring the choice and reasons for timing of ACL reconstruction.

1.6 Overview of thesis

Chapter 2 reports the methodology and results of the systematic review of literature on timing of ACL reconstruction comparing clinical as well as functional and patient reported outcomes. This chapter discusses the implications of this review for further investigation of clinicians' decision-making on timing of ACL reconstruction.
Chapter 3 describes the development and piloting of the vignette-based study, utilising the findings of the systematic review.
Chapter 4 includes the thesis discussion, which provides a brief summary of the findings of the two studies, integrates their findings and reports on the limitations and implications of the thesis.

CHAPTER 2: SYSTEMATIC REVIEW OF THE RELATIONSHIP OF TIMING OF ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION WITH OUTCOMES

2.1 Background

In the previous chapter, the anatomy and the biomechanics of the normal knee were described, explaining the stability of the knee and its contributors. Changes to these, when the ACL is injured (torn), were outlined, along with concomitant injuries and the patients' symptoms in response to a tear. Also, the management of ACL injuries was discussed highlighting the controversies over the timing of ACL reconstruction.

Delayed ACL reconstruction, leaving ACL rupture untreated for a long time after injury, may lead to anterior laxity and rotator instability increasing the risk of meniscal and cartilage injury (Caborn & Johnson 1993; Eckstein *et al*. 2015). These injuries increase the risk of longer-term instability and OA as explained in the introduction (Culvenor *et al*. 2014; Englund *et al*. 2009b; Fithian *et al*. 2002). An unstable knee impairs all knee-related activities so return to high-level activities or sports may not be possible (Paterno 2017; Sepúlveda *et al*. 2017). Operating too early, however, may lead to unnecessary treatment in patients who would benefit from non-operative management. The challenge is to identify the most appropriate time for surgery for most patients and to identify the factors that should influence decisions about the best timing for surgery in subgroups of patients. (Almekinders *et al*. 1995; Anstey *et al*. 2012; Frobell *et al*. 2010; Ghodadra *et al*. 2013 Razi *et al*. 2013; Sri-Ram *et al*. 2013). The question whether to perform an early or a delayed ACL reconstruction is still not clearly answered.

Thus, a systematic review of literature looking at the relationship between timing from ACL rupture to ACL reconstruction and clinical (meniscal tears and chondral injuries), functional and patient-reported outcomes was undertaken. Information was also extracted from this literature on whether patient characteristics affected this relationship.

2.2 Objectives

2.2.1 Objective 1

To determine if there is a relationship between timing from ACL rupture to ACL reconstruction surgery and a) development of further meniscal tears and chondral injuries and b) functional and/or patient-reported outcomes.

2.2.2 Objective 2

Another objective of this study was to determine if patient characteristics are related to the timing of ACL reconstruction and whether timing has an impact on outcomes in different patient groups.

2.3 Methods

2.3.1 Study design

A systematic review aims to summarise available evidence on a certain topic in a transparent manner and answer a clearly formulated research question (Klassen *et al*. 1998). For this systematic review, the Cochrane methodology for systematic reviews was followed (Higgins & Green 2011). This includes an introduction setting the background and objectives, which are described above in sections 2.1 and 2.2. Also, the methodology is described outlining the selection criteria, search methods, data collection and data analysis. The results are reported describing the reasons for excluding studies and describing the characteristics of included studies, their methodological quality and results of analyses. There is a discussion section with the author's conclusions. Tables and/or figures are used throughout showing the characteristics of the included studies, the interventions that were compared, the results of the included studies and also a list of the studies that were excluded and any additional tables and/or figures relevant to the review.

The work was conducted with reference to a predefined protocol, which was submitted on the PROSPERO database for registration as soon as it was complete. It was accepted and published on the database on 13th January 2016. The search was conducted prior to acceptance of the protocol on the PROSPERO database (15th September 2015).

However, the search was conducted according to the protocol registered on the database, and all inclusion and exclusion criteria to identify initial studies were also conducted as in the protocol. Initially, the data was going to be extracted and synthesized about meniscal tears, chondral injuries and patient-reported outcomes after the 4th week from injury to intervention (subacute treatment). However, it was clear when extracting and synthesizing data, that to maximise the use of available evidence from the studies, it would be better to add functional and patient-reported outcomes and to compare outcomes in three different timings to intervention: (i) Early treatment: any intervention performed within 12 weeks (3 months) from injury, including the first 72 hours from injury. (ii) Subacute treatment: any intervention performed between 12th week (3 months) and 24th week (6 months) from injury. (iii) Delayed treatment: any intervention performed between 6th and 36th month from injury. Consequently, the protocol was updated; an updating of the protocol held on the PROSPERO database was also consequently updated (7th February 2018).

It is important when undertaking systematic reviews to have a protocol which is followed to ensure transparency and consistency. However, in systematic reviews, following identification of studies and data, changes in definitions are often required. These must be explicitly reported on any registered protocol, so that it is clear to the readers what has been changed, when and why. Unlike controlled trials, such changes are acknowledged as allowable in systematic reviews (Dwan *et al*. 2011; Silagy *et al*. 2002; Stewart *et al*. 2012). Registration of protocol and changes in a database like PROSPERO contributes to the transparency of the methodology of the systematic review and reduces potential for publication bias, by maintaining a permanent public record of the key elements of the review (Stewart *et al*. 2012). The registration number of this systematic review on PROSPERO database is: CRD42016032846 (Prodromidis *et al*. 2016). A copy of the PROSPERO registered record is shown in Appendix 1.

2.3.2 Selection criteria

- **Population**: The population included in the review were adults with a complete ACL rupture. Studies with adults with partial ACL tear were excluded, because these patients are most often treated non-operatively. Also, studies of re-ruptures of a previously repaired or reconstructed ACL were excluded, as it is known that these

injuries have worse outcomes, and this would potentially bias the results (Ahn *et al*. 2008; Andriolo *et al*. 2015; Griffith *et al*. 2013; Wright *et al*. 2011). Only studies examining skeletally mature patients were included, as the anatomy of children with an immature skeleton is different around the knee with the growth plate and this will influence surgical decisions in ways that differ from those made for adult patients. ACL surgery in skeletally immature patients is often postponed or performed in a different way to avoid disturbing the child's growth (Longo *et al*. 2017; Pierce *et al*. 2017; Price *et al*. 2017). Skeletal maturity is normally achieved around 16 years old. Thus, studies examining the findings of timing of ACL surgery on patients aged less than 16 years old only were excluded; as were studies with both skeletally mature (older) and skeletally immature patients less than 16 years old, when separate results for older patients could not be obtained.

- **Intervention/Comparators:** The interventions were primary ACL reconstruction surgery at a given time from ACL injury and different timings were compared. Only arthroscopic primary ACL surgery was included and any study with open ACL surgery was excluded, because the arthroscopic technique is the most commonly performed (Delay *et al*. 2001).

There is not a generally accepted definition of early and late intervention in an ACL deficient knee. The knee after an ACL rupture needs 6-12 weeks for the inflammation to settle down, as described in the introduction (Mohtadi *et al*. 1991). After that milestone for the knee, any delay is a delay. So, for the purposes of this systematic review, the timing for ACL reconstruction surgery was divided with reference to time from ACL injury as below (the justification is given in section 1.4.2):

(i) Early treatment: any intervention performed within 12 weeks (3 months) from injury including the first 72 hours from injury.
(ii) Subacute treatment: any intervention performed between 12^{th} week (3 months) and 24^{th} week (6 months) from injury.
(iii) Delayed treatment: any intervention performed between 6^{th} and 36^{th} month from injury.

However, when reviewing the papers, it was clear that studies did not always use such clear definitions, or the definitions potentially crossed more than one category. Being

too strict would have led to the exclusion of a considerable number, if not all the studies. Therefore, the student decided to further define the categories such that a study group could be classified into one of the timing groups as above, if the mean time from injury fell within the time-frame. Therefore, a study was included if there were at least two study groups which were either classified as above or the mean time intervals fell into above. For example, if the mean time interval in one study group was eight weeks and the mean time interval of another study group was ten months, the study would be included, and the time intervals classifies as Early and Delayed respectively. It was recognised by the student that this was not an ideal means of classification as there may be patients within each study group who did not fall strictly into the category, but it was felt to be the best way forward given the amount of variation between studies. The issue is discussed further in the review discussion section.

- **Outcomes:**

(i) Clinical outcomes: any type of meniscal tear or any type of chondral injury graded by any system. These injuries were included as they demonstrate damage to intra-articular structures of the knee from ongoing instability and are indicators of long term damage inside the knee leading to OA and impaired function (as explained in section 1.1.2).

(ii) Functional (objective) outcomes: are measured objectively (see section 1.3.3 for examples). These were included as they show the functional status of the knee post-operatively.

(iii) Patient-reported (subjective) outcomes: are reported subjectively. These were included as they are patient-reported and indicate the physical functioning of the patient and/or the quality of life of the patient post-operatively. Such outcomes include knee specific instruments (knee scores), activity-related scales and generic quality-of-life measurements (see section 1.3.4 for examples).

- **Study designs:**

Any comparative study design was eligible. This included randomised controlled studies (RCTs), prospective cohort studies, case control studies, and retrospective comparative studies. Excluded study designs included case reports, reviews, editorials, personal opinions, surveys and case series.

2.3.3 Search

The strategy for the systematic search comprised the following main elements:

- Searching of electronic bibliographic databases.
- Searches in clinical trials databases.
- Scrutiny of references of included studies and any identified systematic review.

The following electronic bibliographic databases were searched on 10th September 2015: MEDLINE (1946 to present) – Interface: EBSCOhost; EMBASE (1974 to present) – Interface: Ovidsp; CINAHL (1961 to present) – Interface: EBSCOhost; AMED (1995 to present) – Interface: EBSCOhost; CENTRAL (1988 to present) – Interface: Cochrane Library; with no publication year limit. These databases were selected as they are databases in which orthopaedic medical and allied health professional journals are indexed, the professions which would have an interest in this topic. There was a language limit because of limited access to translators and resources. Therefore, only studies available in English language were included. Age was not set as a limit to the search because of the difficulty of setting specific search terms, but all titles and abstracts about children (age < 16 years) were excluded whilst screening**.** The search in all databases was performed with a combination of subject headings and key-words. When using subject headings narrowed the results inappropriately, simple key-words were also used. Wildcards were also used trying not to miss any relevant study due to spelling and to increase the scope of the search. A wildcard is a character, such as an asterisk (*) or a question mark (?), used to represent a number of characters. The asterisk (*) matches zero or more non-space characters. The question mark (?) matches exactly on non-space character. Only the asterisk (*) was used in the search. The search was developed using subject headings and key-words for each of 4 parameters (disease, outcome, time, intervention). Subject headings and key-words within each parameter were combined with the Boolean operator OR and then these sets of subject headings and key-words were combined with the Boolean operator AND as illustrated below:

i) **Disease**: anterior cruciate ligament OR ACL [subject heading or key-word]
AND

ii) **Outcome:** menisc* OR cartilag* OR chondral OR function* OR outcome* OR scor* OR pain
AND

iii) **Time:** earl* OR delay* OR tim*

AND

iv) **Intervention:** surgery OR reconstruct*.

This strategy for choosing and combining the certain key-words is also summarised in Table 2.1. Example of this search strategy as applied to the MEDLINE database is shown in Table 2.2. Search strategies for the rest of the databases (EMBASE, CINAHL, AMED, CENTRAL) are shown in Tables 1 - 4 in Appendix 2a.

Table 2.1 Summary of strategy for search performed in all databases

Disease		**Outcome**		**Time**		**Intervention**
anterior cruciate ligament OR ACL	AND	menisc* OR cartilage* OR chondral OR function* OR outcome* OR scor* OR pain	AND	earl* OR delay* OR tim*	AND	surgery OR reconstruct*

Table 2.2 Search strategy applied in MEDLINE database

#	Query	Limiters/Expanders	Last Run Via
S1	anterior cruciate ligament	English language; Human.	Interface – EBSCOhost Database – MEDLINE with Full Text
S2	ACL	Same as S1	Same as S1
S3	menisc*	Same as S1	Same as S1
S4	chondral	Same as S1	Same as S1
S5	cartilag*	Same as S1	Same as S1
S6	function*	Same as S1	Same as S1
S7	outcome*	Same as S1	Same as S1
S8	pain	Same as S1	Same as S1
S9	scor*	Same as S1	Same as S1
S10	delay*	Same as S1	Same as S1
S11	earl*	Same as S1	Same as S1
S12	tim*	Same as S1	Same as S1
S13	surgery	Same as S1	Same as S1
S14	reconstruct*	Same as S1	Same as S1
S15	S1 OR S2	Search modes: Boolean/Phrase	Same as S1
S16	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Search modes: Boolean/Phrase	Same as S1
S17	S10 OR S11 OR S12	Search modes: Boolean/Phrase	Same as S1
S18	S13 OR S14	Search modes: Boolean/Phrase	Same as S1
S19	**S15 AND S16 AND S17 AND S18**	**Search modes: Boolean/Phrase**	**Same as S1**

Archives of clinical trials were searched on 10th September 2015 in addition to the electronic bibliographic databases to identify any additional relevant clinical trials not cited in the databases. These archives were: United Kingdom (UK) Clinical Trials (UK Clinical Trials Gateway, 2015) and Unites States (US) Clinical Trials (ClinicalTrials.gov, 2015).

Based on the above inclusion/exclusion criteria, the titles of studies identified by the searches were screened to remove those obviously not appropriate to the objectives of the study. Any duplicate studies were also removed. Then the abstracts of the selected titles were screened to identify relevant studies and the full manuscripts of these studies retrieved. The full text of studies, where a decision regarding inclusion could not be made from the title and abstract, were also retrieved. The reference lists of all selected articles were also examined for any additional articles not identified through the database search. This search strategy gave the studies that needed to be considered for

inclusion in the review. These full texts were then reviewed against the selection criteria to identify eligible studies.

An integral part of the identification of eligible studies is to have a team of at least two researchers independently screen the titles, abstracts and full texts identified by the searches. The search was put together and run by the research student. Two reviewers assessed the search outputs, the research student and a second reviewer (an Orthopaedic Registrar also undertaking a Masters by Research). This was done independently at the same time using the inclusion and exclusion criteria. The input from the second researcher ensured that relevant studies were not missed and that an over-inclusion of irrelevant studies was avoided. Once both reviewers finished screening studies, they discussed and agreed about the studies that appeared to be eligible and those where additional information needed to be sought. The papers for these studies were obtained and the papers reviewed by both reviewers for eligibility independently first, and then discussed to develop a final list for data extraction. There were a number of studies that after paper review both reviewers agreed that they should be included or excluded. However, there was a number of studies that the two reviewers could not agree about their eligibility. These studies were passed to one of two experienced reviewers (both were thesis supervisors, one an Honorary Professor, Orthopaedic Consultant and the other the Director of Studies) to decide on eligibility for inclusion. After this third review of these studies, the final list of studies eligible for analysis was generated. The references list of all reviewed papers were also scrutinised for any other study eligible for inclusion. This process for reaching agreement and generation of the final list of studies for the systematic review with numbers is shown in detail in the results section 2.4.1.

2.3.4 Data extraction

Data were extracted from the included studies by two reviewers independently (the research student and the same Orthopaedic Registrar) using a standardized data extraction form developed by the research student and inputted onto an appropriate Excel spreadsheet to record the results. The results from each reviewer's data extraction forms for each study were compared and any discrepancies reviewed. Data items that were extracted included:

- Characteristics of each study (country/setting, number of patients, age group, sex).
- Patient factors that might affect outcome (e.g., gender, age group, level of activity, mechanism of injury). The reason for collecting this information is that there are surgeons who proceed to an earlier ACL reconstruction surgery in certain groups of patients. The factors which have previously been investigated include gender and age (Chhadia *et al*. 2011; Granan *et al*. 2009); level of activity or lifestyle including type of job or level of sports (Chen et al. 2015; Smith et al. 2014); and mechanism of injury, such as contact injury (Chen et al. 2015).
- Timing from injury until intervention (ACL reconstruction).
- Types and rates of further meniscal tears.
- Types, grading system and rates of further chondral injuries.
- Functional and/or patient reported outcomes and scores.

2.3.5 Data analysis

If there were sufficient number of studies, which were sufficiently homogenous, it was proposed that a meta-analysis would be performed. Homogenous studies would be considered as studies that had the same study design, comparable population, compared the same or similar time intervals before treatment (early versus delayed, subacute versus delayed) and had the same outcome measures. Meta-analysis would be undertaken separately for meniscal tears, chondral injuries, functional (objective) outcomes and patient-reported (subjective) outcomes.

However, it was anticipated that there was unlikely to be sufficient homogenous studies for a meta-analysis to be performed. If this was confirmed, then the results would be reported and synthesized narratively using tables to summarise the findings and examine the overall effect of elapsed timing of ACL reconstruction surgery for each outcome.

2.3.5.1 Patient subgroups

Data was collected on patient or clinical characteristics which were investigated in identified studies with regards to their relation to the timing of ACL reconstruction, and whether the timing had an impact on outcomes in patients with these characteristics. Within identified studies, when reported, the outcome of patients with a particular characteristic were compared across categories. In the non-randomised studies, the frequency of patients with a particular characteristic in the different time categories were also compared.

2.3.6 Assessment of methodological quality of studies and quality of evidence

The methodological quality of each study was assessed with different assessment criteria as appropriate to the study design. For randomised controlled trials (RCTs), the **Cochrane Risk of Bias Tool** was applied (Higgins *et al*. 2011). The following parameters were assessed:

(i) Sequence generation: "Was the allocation sequence adequately generated?" (Higgins *et al*. 2011).

(ii) Allocation concealment: "Was allocation adequately concealed?" (Higgins *et al*. 2011).

(iii) Blinding of participants, personnel and outcome assessors: "Was knowledge of the allocated intervention adequately prevented during the study?" (Higgins *et al*. 2011).

(iv) Incomplete outcome data: "Were incomplete outcome data adequately addressed?" (Higgins *et al*. 2011).

(v) Selective outcome reporting: "Are reports of the study free of suggestion of selective outcome reporting?" (Higgins *et al*. 2011).

(vi) Other source of bias: "Was the study apparently free of other problems that could put it at a high risk of bias?" (Higgins *et al*. 2011).

Studies were classified by the tool as: low risk of bias, if there was low risk of bias for all key domains; or unclear risk of bias, if there was unclear risk of bias for one or more key domains; or high risk of bias, if there was high risk of bias for one or more key domains (Higgins *et al*. 2011).

For observational comparative (cohort) studies the **Newcastle-Ottawa Scale (NOS**) was used (Wells *et al*. 2014). The following parameters of three domains (selection, comparability, outcome) were assessed with the NOS scale with certain answers getting accredited with one star as a positive point:

Selection domain

1. "Representativeness of the exposed cohort: truly representative * / somewhat representative * / selected group of users / no description" (Wells *et al*. 2014).
2. "Selection of the non-exposed cohort: drawn from same community as the exposed cohort * / drawn from a different source / no description" (Wells *et al*. 2014).
3. "Ascertainment of exposure: secure record * / structured interview * / written self-report / no description" (Wells *et al*. 2014).
4. "Demonstration that outcome of interest was not present at start of study: yes * / no" (Wells *et al*. 2014).

Comparability domain

1. "Comparability of cohorts on the basis of the design or analysis controlled for confounders: study controls for one (most important) factor (like age, sex and marital status) * / study controls for any additional factor * / cohorts are not comparable on the basis of the design or analysis controlled for confounders" (Wells *et al*. 2014).

Outcome domain

1. "Assessment of outcome: independent blind assessment * / record linkage * / self-report / no description / other" (Wells *et al*. 2014).
2. "Follow-up long enough for outcomes to occur: yes * / no" (Wells *et al*. 2014).
3. "Adequacy of follow-up of cohorts: complete follow-up for all subjects accounted for * / subjects lost to follow-up unlikely to introduce bias - number lost ≤ 20% or description of those lost suggested no different from those followed * / follow-up rate less than 80% and no description of those lost / no statement" (Wells *et al*. 2014).

A study could be awarded a maximum of one star for each numbered question and a maximum of 2 stars for comparability domain. The more stars a study was awarded, the

lower was the risk of bias. More specifically there are certain thresholds for NOS scale which assesses the study as good, fair or poor quality. Good quality is with 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain. Fair quality is with 2 stars in selection domain AND 1 or *2* stars in comparability domain AND 2 or 3 stars in outcome domain. Poor quality is with 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain (Wells *et al*. 2014).

For retrospective comparative studies the **Methodological Index for Non-Randomised Studies (MINORS criteria)** was applied (Slim *et al*. 2003). The following 12 parameters were assessed with the MINORS criteria:

1. "Clearly stated aim of the study" (Slim *et al*. 2003).
2. "Inclusion of consecutive patients" (Slim *et al*. 2003).
3. "Prospective collection of data" (Slim *et al*. 2003).
4. "Endpoints appropriate to the study aim" (Slim *et al*. 2003).
5. "Unbiased assessment of the study endpoint" (Slim *et al*. 2003).
6. "Follow-up period appropriate to the aim of the study" (Slim *et al*. 2003).
7. "Loss to follow-up (less than 5%)" (Slim *et al*. 2003).
8. "Prospective calculation of study size" (Slim *et al*. 2003).
9. "Adequate control group" (Slim *et al*. 2003).
10. "Contemporary groups" (Slim *et al*. 2003).
11. "Baseline equivalence of groups" (Slim *et al*. 2003).
12. "Adequate statistical analysis" (Slim *et al*. 2003)

Each parameter/question is scored: 0 if not reported, 1 if reported but inadequate or 2 if reported and adequate. Maximum possible score for comparative studies being 24. There are no thresholds reported for MINORS criteria.

Quality of evidence for the body of literature in the systematic review was assessed using the GRADE approach (Ryan & Hill 2016; Furlan *et al*. 2009). Two raters (research student, Director of Studies) were involved in the assessment. The GRADE system rates the quality evidence as 'high', 'moderate', 'low' or 'very low'. The starting rating of 'high' means that after assessing all the potential problems regarding risk of bias, inconsistency, indirectness, imprecision or publication bias, there is great confidence in the effect estimate, which is the case for RCTs with no concerns about

any of the above domains. When there are serious concerns about any of the above domains the rating is downgraded one level for each domain of concern, and when there are very serious concerns the rating is downgraded two levels for each domain of concern. As the rating list moves from 'high' to 'very low', the confidence in the effect estimate decreases. In case of 'very low' quality evidence, it is very likely that further studies on the same topic for the same outcomes will alter the effect estimate. The starting rating for non-RCT studies is 'low' as the nature of such studies yields concerns regarding risk of bias and publication bias, especially for the retrospective studies.

2.4 Results

2.4.1 Findings of the database searches

The search was performed on 10/09/2015. It identified 5777 articles by title; 5556 through electronic bibliographic databases and 221 through archives of clinical trials. The results from the individual searches with results by each subject heading/key word according to the search strategy described above (section 2.3.2) is presented in Table 2.3 for MEDLINE database and then in tables 1-4 of Appendix 2a for the rest of the databases (EMBASE, CINAHL, AMED, CENTRAL).

Table 2.3 Results for MEDLINE database

#	Query	Results
S1	anterior cruciate ligament	10,020
S2	ACL	10,313
S3	menisc*	7,426
S4	chondral	1,470
S5	cartilag*	43,590
S6	function*	1,405,082
S7	outcome*	1,221,531
S8	pain	360,988
S9	scor*	460,339
S10	delay*	224,407
S11	earl*	768,826
S12	tim*	1,819,520
S13	surgery	1,571,702
S14	reconstruct*	139,891
S15	S1 OR S2	14,898
S16	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	2,924,411
S17	S10 OR S11 OR S12	2,486,952
S18	S13 OR S14	1,608,516
S19	**S15 AND S16 AND S17 AND S18**	**1,959**

Once both reviewers finished screening the search outputs of the five bibliographic databases, there were 254 titles selected in total; initially 213 titles were selected by the first reviewer and 86 titles were selected by the second reviewer. There was a significant discrepancy between the two reviewers, probably because the second reviewer did not fully understand, and did not apply, the selection criteria appropriately, so a discussion took place between the two reviewers. After discussion between the two reviewers about the titles they had selected, 132 abstracts were agreed by both reviewers as appearing to be eligible; 37 abstracts had been selected by both reviewers, 87 only by the first reviewer and eight only by the second reviewer before discussion. Amongst these abstracts selected, 58 were duplicates and were removed. The articles for the remaining 74 studies were obtained and reviewed by both reviewers independently for eligibility. These were then discussed to develop a final list for data extraction. While reviewing these 74 full texts, authors of nine studies were contacted for further information regarding data, to clarify the range of age of the patients or the range of time from injury (TFI) before a final decision was made on inclusion. Only two authors replied, with one study meeting the inclusion criteria after the answers were received.

Seven did not reply and these studies were excluded. In summary, of the 74 articles, the two reviewers agreed to exclude 48 of these articles and include nine, but they could not agree about the eligibility of 17 articles. These 17 articles were passed to one of the two experienced reviewers to decide on eligibility for inclusion. The experienced reviewer decided to exclude 15 of these articles as they failed the inclusion criteria and to include two of them for analysis. Finally, after the agreement between the two main reviewers and the third review from the experienced reviewer, there were 11 articles considered eligible for analysis. The references list of articles were also scrutinised but no other relevant paper was identified that met the inclusion criteria. Amongst the 11 articles, two were about the same study: one was on 2-year follow-up and the other on 5-year follow-up (Frobell *et al*. 2010; Frobell *et al*. 2013). So, data from these two articles were put together as it was about the same study. Therefore, there were 11 articles about 10 studies.

With regards to the search in archives of clinical trials which was performed on the same date (10/09/2015), using the key words: "anterior cruciate ligament" OR "ACL" revealed 7 results from UK clinical trials (UK Clinical Trials Gateway, 2015) and 214 from US clinical trials (ClinicalTrials.gov, 2015). Both reviewers excluded all of these studies.

The process of identification of the papers, as described above, is presented in a PRISMA flow diagram in Figure 2.1 (Moher *et al*. 2010).

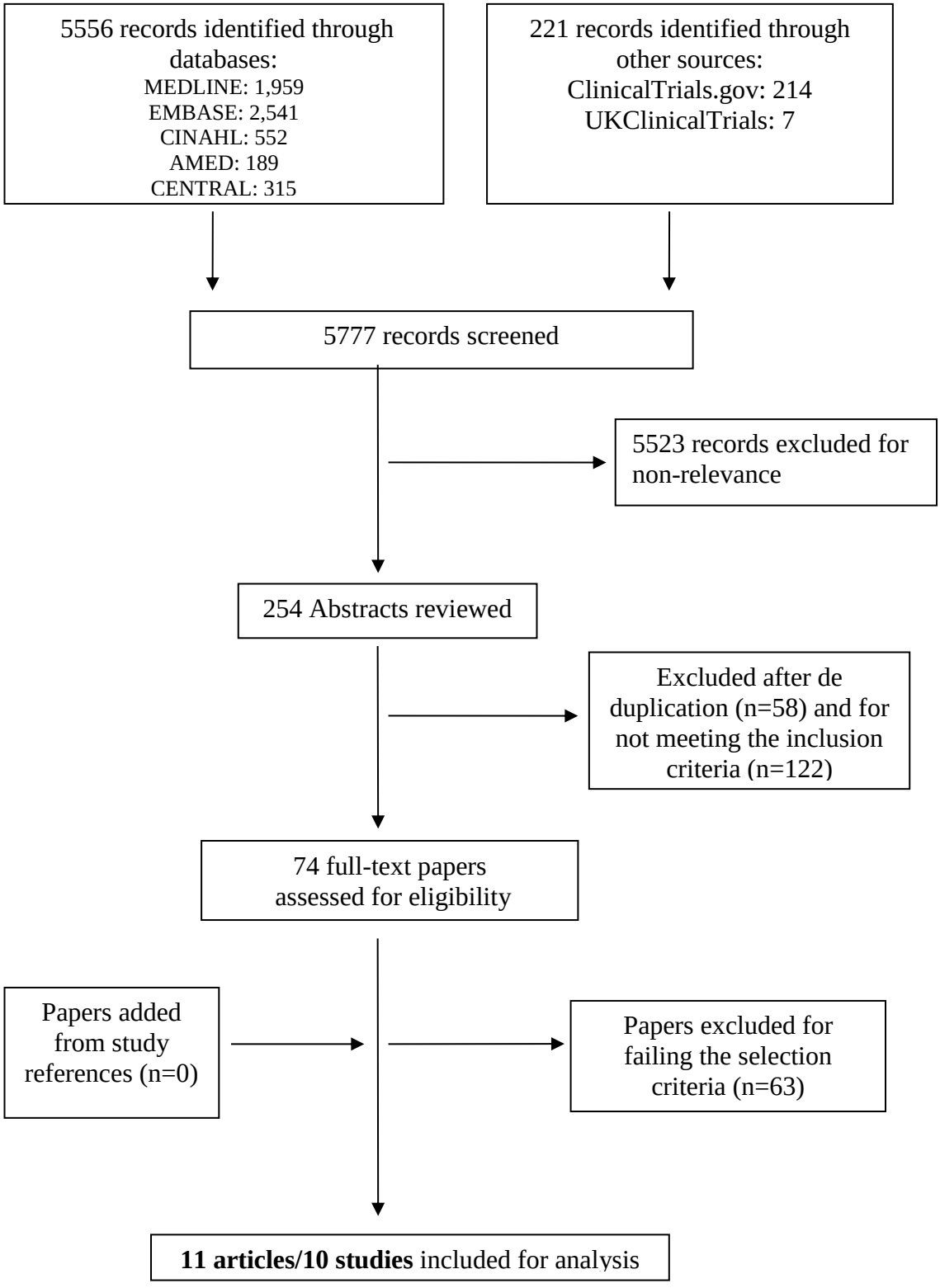


Figure 2.1. Methodology of identification and selection of studies (PRISMA flow chart)

The main reasons for exclusion of the 63 articles are summarised in Table 2.4. Further details on the excluded papers are shown in Table 1 of Appendix 2b.

Table 2.4 Main reasons for excluding articles

Reason for exclusion	**Number of articles**
Patients of age < 16 years included. Data for adults not extractable.	24
Did not group patients by time interval and results could not be grouped by TFI into early, subacute and/or delayed groups.	9
Inclusion of chronic ACL tears > 36 months. Data per appropriate TFI not extractable.	7
Ineligible study design	7
Did not clarify range of age and/or TFI. Did not respond to email sent for clarification.	4
Appropriate data not extractable from text and figures. Did not respond to email sent for clarification.	3
No correlation of outcomes with TFI.	2
Full paper unavailable. Cannot extract relevant data from abstract.	2
Ineligible outcomes	2
Included partial ACL tears	1
Included open ACL surgery	1
Study which compared early/acute ACLR with conservative (non-surgical) management.	1
Total	63

ACL: Anterior cruciate ligament, **TFI:** time from injury, **ACLR:** Anterior cruciate ligament reconstruction

The most common reason for exclusion was the age of participants with 24 studies being excluded because their population included patients < 16 years old and data about adults > 16 years old could not be extracted. Another common reason (9 studies) was the grouping of patients into timings that could not fit into the defined early, subacute and delayed groups. Another common reason (7 studies) was the inclusion of chronic ACL tears (TFI >36 months from time from injury) in which data for tears within the appropriate TFI could not be extracted. Seven studies were excluded after reading the full paper as the study design was not eligible for inclusion, e.g. reviews (none

systematic) or editorial. Two RCTs were excluded as they compared two early ACL reconstruction groups (Bottoni *et al*. 1008; Raviraj *et al*. 2010).

2.4.2 Characteristics of included studies

2.4.2.1 Demographic characteristics of participants

The demographic characteristics of participants in all 10 included studies are shown in Table 1 of Appendix 2c. There was: one study from the UK (Kennedy *et al*. 2010); two from USA (Chhadia *et al*. 2011; Anstey *et al*. 2012); two from India (Joseph *et al*. 2008; Jacob & Oommen 2012); one from China (Chen *et al*. 2015); one from Sweden (Ahlén & Lidén 2011); one from Sweden and Denmark (Frobell *et al*. 2010); one from Greece (Michalitsis *et al*. 2013); and one from Turkey (Yüksel *et al*. 2006).

Eight studies reported that there were more male participants than females, one study included only male patients (Yüksel *et al*. 2006), and one study did not provide details on the sex distribution of the included patients (Chhadia *et al*. 2011). Regarding age of patients, the mean age of the population ranged between 22.9 and 33.7 years old, but the age distribution of the patients was not mentioned in five studies (Anstey *et a*l. 2012; Chhadia *et al*. 2011; Jacob & Oommen 2012; Kennedy *et al*. 2010; Michalitsis *et al*. 2013). Regarding level of activity of the patients before the ACL injury, there was one study that had a population of competitive athletes (Frobell *et al*. 2010); two studies included both athletes and non-athletes (Chen *et al*. 2015; Joseph *et al*. 2008); one study had military personnel who participated in sports, but at an unknown level (Yüksel *et al*. 2006); one study had general community patients with different levels of activity (Chhadia *et al*. 2011); one study had patients with both low and high level of activity (TAS: 4-8) (Ahlén & Lidén 2011); but four studies did not state the level of activity of their population (Anstey *et al*. 2012; Jacob & Oommen 2012; Kennedy *et al*. 2010; Michalitsis *et al*. 2013).

2.4.2.2 Study characteristics

The studies were published after 2006 with the latest published in 2015. The rest of the characteristics of all 10 included studies which were critical for the data analysis are shown in Table 2.5 and these include the study design, timings of intervention (ACL reconstruction), sample size overall and for groups of patients and the types of outcomes measured in each study.

The total number of participants included in the analysis from these studies was 3,329 with most studies having a population of more than 100 patients, apart from two studies which had less than 100 (Ahlén & Lidén 2011; Jacob & Oommen 2012). There were two studies with a large sample size, one having 1,252 patients (Chhadia *et al*. 2011), and one having 807 patients (Joseph *et al*. 2008).

Table 2.5 Characteristics of all included studies in the systematic review

Author (Year)	Study design	Sample size overall (n)	Patient groups as defined by the study	Outcomes measured
Frobell *et al.* (2010)	Randomised controlled trial	121	Group 1: TFI ≤ 10 weeks, n=62 Group 2: TFI > 10 weeks, n=59	Functional outcomes: Stability (clinical tests), Laxity: Arthrometry (KT-1000) Patient-reported outcomes: KOOS, SF-36, TAS, Return to pre-injury activity level or higher
Chhadia *et al*. (2011)	Prospective cohort	1252	Group 1: TFI < 3 months, n=340 Group 2: TFI 3 – 6 months, n=352 Group 3: TFI 6 – 12 months, n=246 Group 4: TFI > 12 months, n=314	Clinical outcomes: Meniscal tears, Chondral injuries
Michalitsis *et al*. (2013)	Prospective cohort	109	Group 1: TFI ≤ 3 months, n=35 Group 2: TFI 3-12 months, n=39 Group 3: TFI > 12 months, n=35	Clinical outcomes: Meniscal tears, Chondral injuries
Chen *et al*. (2015)	Retrospective comparative	227	Group 1: TFI 2 – 12 months, n=129 Group 2: TFI > 12 months, n-98	Clinical outcomes: Meniscal tears, Chondral injuries
Yüksel *et al*. (2006)	Retrospective comparative	201	Group 1: TFI ≤ 6 weeks, n=45 Group 2: TFI > 12 months, n=156	Clinical outcomes: Meniscal tears, Chondral injuries
Jacob & Oommen (2012)	Retrospective comparative (chart audit)	87	Group 1: TFI < 6 weeks, n=6 Group 2: TFI > 6 months, n=81	Clinical outcomes: Meniscal tears
Kennedy *et al.* (2010)	Retrospective comparative	269	Group 1: TFI 0 – 2 months, n=62 Group 2: TFI 2 – 6 months, n=142 Group 3: TFI 6 – 12 months, n=44 Group 4: TFI 12 – 18 months, n=21	Clinical outcomes: Meniscal tears, Chondral injuries
Joseph *et al*. (2008)	Retrospective comparative	807 Non-athletes: 512 Athletes: 295	Group 1: TFI <3 months, n=487 Non-athletes: 350, Athletes: 137 Group 2: TFI 12 – 36 months, n=320 Non-athletes: 162, Athletes: 158	Clinical outcomes: Meniscal tears, Chondral injuries
Anstey *et al*. (2012)	Retrospective comparative	195	Group 1: TFI ≤ 6 months, n=171 Group 2: TFI > 6 months, n=24	Clinical outcomes: Meniscal tears, Chondral injuries
Ahlén & Lidén (2011)	Retrospective comparative	61	Group 1: TFI ≤ 5 months, n=30 Group 2: TFI ≥ 24 months, n=31	Clinical outcomes: Meniscal tears, Chondral injuries Functional outcomes: Stability: Lachman test, Laxity: Arthrometry (KT-1000), ROM Patient reported outcomes: Lysholm scale, TAS

n = number of patients, **ACLR =** Anterior cruciate ligament reconstruction, **TFI =** time from injury, **ROM =** range of motion, **TAS =** Tegner-Activity Score, **KOOS:** Knee Injury and Osteoarthritis Outcome Score, **SF-36:** 36-Item Short-Form Health Survey

With regards to study designs, the 10 studies had three different study designs, there was: one randomised controlled trial (RCT) (Frobell *et al*. 2010); two prospective cohort studies (Chhadia *et al*. 2011; Michalitsis *et al*. 2013); seven retrospective studies, of which six explicitly stated that outcomes were examined retrospectively (Anstey *et al*. 2012; Chen *et al*. 2015; Jacob & Oommen 2012; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006), and one study in which there was no information on when data was collected (i.e., there was no evidence that outcomes were collected prospectively), so was grouped with the retrospective comparative studies (Ahlén & Lidén 2011).

With regards to outcomes measured, there were nine studies that compared rates of meniscal tears: two prospective cohorts (Chhadia *et al*. 2011; Michalitsis *et al*. 2013) and seven retrospective comparative studies (Ahlén & Lidén 2011; Anstey *et al*. 2012; Chen *et al*. 2015; Jacob & Oommen 2012; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006). Eight studies compared chondral injuries: two prospective cohorts (Chhadia *et al*. 2011; Michalitsis *et al*. 2013) and six retrospective comparative studies (Ahlén & Lidén 2011; Anstey *et al*. 2012; Chen *et al*. 2015; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006). Two studies examined functional (objective) outcomes: one RCT (Frobell *et al*. 2010) and one retrospective comparative study (Ahlén & Lidén 2011). Two studies examined patient-reported (subjective) outcomes: one RCT (Frobell *et al*. 2010) and one retrospective comparative study (Ahlén & Lidén 2011).

With regards to time intervals before treatment, for the purposes of this thesis the time from injury to treatment was defined as early, subacute and delayed as described in section 2.3.2:

(i) Early: any intervention performed within 12 weeks (3 months) from injury including the first 72 hours from injury.
(ii) Subacute: any intervention performed between 12th week (3 months) and 24th week (6 months) from injury.
(iii) Delayed: any intervention performed between 6th and 36th month from injury.

When the time intervals did not exactly co-incide with those used in the definitions, the patient group was allocated to the timing group if the mean time from injury fell within the time-frame for that timing group. For example: one study had one group which had

ACL reconstruction within 6 months from injury but with a mean time from injury being 77 days was allocated as early group; the second group of the study had ACL reconstruction after 6 months from injury with a mean time from injury being 301 days, so it was allocated as delayed group (Anstey *et al*. 2012). Sometimes there was more than one patient group within the study that fell within one of the specified timing groups: when this was the case data has been pooled where possible. The timing groups for each study are shown in Table 2.6 below.

As already described in section 2.3.5, studies would be considered as homogenous if they had the same study design, comparable populations, compared the same or similar time intervals before treatment (e.g., early versus delayed, early versus subacute, subacute versus delayed) and had the same outcome measures. Within the intervention groups for each outcome, available study designs differed substantially as described above. Even among the seven retrospective studies there was heterogeneity in the type of population investigated. With regards to the population of the studies, there were significant discrepancies regarding age, gender and level of activity of patients. Three of the studies included young adult patients < 50 years old (Chen *et al*. 2015; Frobell *et al*. 2010; Joseph *et al*. 2008); but two studies included patients > 50 years old (Anstey *et al*. 2012; Yüksel *et al*. 2006); and five studies did not even clarify the range of age of their adult population (Anstey et al. 2012; Chhadia *et al*. 2011; Jacob & Oommen 2012; Kennedy *et al*. 2010; Michalitsis *et al*. 2013).

With regards to the gender of the patients, one study included only males (Yüksel *et al*. 2006); and one study did not state the gender of the patients (Chhadia *et al*. 2011). The level of activity was significantly different as well, with one study having a population of competitive athletes (Frobell *et al*. 2010); two studies including both athletes and non-athletes (Chen *et al*. 2015; Joseph *et al*. 2008); one study having military personnel who participated in sports but at an unknown level (Yüksel *et al*. 2006); one study having general community patients with different levels of activity (Chhadia *et al*. 2011); one study having patients with both low and high level of activity (TAS: 4-8) (Ahlén & Lidén 2011); and four studies not stating the level of activity of their population (Anstey *et al*. 2012; Jacob & Oommen 2012; Kennedy *et al*. 2010; Michalitsis *et al*. 2013).

Table 2.6 Timing groups for early, subacute and delayed in all studies

Study	Timing groups		
	Early ACLR	**Subacute ACLR**	**Delayed ACLR**
Frobell *et al*. (2010) and (2013)	TFI ≤ 10 weeks	N/A	TFI > 10 weeks (Mean TFI: 11.5 months)
Chhadia *et al*. (2011)	TFI < 3 months	TFI 3 – 6 months	(1): TFI 6 – 12 months (2): TFI > 12 months
Michalitsis *et al*. (2013)	TFI ≤ 3 months	N/A	(1): TFI 3 – 12 months (Mean TFI: 6.9 months) (2): TFI > 12 months
Chen *et al*. (2015)	(1) TFI ≤ 1 month (2) TFI 2 – 3 months	TFI 4 – 6 months	(1) TFI 7 - 12 months (2) TFI > 12 months
Yüksel *et al*. (2006)	TFI ≤ 6 weeks (Mean TFI ~ 1.1 months)	N/A	TFI > 12 months
Jacob & Oommen (2012)	TFI < 6 weeks	N/A	TFI > 6 months
Kennedy *et al*. (2010)	TFI ≤ 2 months	TFI 2 – 6 months	(1): TFI: 6 – 12 months (2): TFI 12 – 18 months
Joseph *et al*. (2008)	TFI < 3 months	N/A	TFI 12 – 36 months
Anstey *et al*. (2012)	TFI ≤ 6 months (Mean TFI ~ 11 weeks)	N/A	TFI > 6 months (Mean TFI ~ 10 months)
Ahlén & Lidén (2011)	N/A	TFI 2 - 5 months (Mean TFI: 3 months)	TFI ≥ 24 months (Mean TFI: 30 months)

ACLR: Anterior cruciate ligament reconstruction, **TFI**: Time from injury, **N/A**: not applicable

Hence, the included studies appeared to demonstrate considerable heterogeneity and it was considered that there were insufficient similar studies to undertake a meta-analysis for each outcome. Therefore, the results are presented and synthesized narratively in text and tables according to outcome measured and within each outcome they are sub-grouped according to timing of ACL reconstruction and study design. In this way, the effect of timing from injury to ACL reconstruction was examined from early up to delayed ACL reconstruction.

2.4.3 Meniscal tears

The results from all studies reporting on meniscal tears are summarised in tables and then analysed and synthesized narratively in groups according to timing comparisons:

(i) Three studies that compared early and subacute ACL reconstruction (Table 2.7) (Chen *et al*. 2015; Chhadia *et al*. 2011; Kennedy *et al*. 2010).

(ii) Eight studies that compared early and delayed ACL reconstruction (Table 2.8) (Anstey *et al*. 2012; Chen *et al*. 2015; Chhadia *et al*. 2011; Jacob & Oommen 2012; Joseph *et al*. 2008; Kennedy *et al*. 2010; Michalitsis et al. 2015; Yüksel *et al*. 2006).

(iii) Three studies that compared subacute and delayed ACL reconstruction (Table 2.9) (Ahlén & Lidén 2011;Chen *et al*. 2015; Kennedy *et al*. 2010).

2.4.3.1 Early versus subacute Anterior Cruciate Ligament reconstruction

Three studies (n=1,056) compared meniscal tears between early and subacute ACL reconstruction. One was a prospective cohort study (Chhadia *et al*. 2011). Two were retrospective comparative studies (Chen *et al*. 2015; Kennedy *et al*. 2010). Two of the studies did not show any significant difference in meniscal tears between early and subacute ACL reconstruction. The results from these four studies are summarised in Table 2.7.

Table 2.7 Meniscal tears reported in studies that compared early and subacute ACL reconstruction*

Author **Study design**	**Meniscal tears**		**Overall comparisons**
	Early ACLR	**Subacute ACLR**	
Chhadia *et al*. Prospective cohort	n=340 (Reference group)	n=352	MM: OR 1.35, 95%CI 0.99 to 1.84, p=0.06 LM: OR 1.16, 95%CI 0.85 to 1.57, p=0.35
Kennedy *et al*. Retrospective comparative	n=62 MM: 9 (14.5%) LM: 33 (53.2%) Both: 4 (6.5%)	n=142 MM: 21 (14.8%) LM: 72 (50.7%) Both: 6 (4.2%)	 MM: difference +0.3%, p=0.99 LM: difference -2.5%, p=0.61 Both: difference -2.3%, p=0.49
Chen *et al*. Retrospective comparative	<u>All TFI 0-3 months</u> n=112 MM: 16 (14.3%) LM: 33 (29.5%) Both: 5 (4.5%) <u>Early 1: TFI ≤ 1 month</u> n=66 MM: 8 (12.1%) LM: 19 (28.8%) Both: 3 (4.5%) <u>Early 2: TFI 2 – 3 months</u> n=46 MM: 8 (17.4%) LM: 14 (30.4%) Both: 2 (4.3%)	n=48 MM: 15 (31.3%) LM: 11 (22.9%) Both: 6 (12.5%)	<u>Subacute vs any early</u> MM: difference +17%, **p=0.01** LM: difference -6.6%, p=0.26 Both: difference +8%, p=0.06 <u>Subacute vs Early 1</u>: MM: difference +19.2%, **p=0.01** LM: difference -5.9%, p=0.48 Both: difference +8%, p=0.11 <u>Subacute vs Early 2</u>: MM: difference +13.9%, p=0.11 LM: difference -7.5%, p=0.4 Both: difference 8.2%, p=0.15

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time form injury, **n:** number of patients, **MM:** medial meniscal, **LM:** lateral meniscus, **OR:** odds ratio, *Percentages in some studies may be >100% in distribution because of combined tears.

The prospective cohort study reported no significant difference in rates of meniscal tears between early and subacute ACL reconstruction (Chhadia *et al*. 2011). This finding of no difference in rates of meniscal tears between early and subacute ACL surgery was supported for MM tears by one retrospective study (Kennedy *et al*. 2010) and for LM tears, was supported by two of the retrospective studies (Chen *et al*. 2015; Kennedy *et al*. 2010). However, a significantly increased rate of MM tears is reported in the subacute group in one retrospective comparative study (Chen *et al*. 2015).

2.4.3.2 Early versus delayed Anterior Cruciate Ligament reconstruction

Eight studies (n=2,671) compared meniscal tears between early and delayed ACL reconstruction. Two were prospective cohort studies (Chhadia *et al*. 2010; Michalitsis *et al*. 2013). Six were retrospective comparative studies (Anstey *et al*. 2012; Chen *et al*. 2015; Jacob & Oommen 2012; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006). The majority of the studies showed significantly more MM tears in delayed ACL reconstruction as compared to early ACL reconstruction. The results from the eight studies that compared early and delayed ACL reconstruction with regards to meniscal tears are summarised in Table 2.8.

Table 2.8 Meniscal tears reported in studies that compared early and delayed ACL reconstruction*

Author **Study design**	**Meniscal tears**		**Overall comparisons**
	Early ACLR	**Delayed ACLR**	
Chhadia *et al*. Prospective cohort	n=340 (Reference group)	Delayed 1 n=246 TFI 6 – 12 months Delayed 2 n=314 TFI > 12 months	 Delayed 1 vs early: MM: OR 1.81, 95%CI 1.29 to 2.54, **p=0.001** LM: OR 1.24, 95%CI 0.89 to 1.73, p=0.211 Delayed 2 vs early: MM: OR 2.19, 95%CI 1.58 to 3.02, **p<0.001** LM: OR 1.08, 95%CI 0.78 to 1.49, p=0.643
Michalitsis *et al*. Prospective cohort	n=35 MM: 10 (29%) LM: 9 (26%) Both: 3 (8%)	All TFI 3 to > 12 months n=74 MM: 22 (30%) LM: 11 (15%) Both: 14 (19%) Delayed 1: TFI 3-12 months n=39 MM: 9 (24%) LM: 6 (15%) Both: 6 (15%) Delayed 2: TFI > 12 months n=35 MM: 13 (38%) LM: 5 (13%) Both: 8 (23%)	Any delayed vs early: MM: difference +1%, p=0.901 LM: difference -11%, p=0.171 Both: difference +11%, p=0.164 Delayed 1 vs early: MM: difference -5%, p=0.91 LM: difference -11%, p=0.93 Both: difference -7%, p=0.37 Delayed 2 vs early MM: difference +9%, p>0.05 LM: difference -13%, p>0.05 Both: difference +15%, p>0.05
Joseph *et al*. Retrospective comparative	n=487 MM: 116 (24%) LM: 177 (36%)	n=320 MM: 219 (68%) LM: 131 (41%)	 MM: difference +44%, **p<0.05** LM: difference +5%, p>0.05
Yüksel *et al*. Retrospective comparative	n=45 MM: 15 (33%) LM: 18 (40%)	n=156 MM: 124 (80%) LM: 96 (62%)	 MM: difference +47%, **p=0.0001** LM: difference +22%, **p=0.026**
Anstey *et al*. Retrospective comparative	n=171 MM: 7 (4.1%) LM: 26 (15.2%)	n=24 MM: 4 (16.7%) LM: 4 (16.7%)	 MM: difference +12.6%, **p=0.01** LM: difference +1.5%, p=0.85 RR associated with MM tear in delayed vs early ACLR: 4.07 (CI,1.29-12.88)

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time form injury, **n:** number of patients, **MM:** medial meniscal, **LM:** lateral meniscus, **OR:** odds ratio, *Percentages in some studies may be >100% in distribution because of combined tears.

Table 2.8 Meniscal tears reported in studies that compared early and delayed ACL reconstruction* (continued)

Author Study design	Meniscal tears		Overall comparisons
	Early ACLR	**Delayed ACLR**	
Jacob & Oommen Retrospective comparative	n=6 MM: 2 (33.3%) LM: 0 Both: 1 (16.7%)	n=81 MM: 38 (46.9%) LM: 16 (19.8%) Both: 23 (28.4%)	MM: difference 13.6%, p=0.17 LM: difference +19.8%, p=0.14 Both: difference +11.7%, **p=0.0001**
Kennedy *et al.* Retrospective comparative	n=62 (Reference group) MM: 9 (14.5%) LM: 33 (53.2%) Both: 4 (6.5%)	All TFI 6 – 18 months n=65 MM: 22 (34%) LM: 33 (51%) Both: 4 (6%) Delayed 1: TFI 6 – 12 months n=44 MM: 11 (25%) LM: 21 (47.7%) Both: 2 (4.5%) Delayed 2: TFI 12 – 18 months n=21 MM: 11 (52.4%) LM: 12 (57.1%) Both: 6 (24.6%)	Any delayed vs early MM: difference +19.5%, **p=0.01** LM: difference -2.2%, p=0.78 Both: difference -0.5%, p=0.94 Delayed 1 vs early MM: difference +11.5%, p=0.311 LM: difference -5.5%, p=0.57 Both: difference -2%, p=0.67 Delayed 2 vs early MM: difference +37.9%, **p<0.0001** LM: difference +3.9%, p=0.34 Both: difference +18.1%, **p=0.007** Significantly higher relative odds of MM tear (OR 7.99, 95% CI 1.48 to 43.06) if TFI > 12 months (p=0.004).
Chen *et al.* Retrospective comparative	All TFI 0-3 months n=112 MM: 16 (14.3%) LM: 33 (29.5%) Both: 5 (4.5%) Early 1: TFI≤1 month n=66 MM: 8 (12.1%) LM: 19 (28.8%) Both: 3 (4.5%) Early 2: TFI 2 – 3 months n=46 MM: 8 (17.4%) LM: 14 (30.4%) Both: 2 (4.3%)	All TFI 7 to >12 months n=133 MM: 61 (45.9%) LM: 21 (15.8%) Both: 27 (20.3%) Delayed 1: TFI 7-12 months n=35 MM: 15 (42.9%) LM: 5 (14.3%) Both: 6 (17.1%) Delayed 2: TFI > 12 months n=98 MM: 46 (46.9%) LM: 16 (16.3%) Both: 21 (21.4%)	Any delayed vs any early MM: difference +31.6%, **p<0.05** LM: difference -13.7%, **p=0.01** Both: difference +15.8%, **p=0.0002** Any delayed vs early 1: MM: difference +33.8%, **p<0.05** LM: difference -13%, **p=0.03** Both: difference +15.8%, **p=0.003** Any delayed vs early 2: MM: difference +28.5%, **p=0.0006** LM: difference -14.6%, **p=0.03** Both: difference +16%, **p=0.01**

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time form injury, **n:** number of patients, **MM:** medial meniscal, **LM:** lateral meniscus, **OR**: odds ratio, **RR:** Relative risk, *Percentages in some studies may be >100% in distribution because of combined tears.

For MM tears, there were significantly more MM tears in the delayed ACL reconstruction group as compared to the early group in one of the prospective cohort studies (Chhadia *et al*. 2011) and this finding was supported by the majority (five) retrospective comparative studies (Anstey *et al*. 2012; Chen *et al*. 2015; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006). The prospective study (n=900) had two delayed groups; one being within 6 – 12 months from injury and one being more than 12 months from injury (Chhadia *et al*. 2011). It reported increased odds ratios for MM tear in both delayed groups with reference to the early group (≤ 3 months). Similarly, another two retrospective studies(n=372) had the same two delayed groups; one group having ACL surgery 6-12 months from injury and another group after 12 months from injury. One study reported significantly increased rates of MM tears in both delayed groups as compared to the early group (Chen *et al*. 2015). The other study reported a significantly increased rate only in the delayed group > 12 months from injury as compared to the early group (Kennedy *et al*. 2010). The other prospective cohort study (n=109) showed no significant difference in MM tears between early and delayed ACL reconstruction groups (Michalitsis *et al*. 2013), but this finding was supported by only one retrospective study (Jacob & Oommen 2012).

Overall, it is important to highlight that four studies showed significantly increased rates of MM tears in the delayed group of ACL surgery defined as > 6 months from injury as compared to early groups, with one being a prospective cohort study (Anstey *et al*. 2012; Chen *et al*. 2015; Chhadia *et al*. 2011; Kennedy *et al*. 2010). Five studies reported significantly increased rates of MM tears in the delayed group of ACL surgery defined as > 12 months from injury as compared to early groups, with one being prospective (Chen *et al*. 1015; Chhadia *et al*. 2011; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006).

For LM tears, more LM tears in the early group was reported by one retrospective comparative study (Chen *et al*. 2015). The opposite result, fewer LM tears, was reported by another retrospective comparative study, showing an increased rate of LM tears in the delayed group (Yüksel *et al*. 2006). The remaining six studies showed no significant difference in LM tears between early and delayed groups of treatment, with two studies being prospective (Anstey *et al*. 2012; Chhadia *et al*. 2011; Jacob & Oommen 2012; Joseph *et al*. 2008; Kennedy *et al*. 2010; Michalitsis *et al*. 2013).

2.4.3.3 Subacute versus delayed Anterior Cruciate Ligament reconstruction

Three retrospective comparative studies (n=449) compared meniscal tears between subacute and delayed ACL reconstruction (Ahlén & Lidén 2011;Chen *et al*. 2015; Kennedy *et al*. 2010). Two of the studies showed significantly more MM tears in delayed ACL reconstruction as compared to subacute ACL reconstruction. The results from the three studies that compared subacute and delayed ACL reconstruction with regards to meniscal tears are first summarised in Table 2.9.

Table 2.9 Meniscal tears reported in studies that compared subacute and delayed ACL reconstruction*

Author **Study design**	**Meniscal tears**		**Overall comparisons**
	Subacute ACLR	**Delayed ACLR**	
Chen *et al*. Retrospective comparative	n=48 MM: 15 (31.3%) LM: 11 (22.9%) Both: 6 (12.5%)	All TFI 7 to > 12 months n=133 MM: 61 (45.9%) LM: 21 (15.8%) Both: 27 (20.3%) Delayed 1: TFI 7 – 12 months n=35 MM: 15 (42.9%) LM: 5 (14.3%) Both: 6 (17.1%) Delayed 2: TFI > 12 months n=98 MM: 46 (46.9%) LM: 16 (16.3%) Both: 21 (21.4%)	Any delayed vs subacute MM: difference +14,6, p=0.78 LM: difference -7.1%, p=0.26 Both: difference +7.8%, p=0.23 Delayed 1 vs Subacute: MM: difference +11.6%, p=0.27 LM: difference -8.6%, p=0.32 Both: difference +4.6%, p=0.55 Delayed 2 vs Subacute: MM: difference +15.6%, p=0.07 LM: difference -6.6%, p=0.33 Both: difference +8.9%, p=0.19
Ahlén & Lidén Retrospective comparative	n=30 MM: 4 (13%) LM: 9 (30%) Both: 2 (7%)	n=31 MM: 14 (45%) LM: 2 (6%) Both: 4 (13%)	 MM: difference +32%, **p=0.006** LM: difference -24%, **p=0.017** Both: difference +6%, p=0.678
Kennedy *et al*. Retrospective comparative	n=142 MM: 21 (14.8%) LM: 72 (50.7%) Both: 6 (4.2%)	All TFI 6 – 18 months n=65 MM: 22 (33.8%) LM: 33 (50.8%) Both: 8 (12.3%) Delayed 1: TFI 6 – 12 months n=44 MM: 11 (25%) LM: 21 (47.7%) Both: 2 (4.5%) Delayed 2: TFI 12 – 18 months n=21 MM: 11 (52.4%) LM: 12 (57.1%) Both: 6 (24.6%)	Any delayed vs subacute MM: difference +19%, **p=0.001** LM: difference +0.1%, p=0.99 Both: difference +8.1%, **p=0.03** Delayed 1 vs subacute MM: difference +10.2%, p=0.11 LM: difference -3%, p=0.73 Both: difference +8.1%, p=0.92 Delayed 2 vs subacute MM: difference +35.2%, **p<0.05** LM: difference +7.1%, p=0.58 Both: difference +20.3%, **p=<0.05**

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time form injury, **n:** number of patients, **MM:** medial meniscal, **LM:** lateral meniscus, **OR:** odds ratio, *Percentages in some studies may be >100% in distribution because of combined tears.

With regards to MM tears, two studies showed significantly increased rates of MM tears in the delayed groups (Ahlén & Lidén 2011; Kennedy *et al*. 2010). One retrospective study reported no significant difference in rates of MM tears between subacute and delayed groups (Chen *et al*. 2015). For LM tears, two studies showed no significant difference in LM tears between subacute and delayed groups (Chen *et al*. 2015; Kennedy *et al*. 2010). Only one study reported more LM tears in the subacute group as compared to the delayed group (Ahlén & Lidén 2011).

2.4.4 Chondral injuries

The results from all studies reporting on chondral injuries are summarised in tables and then analysed and synthesized narratively in groups according to timing:

(i) Three studies that compared early and subacute ACL reconstruction (Table 2.10) (Chen *et al*. 2015; Chhadia *et al*. 2011; Kennedy *et al*. 2010).

(ii) Seven studies that compared early and delayed ACL reconstruction (Table 2.11) (Anstey *et al*. 2012; Chen *et al*. 2015; Chhadia *et al*. 2011; Joseph *et al*. 2008; Kennedy *et al*. 2010; Michalitsis *et al*. 2015; Yüksel *et al*. 2006).

(iii) Three studies that compared subacute and delayed ACL reconstruction (Table 2.12) (Ahlén & Lidén 2011; Chen *et al*. 2015; Kennedy *et al*. 2010).

Chondral injuries were not graded with the same classification system across the studies. Four different classification systems were used: Noyes classification (Noyes & Stabler 1989), International Cartilage Repair Society (ICRS) classification (Society 1998), Outerbridge classification (Outerbridge 1964), and French Society of Arthroscopy (SFA) classification (Dougados *et al*. 1994). More studies used the Outerbridge system to grade chondral injuries (Ahlén & Lidén 2011; Anstey *et al*. 2012; Chen et al. 2015; Joseph *et al*. 2008; Yüksel *et al*. 2006). One (retrospective) study used the SFA system (Kennedy *et al*. 2010). One prospective cohort study used the Noyes system (Chhadia *et al*. 2011); the other prospective cohort used the ICRS system (Michalitsis *et al*. 2013). These systems are described in Table 1.1 in Chapter 1.

2.4.4.1 Early versus subacute Anterior Cruciate Ligament reconstruction

Three studies (n=1,056) compared chondral injuries between early and subacute ACL reconstruction. Two were prospective cohort studies (Chhadia *et al*. 2011; Michalitsis *et al*. 2013). Four were retrospective comparative studies (Chen *et al*. 2015; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006). The majority of the studies did not show any significant difference in chondral injuries between early and subacute ACL reconstruction. The results from the six studies that compared early and subacute ACL reconstruction with regards to chondral injuries are first summarised in Table 2.10.

Table 2.10 Chondral injuries reported in studies that compared early and subacute ACL reconstruction

Author Study design	Classification system of chondral injuries used	Chondral injuries		Overall comparisons
		Early ACLR	Subacute ACLR	
Chhadia *et al*. Prospective cohort	Noyes: Grades I, IIA, IIB, III	n=340 Reference group	n=352	OR 1.28, 95%CI 0.91 to 1.78, p=0.15
Kennedy *et al*. Retrospective comparative	SFA: Grades 1-2 (low), 3-4 (high)	n=62 Grades 1-2: 12 (19%) Grades 3-4: 4 (6.5%) Grades 1-4: 16 (26%)	n=142 Grades 1-2: 42 (30%) Grades 3-4: 7 (5%) Grades 1-4: 49 (35%)	Grades 1-2: difference +11%, p=0.12 Grades 3-4: difference -1.5%, p=0.65 Grades 1-4: difference +9%, p=0.36
Chen *et al*. Retrospective comparative	Outerbridge: Grades I, II, III, IV	<u>All TFI 0 – 3 months</u> n=112 Grades I-IV: 51 (45.5%) <u>Early 1: TFI ≤ 1 month</u> n=66 Grades I-IV: 28 (43%) <u>Early 2: TFI 2 -3 months</u> n=46 Grades I-IV: 23 (50%)	n=48 Grades I-IV: 32 (67%)	<u>Subacute vs any early</u> Grade I-IV: difference +21.5%, **p=0.01** <u>Subacute vs early 1</u> Grade I-IV: difference +24%, **p=0.01** <u>Subacute vs early 2</u> Grade I-IV: difference +17%, p=0.1

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time from injury, **n:** number of patients, **ICRS:** International Cartilage Repair Society, **SFA:** French Society of Arthroscopy, **n.s.:** not significant, **OR**: odds ratio

The prospective cohort study (n=692) showed no significant difference in chondral injuries between early and subacute ACL reconstruction groups (Chhadia *et al*. 2011). Similar results with no difference for chondral injuries between groups was reported by one retrospective comparative study (n=204) (Kennedy *et al*. 2010). However, one retrospective study (n=160) reported a significantly increased rate of chondral injuries in the subacute group of treatment as compared to the early group (Chen *et al*. 2015).

2.4.4.2 Early versus delayed Anterior Cruciate Ligament reconstruction

Seven studies (n=2,538) compared chondral injuries between early and delayed ACL reconstruction. Two were prospective cohort studies (Chhadia *et al*. 2011; Michalitsis *et al*. 2013) and five were retrospective comparative studies (Anstey *et al*. 2012; Chen *et al*. 2015; Joseph et al. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006). The majority of the studies showed significantly more chondral injuries in delayed ACL reconstruction as compared to early ACL reconstruction. The results from the seven studies that compared early and delayed ACL reconstruction with regards to chondral injuries are first summarised in Table 2.11.

Table 2.11 Chondral injuries reported in studies that compared early and delayed ACL reconstruction

Author Study design	Classification system of chondral injuries used	Chondral injuries		Overall comparisons
		Early ACLR	**Delayed ACLR**	
Chhadia *et al*. Prospective cohort	Noyes: Grades I, IIA, IIB, III	n=340 Reference group	Delayed 1 TFI 6 – 12 months n=246 Delayed 2 TFI > 12 months n=314	Delayed 1 OR 1.34, 95%CI 0.93 to 1.93, p=0.112 Delayed 2 OR 1.57, 95%CI 1.12-2.20, **p=0.009**
Michalitsis *et al*. Prospective cohort	ICRS: Grades 0, I, II, III, IV	n=35 Grade 0: 22 (63%) Grade I+II: 9 (26%) Grade III+IV: 4 (11%) Grades I-IV: 13 (37%)	All TFI 3 to >12 months n=74 Grade 0: 33 (45%) Grade I+II: 23 (31%) Grade III+IV: 18 (24%) Grades I-IV: 41 (55%) Delayed 1: TFI 3 – 12 months n=39 Grade 0: 24 (62%) Grade I+II: 13 (33%) Grade III+IV: 2 (5%) Grades I-IV: 15 (38%) Delayed 2: TFI > 12 months n=35 Grade 0: 9 (26%) Grade I+II: 10 (28%) Grade III+IV: 16 (46%) Grades I-IV: 26 (74%)	Any delayed vs early: Grades I+II: difference +5%, p=0.565 Grades III+IV: difference +13%, p=0.117 Grades I-IV: difference +18%, p=0.074 Delayed 1 vs early: Grades I+II: difference +7%, p=0.47 Grades III+IV: difference -6%, p=0.41 Grades I-IV: difference +1%, p=0.91 Delayed 2 vs early: Grade I+II: difference +2%, p=0.79 Grade III+IV: difference +35%, **p<0.05** Grades I-IV: difference +37**%, p<0.05** OR for grade III/IV injury: increased by 5.52 from early to delayed group.
Joseph *et al*. Retrospective comparative	Outerbridge: Grades III, IV	n =487 79 (16%)	n=320 84 (26%)	Difference +10%, **p=0.0005**
Yüksel *et al*. Retrospective comparative	Outerbridge: Grades II, III, IV	n=45 4 (8.9%)	n=156 109 (69.9%)	Difference +61%, **p<0.05**
Anstey *et al*. Retrospective comparative	Outerbridge: Grades I, II, III, IV	n=171 Grades III-IV: 34 (19.8%) Any Grade: 49 (28.7%)	n=24 Grades III-IV: 6 (25%) Any Grade: 9 (37.5%)	Grades III-IV: difference 5.2%, p=0.56 Any grade: difference +8.8, p=0.37

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time from injury, **n:** number of patients, **ICRS:** International Cartilage Repair Society, **SFA:** French Society of Arthroscopy, **OR**: odds ratio

Table 2.11 Chondral injuries reported in studies that compared early and delayed ACL reconstruction (continued)

Author Study design	Classification system of chondral injuries used	Chondral injuries		Overall comparisons
		Early ACLR	**Delayed ACLR**	
Chen *et al.* Retrospective comparative	Outerbridge: Grades I, II, III, IV	n=66 Grades I-IV: 28 (42.4%)	<u>All TFI 7 to > 12 months</u> n=133 Grades I-IV: 112 (84.2%) <u>Delayed 1: TFI 7-12 months</u> n=35 Grades I-IV: 26 (74%) <u>Delayed 2: TFI > 12 months</u> n=98 Grades I-IV: 86 (88%)	<u>Any delayed vs early</u> Grades I-IV: difference +41.8%, **p<0.05** <u>Delayed 1 vs early</u>: Grades I-IV: difference +31.6%, **p<0.05** <u>Delayed 2 vs early</u>: Grade I-IV: difference 43.6%, **p<0.05** <u>Increased TFI</u>: Increased risk and severity of chondral injury (**p<0.05**)
Kennedy *et al.* Retrospective comparative	SFA: Grades 1-2 (low), 3-4 (high)	<u>TFI ≤ 2 months</u> n=62 Grades 1-2: 12 (19.4%) Grades 3-4: 4 (6.4%) Grades 1-4: 16 (25.8%)	<u>All TFI 6 – 18 months</u> n=65 Grades 1-2: 28 (43,1%) Grades 3-4: 9 (13.8%) Grades 1-4: 37 (56.9%) <u>Delayed 1: TFI 6 – 12 months</u> n=44 Grades 1-2: 18 (40.9%) Grades 3-4: 5 (11.4%) Grades 1-4: 23 (52.3%) <u>Delayed 2: TFI 12 – 18 months</u> n=21 Grades 1-2: 10 (47.6%) Grades 3-4: 4 (19.1%) Grades 1-4: 14 (66.7%)	<u>Any delayed vs early</u> Grades 1-4: difference 31.1%, **p<0.05** <u>Delayed 1 vs Early</u> Grades 1-4: difference +21.5%, **p<0.05** <u>Delayed 2 vs Early</u> Grades 1-4: difference +47.3%, **p<0.05** <u>TFI > 6 months</u>: Significant increase in OR (4.04, 95% CI 1.41 to 11.58) of patients having chondral damage after 6 months, compared to early group (Mantel-Haenszel age-adjusted test, **p=0.005**)

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time from injury, **n=** number of patients, **ICRS:** International Cartilage Repair Society, **SFA:** French Society of Arthroscopy, **OR**: odds ratio

The two prospective cohort studies (n=1,009) reported a significantly increased rate of chondral injuries in the delayed group of ACL surgery defined as > 12 months from injury as compared to the early group (Chhadia *et al*. 2011; Michalitsis *et al*. 2013). Chhadia *et al*. (2011) had two delayed ACL reconstruction groups: (i) within 6 – 12 months from injury and (ii) more than 12 months from injury. The odds ratios for chondral injuries were significantly increased in the second delayed group (TFI > 12 months from injury) as compared to the early group, but not in the first delayed group (TFI 6 – 12 months from injury). Same for the other prospective cohort study which also had two delayed groups: (i) within 3 – 12 months from injury and (ii) more than 12 months from injury. Four of the rest lower quality retrospective comparative studies (n=1,334) showed also a significantly increased rate of chondral injuries in the delayed group of treatment as compared to the early group (Chen *et al*. 2015; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006).

Overall, it is important to highlight that two studies showed significantly increased rates of chondral injuries in the delayed group of ACL surgery when the TFI was defined as > 6 months from injury as compared to early groups (Chen *et al*. 2015; Kennedy *et al*. 2010). Six studies reported significantly increased rates of chondral injuries in the delayed group of ACL surgery when the TFI was defined as > 12 months from injury as compared to early groups, with two being prospective cohorts (Chen *et al*. 1015; Chhadia *et al*. 2011; Joseph *et al*. 2008; Kennedy *et al*. 2010; Michalitsis *et al*. 2013; Yüksel *et al*. 2006).

2.4.4.3 Subacute versus delayed Anterior Cruciate Ligament reconstruction

Three retrospective comparative studies (n=449) compared chondral injuries between subacute and delayed ACL reconstruction (Ahlén & Lidén 2011; Chen *et al*. 2015; Kennedy *et al*. 2010). Only one study showed significantly more chondral injuries in delayed ACL reconstruction as compared to subacute ACL reconstruction. The results from the three studies that compared subacute and delayed ACL reconstruction with regards to chondral injuries are first summarised in Table 2.12 below.

Table 2.12 Chondral injuries reported in studies that compared subacute and delayed ACL reconstruction

Author Study design	Classification system of chondral injuries used	Chondral injuries		Overall comparisons
		Subacute ACLR	**Delayed ACLR**	
Kennedy *et al*. Retrospective comparative	SFA: Grades 1-2 (low), 3-4 (high)	n=142 Grades 1-2: 60 (42.2%) Grades 3-4: 12 (8.5%) Grades 1-4: 72 (50.7%)	<u>All TFI 6 – 18 months</u> n=65 Grades 1-2: 28 (43,1%) Grades 3-4: 9 (13.8%) Grades 1-4: 37 (56.9%) <u>Delayed 1: TFI 6 – 12 months</u> n=44 Grades 1-2: 18 (40.9%) Grades 3-4: 5 (11.4%) Grades 1-4: 23 (52.3%) <u>Delayed 2: TFI 12 – 18 months</u> n=21 Grades 1-2: 10 (47.6%) Grades 3-4: 4 (19.1%) Grades 1-4: 14 (66.7%)	<u>Any delayed vs early</u> Grades 1-4: difference +6.2%, p=0.40 <u>Delayed 1 vs Subacute</u>: Grades 1-4: difference +1.6%, p=0.86 <u>Delayed 2 vs Subacute:</u> Grades 1-4: difference 16%, p=0.17
Chen *et al*. Retrospective comparative	Outerbridge: Grades I, II, III, IV	n=48 Grades I-IV: 32 (67%)	<u>All TFI 7 to > 12 months</u> n=133 Grades I-IV: 112 (84.2%) <u>Delayed 1: TFI 7-12 months</u> n=35 Grades I-IV: 26 (74%) <u>Delayed 2: TFI > 12 months</u> n=98 Grades I-IV: 86 (88%)	<u>Any delayed vs subacute</u> Grades I-IV: difference +17.2%, **p=0.009** <u>Delayed 1 vs subacute</u> Grades I-IV: difference +7%, p=0.45 <u>Delayed 2 vs Subacute</u> Grades I-IV: difference +21%, **p=0.002**
Ahlén & Lidén Retrospective comparative	Outerbridge: Grades II, III, IV	n=30 Grades II-III: 6 (20%)	n=31 Grades II-III: 9 (29%)	Grades II-IV: difference +9%, p=0.3

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time from injury, **n:** number of patients, **ICRS:** International Cartilage Repair Society, **SFA:** French Society of Arthroscopy

Significantly increased rates of chondral injuries were reported in the delayed group of treatment as compared to the subacute group from one of the studies (Chen *et al*. 2015). However, this finding was not supported by the other two studies that showed no significant difference in chondral injuries between subacute and delayed groups (Ahlén & Lidén 2011; Kennedy *et al*. 2010).

2.4.4.4 Assessment of methodological quality for meniscal tears and chondral injuries

The results for the meniscal tears were based on nine studies. There was no RCT, two prospective cohorts (Chhadia *et al*. 2011; Michalitsis *et al*. 2013) and seven retrospective comparative studies (Ahlén & Lidén 2011; Anstey *et al*. 2012; Chen *et al*. 2015; Jacob & Oommen 2012; Joseph *et al*. 2008; Kennedy *et al*. 2010; Yüksel *et al*. 2006). The same studies, apart from one retrospective study (Jacob & Ooommen 2012), compared chondral injuries. So, there were eight studies looking into chondral injuries, none of which was RCT.

Assessment of methodological quality of prospective cohort studies

The prospective cohort studies were assessed for their methodological quality using the Newcastle-Ottawa Scale (NOS) (Wells *et al*. 2014). The parameters assessed and the thresholds are described in section 2.3.4. Both the prospective cohort studies compared meniscal tears and chondral injuries. The results of the assessment are shown in Table 2.13 and the scores were the same for each outcome in each study.

Both studies scored high (8 and 9 stars). One study scored 9 stars and had a sample of 109 patients (Michalitsis *et al*. 2015). It scored 4 stars in selection domain, 2 stars in comparability domain and 3 stars in outcome/exposure domain; so, it was a prospective study of good quality. The other prospective cohort study scored 8 stars (Chhadia *et al*. 2011). It had a large sample size derived from a community-based health maintenance organization, representative of the types of patients undergoing ACL reconstruction in the general population; groups were comparable for both outcomes. Participants and data were drawn from The Kaiser Permanente Anterior Cruciate Ligament Reconstruction Registry, which is a longitudinal cohort of patients with prospective data collection. It scored 3 stars in selection domain, 2 stars in comparability domain and 3 stars in outcome/exposure domain; so, it was also a prospective study of good quality.

Table 2.13 Risk of bias for prospective cohort studies that compared meniscal tears and chondral injuries with the Newcastle-Ottawa Scale (NOS)

Author (Year)	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	NOS score
Michalitsis *et al*. (2015)	Somewhat representative*	Drawn from same community as the exposed cohort*	Secure record*	Yes*	Study controls for time to surgery* Study controls for sex, age. *	Record linkage*	Yes*	Complete follow-up for all subjects *	9 stars
Chhadia *et al*. (2011)	Truly representative*	Drawn from same community as the exposed cohort*	Secure record*	No	Study controls for time to surgery* Study controls for sex, age. *	Record linkage*	Yes*	Complete follow-up for all subjects *	8 stars

A study can be awarded a maximum of one star for each question and a maximum of 2 stars for comparability of cohorts. The more stars a study was awarded, the lower was the risk of bias.

Assessment of methodological quality of retrospective comparative studies

The methodological quality of the retrospective comparative studies was assessed using MINORS criteria (Slim *et al*. 2003). The results of the assessment are shown in Table 2.14. The lowest score for the retrospective comparative studies was 15 points out of 24 points for one study (Ahlén & Lidén 2011). Two retrospective studies scored high in the assessment, but not more than 19 out of 24 points (Yüksel *et al*. 2006; Kennedy *et al*. 2010). All these retrospective studies clearly stated their aim, had endpoints appropriate to the aim, their groups were equivalent and comparable, and they had performed adequate statistical analysis. However, only two included consecutive patients (Yüksel *et al*. 2006; Kennedy *et al*. 2010).

Seven of these retrospective studies compared meniscal tears and there was 1 study scoring the lowest score of 15, 3 studies scoring 16 and 3 studies scoring the maximum score of 19. Six of these retrospective studies compared chondral injuries and there was 1 study scoring the lowest score of 15, 2 studies scoring 16 and 3 studies scoring the maximum score of 19.

Table 2.14 Assessment of methodological quality of the retrospective comparative studies using MINORS criteria (Slim *et al*. 2003)

	Authors						
Criteria	**Yüksel *et al*.**	**Joseph *et al*.**	**Kennedy *et al*.**	**Anstey *et al*.**	**Chen *et al*.**	**Ahlén & Lidén**	**Jacob & Oommen**
A clearly stated aim	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	0	2	0	0	0	0
Prospective collection of data	1	1	1	1	1	0	1
Endpoints appropriate to the aim of study	2	2	2	2	2	2	2
Unbiased assessment of the study endpoint	2	1	2	1	2	1	1
Follow-up period appropriate to the aim of study	2	2	2	2	2	2	2
Loss to follow-up <5%	2	2	2	2	2	2	2
Prospective calculation of the study size	0	0	0	0	0	0	0
Adequate control group	0	0	0	0	0	0	0
Contemporary group	2	2	2	2	2	2	2
Baseline equivalence of groups	2	2	2	2	2	2	2
Adequate statistical analysis	2	2	2	2	2	2	2
TOTAL	19	16	19	16	17	15	16

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).

Maximum possible score being 24 for comparative studies.

2.4.5 Functional (objective) outcomes

In studies that compared functional outcomes, there was: (i) one RCT that compared early and delayed ACL reconstruction (Frobell *et al*. 2010); (ii) one study that compared subacute and delayed ACL reconstruction (Ahlén & Lidén 2011).

2.4.5.1 Early versus delayed Anterior Cruciate Ligament reconstruction

The RCT (n=121) measured the following functional outcomes (Frobell *et al*. 2010): stability (assessed with the Lachman and Pivot shift tests), and laxity (assessed with the KT-1000 Arthrometry). It reported significantly better stability (assessed with the Lachman and Pivot shift tests) and reduced laxity (assessed with the KT-1000 Arthrometry) in the early group as compared to the delayed group at 2-year follow-up (Frobell *et al*. 2010). The same RCT also measured the same outcomes at 5-year follow-up and again showed significantly better results for the early group (Frobell *et al*. 2013). This study did not report on ROM. These results are summarised in Table 2.15 below.

Table 2.15 Functional outcomes reported in the RCT that compared early and delayed ACL reconstruction

Author Study design	Functional outcomes				Follow-up - Overall comparisons
	Stability Lachman test	**Stability Pivot shift test**	**Laxity: Arthrometry (KT-1000)**	**ROM**	
Frobell *et al*. RCT	Early ACLR n=62 Normal: 39 (65%) Delayed ACLR n=59 Normal: 17 (29%)	Early ACLR n=62 Normal: 45 (75%) Delayed ACLR n=59 Normal: 27 (47%)	Early ACLR n=62 6mm Delayed ACLR n=59 8.3mm	Not examined	Follow-up: 2 years Normal stability and reduced laxity. Stability Difference -36%, better in early group (Lachman test **p<0.001**, Pivot shift test **p=0.003**) Laxity: Arthrometry Difference +2.3 mm, reduced in early group (**p=0.001**)

RCT: Randomised controlled trial, **ROM:** Range of motion, **ACLR:** Anterior cruciate ligament reconstruction, **TFI:** time from injury

Table 2.16 Functional outcomes reported in the retrospective study that compared subacute and delayed ACL reconstruction

Author Study design	Functional outcomes			Follow-up - Overall comparisons
	Stability Lachman test	**Laxity: Arthrometry (KT-1000)**	**ROM**	
Ahlén & Lidén Retrospective comparative	Subacute ACLR n=30 Normal: 10 (33.3%) Delayed ACLR n=31 Normal: 8 (25.8%)	Subacute ACLR n=30 2.5mm Range: -4 to 9 mm Delayed ACLR n=31 2.6mm Range: -6 to 10.5 mm	Subacute ACLR n=30 Extension: -10^0 to 5^0 Flexion: 125^0 to 150^0 Delayed ACLR n=31 Extension: -10^0 to 5^0 Flexion: 105^0 to 155^0	Follow-up: Mean: 25 months Normal stability, reduced laxity and ROM. Stability Lachman test: p=0.6 Laxity: Arthrometry: p=0.8 ROM Extension: p=0.5 Flexion: p=0.9

ROM: Range of motion, **ACLR:** Anterior cruciate ligament reconstruction, **TFI:** time from injury

2.4.5.2 Subacute versus delayed Anterior Cruciate Ligament reconstruction

The retrospective comparative study, with 61 patients, measured the following functional outcomes (Ahlén & Lidén 2011): stability (assessed with the Lachman and Pivot shift tests), laxity (assessed with the KT-1000 Arthrometry) and ROM. It showed no significant difference between subacute and delayed groups of ACL surgery in these outcomes. These results are summarised in Table 2.16 above.

2.4.6 Patient-reported (subjective) outcomes

In studies that compared patient-reported outcomes, there was: (i) one RCT that compared early and delayed ACL reconstruction (Frobell *et al*. 2010); (ii) one study that compared subacute and delayed ACL reconstruction (Ahlén & Lidén 2011).

2.4.6.1 Early versus delayed Anterior Cruciate Ligament reconstruction

The RCT measured the following patient-reported outcomes (Frobell *et al*. 2010): KOOS knee score, activity related scales (TAS, return to pre-injury activity level) and quality of life measurements (SF-36, knee related quality of life). It showed no difference in all patient-reported outcomes 2 years post-operatively for patients of both early and delayed groups. The follow-up in this RCT was continued and patients were re-assessed at the longer follow-up of 5 years using the same outcomes and the results reported were similar for and between both timing groups (Frobell *et al*. 2013). The RCT findings are summarised in Table 2.17 below.

2.4.6.2 Subacute versus delayed Anterior Cruciate Ligament reconstruction

The retrospective comparative study measured the following patient-reported outcomes (Ahlén & Lidén 2011): Lysholm and TAS scores. It reported significantly better scores for the subacute group as compared to the delayed group at a mean follow-up of 25 months. The findings from this retrospective study are summarised in Table 2.18 below.

Table 2.17 Patient-reported outcomes reported in the RCT that compared early and delayed ACL reconstruction

Author Study design	KOOS	TAS	Return to pre-injury activity level	SF-36	Knee related QoL	Follow-up - Overall comparisons
Frobell *et al*. RCT	Early ACLR n=62 Mean change: 39.2 (95%CI: 34.5-43.8) Delayed ACLR n=59 Mean change: 39.4 (95%CI: 34.6-44.1)	Early ACLR n=62 5.8 Delayed ACLR n=59 4.9	Early ACLR n=62 27 (44%) Delayed ACLR n=59 21 (36%)	Early ACLR n=62 Physical: 82.1 (95%CI: 77.2-87.0) Mental: 88.3 (95%CI: 85.0-91.7) Delayed ACLR n=59 Physical: 78.0 (95%CI: 73.0-82.9) Mental: 83.8 (95%CI: 79.7-87.9)	Early ACLR n=62 67.3 (61.3-73.3) Severely decreased: 11 (18%) Delayed ACLR n=59 63.0 (56.9-69.2) Severely decreased: 16 (27%)	Follow-up: 2 years KOOS mean change, TAS, Patients returned to pre-injury activity level, SF-36 (Physical + Mental), decreased Knee related QoL KOOS: p=0.96 TAS: difference -0.9, p=0.82 Return to pre-injury activity level: difference -8%, p=0.37 SF-36: p>0.05 Knee related QoL: Difference +9%, p=0.22

RCT: Randomised clinical trial, **TFI:** time from injury, **n:** number of patients, **KOOS**: Knee injury and Osteoarthritis Outcome Score, **TAS:** Tegner-Activity Scale, **SF-36:** Medical Outcomes Study 36-Item Short-Form Health Survey, **QoL**: Quality of Life, **ACLR:** Anterior cruciate ligament reconstruction

Table 2.18 Patient-reported outcomes reported in the retrospective study that compared subacute and delayed ACL reconstruction

Author Study design	Lysholm score	TAS	Follow-up - Overall comparisons
Ahlén & Lidén Retrospective Comparative	Subacute ACLR n=30 90 (58-100) Delayed ACLR n=31 81 (38-100)	Subacute ACLR n=30 6 (2-9) Delayed ACLR n=31 5 (0-9)	Follow-up: Mean: 25 months Lysholm score Better in early group (**p=0.01**) TAS Better in early group (**p=0.01**)

TFI: time from injury, **n:** number of patients, **TAS:** Tegner-Activity Scale, **ACLR:** Anterior cruciate ligament reconstruction

2.4.6.3 Assessment of methodological quality for functional and patient-reported outcomes

The results for both functional and patient-reported outcomes were based on two studies; one RCT (Frobell *et al*. 2010), and one retrospective comparative study (Ahlén & Lidén 2011).

Assessment of methodological quality of the RCT

The RCT was assessed for its methodological quality using the Cochrane Risk of Bias Tool (Higgins *et al*. 2011). It had adequately concealed allocation and adequate blinding of participants and can be classified as low risk of bias for all outcomes measured in the study (Frobell *et al*. 2010). The results of the assessment are shown in Table 2.19 and were the same for both functional and patient-reported outcomes.

Table 2.19 Risk of bias of the RCT that compared functional and patient-reported outcomes with the Cochrane Risk of Bias Tool

Author (Year)	Sequence generation	Allocation concealment	Blinding of participants	Incomplete outcome data	Selective outcome reporting	Other source of bias	Total Risk of bias
Frobell *et al.* (2010)	Adequate	Adequate	Yes	Adequate	Free	No	Low Risk of Bias

Assessment of methodological quality of the retrospective comparative study

The methodological quality of the retrospective study (Ahlén & Lidén 2011) was assessed using MINORS criteria (Slim *et al*. 2003). This study had a relatively low score of 15 (out of 24 points); but it clearly stated its aim, had endpoints appropriate to the aim, had appropriate follow-up, baseline equivalent and comparable groups and adequate statistical analysis (see Table 2.14 above).

2.4.7 Quality of the evidence

Having used the GRADE approach to assess the overall quality of the evidence in this systematic review the following ratings are reported (Furlan *et al.* 2009; Ryan & Hill 2016):

For clinical outcomes (meniscal tears and chondral injuries), all studies were non-RCTs, so the starting rating was 'low quality' evidence. There was some inconsistency, with methodological and clinical heterogeneity, as there were two different designs of studies (both non-randomised) with differences in populations, time intervals before treatment and outcome measures, even among the same study designs. However, there was no significant variability in the reported results. There were no concerns for indirectness, publication bias and imprecision overall. Based on this assessment, evidence is 'low quality' for clinical outcomes.

For functional and patient-reported outcomes, there was one RCT (Frobell *et al*. 2010), and one retrospective study (Ahlén & Lidén 2011). The starting rating was 'high quality' evidence for the RCT, but 'low quality' for the retrospective study. There was no serious risk of bias for the RCT, there was some inconsistency in terms of methodological heterogeneity and clinical heterogeneity as the two studies had differences associated with their population, time intervals before treatment and outcome measures. There were no concerns with regards to indirectness and publication bias, but both studies had a small sample size and there is some concern about imprecision. So, evidence for functional and patient-reported outcomes is downgraded to 'low quality' overall.

2.4.8 Summary of results

Comparing early and delayed ACL reconstruction, in eight studies that examined meniscal tears, six reported an increased rate in the delayed group for MM tears; for LM tears one study reported an increase rate in the early group and one study in the delayed group. In seven studies that examined chondral injuries, six showed an increased rate of chondral injuries in the delayed group. One study (RCT) that examined functional and patient-reported outcomes, reported better functional outcomes in the early group but no difference in patient-reported outcomes. So, the majority of the studies showed significantly more MM tears and chondral injuries and limited evidence for worse functional outcomes in delayed ACL reconstruction as compared to early ACL reconstruction.

Comparing subacute and delayed ACL reconstruction, in three studies that examined meniscal tears, two showed an increased rate of MM tears in the delayed group. In three studies that examined chondral injuries, one reported an increased rate of chondral injuries in the delayed group. One retrospective study, that examined functional and patient-reported outcomes, showed better patient-reported outcomes in the subacute group but no difference in functional outcomes. So, the majority of the studies showed significantly more MM tears and limited evidence for worse patient-reported outcomes in delayed ACL reconstruction as compared to subacute ACL reconstruction

However, comparing early and subacute ACL reconstruction, in three studies that examined meniscal tears, only one retrospective study showed an increased rate in the subacute group for MM tears. In three studies that examined chondral injuries only one retrospective study showed an increased rate in the subacute group. So, the majority of the studies did not show any significant difference in meniscal tears and chondral injuries between early and subacute ACL reconstruction. The results from all studies included in the systematic review regarding all outcomes are summarised in Table 2.19.

Table 2.20 Summary of results

Outcomes - Studies	Early versus delayed ACLR	Subacute versus delayed ACLR	Early versus subacute ACLR
MM			
2 Prospective cohort	1 no difference, 1↑ in delayed	N/A	1 no difference
7 Retrospective comparative	5↑ in delayed, 1 no difference	2↑ in delayed, 1 no difference	1 no difference, 1↑ in subacute
LM			
2 Prospective cohort	2 no difference	N/A	1 no difference
7 Retrospective comparative	1↑ in early, 1↑ in delayed, 4 no difference	1↑ in subacute, 2 no difference	2 no difference
Chondral injuries			
2 Prospective cohort	2↑ in delayed (when TFI >12 months)	N/A	1 no difference
6 Retrospective comparative	4↑ in delayed, 1 no difference	1↑ in delayed, 2 no difference	1 no difference, 1↑ in subacute
Functional outcomes			
1 RCT	1 better in early (RCT)	N/A	N/A
0 Prospective cohort	N/A	N/A	N/A
1 Retrospective comparative	N/A	1 no difference	N/A
Patient-reported outcomes			
1 RCT	1 no difference (RCT)	N/A	N/A
0 Prospective cohort	N/A	N/A	N/A
1 Retrospective comparative	N/A	1 better in subacute	N/A

ACLR: Anterior cruciate ligament reconstruction, **RCT:** Randomised clinical trial, **MM:** medial meniscal tears, **LM:** lateral meniscal tears, **TFI:** time from injury, **N/A:** not applicable

2.4.9 Patient risk factors affecting the relationship between the timing of Anterior Cruciate Ligament reconstruction and outcomes

The objective was to determine if patient characteristics were related to the timing of ACL reconstruction and whether timing had an impact on outcomes in different patient groups. This was investigated as follows:

1. Data from non-randomised studies, already included in the systematic review, were analysed to determine whether patients with a particular characteristic were more likely to be treated earlier or later.
2. Within the studies, it was evaluated whether the patients with a particular characteristic did better in one timing group than in another.

Data was extracted from each of the eligible studies if they reported on the patient characteristics and other clinical factors previously identified as potentially important risk factors (see section 1.4.2), when these characteristics were compared across timing groups and/or when the outcome for each factor was compared across timing groups. Information on whether a study investigated if the characteristic was a risk factor for the outcome was also extracted.

2.4.9.1 Age

Four studies investigated age as a patient risk factor for subsequent meniscal tears and/or chondral injuries; one prospective cohort study (Chhadia *et al*. 2011) and three retrospective comparative studies (Jacob & Oommen 2012; Kennedy *et al*. 2010; Yüksel *et al*. 2006). All studies reported no association of age with meniscal tears but three showed that increased age was associated with higher rates of chondral injuries (Chhadia *et al*. 2011; Kennedy *et al*. 2010; Yüksel *et al*. 2006). Two of these studies examined the relationship of age with the timing of ACL surgery. The prospective study showed that younger patients (< 30 years old) were more likely to have earlier ACL surgery than older patients (Chhadia *et al*. 2011). Another study also showed that younger patients (< 30 years old) had earlier surgery (mean time within 33.4 weeks) than older patients (mean time 54.6 weeks) (Kennedy *et al*. 2010). None of the studies investigated whether younger or older patients did better with early or delayed surgery.

2.4.9.2 Gender

Four studies investigated gender as a patient risk factor for subsequent meniscal tears and/or chondral injuries (Chhadia *et al*. 2011; Jacob & Oommen 2012; Kennedy *et al*. 2010; Yüksel *et al*. 2006). Only one prospective study showed a relationship of gender with meniscal tears and chondral injuries, reporting a higher risk of LM tears and chondral injuries for male patients (Chhadia *et al*. 2010). The same study reported two other interesting findings (Chhadia *et al*. 2010). Regarding the relationship of gender with the timing of surgery, female patients were more likely to have earlier ACL reconstruction, that is, within 6 months from injury. However, females were < 20 years-old at time of surgery, whereas males were 20 – 40 years-old at time of surgery, so it is unclear whether this was a function of age or gender. None of the studies investigated whether male or female patients did better with early or delayed surgery.

2.4.9.3 Level of activity

Three studies investigated level of activity as a patient risk factor for subsequent meniscal tears and/or chondral injuries (Chen *et al*. 2015; Joseph *et al*. 2008; Michalitsis *et al*. 2013). Two studies, one prospective and one retrospective, showed that patients with higher level of activity had fewer chondral injuries (Michalitsis *et al*. 2013; Joseph *et al*. 2008). To the contrary, one retrospective study reported that patients with higher pre-operative levels of activity were more likely to have a meniscal or chondral injury (Chen *et al*. 2015). None of these studies examined the relationship of this factor with timing of ACL surgery.

One retrospective study (n=807) that had two sub-populations of athletes (n=295) and non-athletes (n=512) reported a significantly increased rate of MM tears and chondral injuries in the delayed group as compared the early group for both athletes and non-athletes (Joseph et al. 2008). These findings of this study per sub-population and per timing group are summarised in table 2.18.

2.4.9.4 Mechanism of injury

Only two retrospective studies investigated mechanism of injury as a patient risk factor for subsequent meniscal tears and/or chondral injuries (Chen *et al*. 2015; Jacob & Oommen). One of these two studies showed a relationship of that factor with chondral injuries (Chen *et al*. 2015). It reported that contact injury was associated with increased

incidence and severity of chondral injury as compared to non-contact injury (Chen *et al*. 2015). None of these two studies examined the relationship of mechanism of injury with timing and with outcomes per timing group.

2.4.10 Summary of results

This systematic review identified limited information in the included studies about some potentially important patient characteristics related with outcomes after ACL reconstruction, but a relationship of these characteristics with timing of ACL reconstruction cannot be identified. The suggestion was that older and less active patients had higher rates of chondral injuries and male patients had more chondral and meniscal injuries. In relation with timing, younger (<30 years old) and female patients were more likely to have earlier ACL surgery than older and male patients. Also, athletes had less MM tears and chondral injuries when they had early ACL surgery rather than delayed surgery. So, these findings imply that age and gender may have played a role in these studies for decision-making regarding the timing of ACL reconstruction. None of these studies investigated though whether these patient sub-groups (e.g. younger or female or more/less active) did better with early or subacute ACL surgery. They only assessed the effect of these patient characteristics overall.

Table 2.21 Joseph *et al*. (2008): Summary of results per sub-population and per timing group

Early ACLR (n=487)		**Delayed ACLR (n=320)**		**Overall comparisons**
Meniscal tears	**Chondral injuries***	**Meniscal tears**	**Chondral injuries***	
Non-athletes (n=350) MM: 74 (21%) LM: 126 (36%) Athletes (n=137) MM: 42 (31%) LM: 51 (37%)	Non-athletes (n=350) 60 (17%) Athletes (n=137) 19 (14%)	Non-athletes (n=162) MM: 109 (67%) LM: 55 (34%) Athletes (n=158) MM: 110 (70%) LM: 76 (48%)	Non-athletes (n=162) 44 (27%) Athletes (n=158) 40 (25%)	Early vs delayed ACLR: Non-athletes: MM: **p<0.05** LM: p>0.05 Chondral injuries: **p<0.05** Athletes: MM: **p<0.05** LM: p>0.05 Chondral injuries: **p<0.05**

ACLR: Anterior cruciate ligament reconstruction, **TFI:** time from injury, **n:** number of patients, **MM:** medial meniscal tears, **LM:** lateral meniscal tears,
*The Outerbridge system classification system was used for chondral injuries and Grade III and IV injuries were reported.

2.5 Discussion

In this systematic review, outcomes after ACL injury at different timings from injury were narratively synthesized. A narrative approach was undertaken because it was considered that there was too much heterogeneity in study design and the populations to warrant a meta-analysis. In a total of 10 studies that met the eligibility criteria, there was only one high quality RCT and two prospective cohort studies. The systematic review investigated clinical, functional and patient-reported outcomes after primary ACL reconstruction and focused on adult patients (> 16 years old) as explained in the methodology. Timings of early, subacute and delayed ACL reconstruction were defined, and different timings of ACL reconstruction were compared with regards to outcomes.

2.5.1 Summary – synthesis of findings

Objective 1: To determine the relationship between the timing from ACL rupture to ACL reconstruction surgery and a) clinical outcomes (meniscal tears, chondral injuries) and b) functional and patient-reported outcomes.

a. Clinical outcomes (meniscal tears, chondral injuries)

Our results have shown that a temporal relationship exists between timing of ACL reconstruction surgery and meniscal tears as well as chondral injuries, with delays in ACL reconstruction increasing the rates of such injuries.

In particular, for MM tears, the overall conclusion was that timing of ACL surgery influences tears if delay is > 6 months from injury. But there was no significant difference in MM tears between early and subacute ACL reconstruction. For LM tears the overall conclusion was different. The vast majority of the studies showed no effect of timing on tears, reporting no difference in LM tears between all timings (early versus subacute versus delayed ACL reconstruction).

Similarly, for chondral injuries, the overall conclusion was again that timing of ACL surgery influences injuries if delay is > 6 months from injury. The majority of the studies showed that delayed ACL reconstruction surgery > 6 months was associated

with significantly more chondral injuries as compared to subacute and early ACL surgery. But there was again no difference in such injuries between early and subacute ACL reconstruction.

Knee condition and function before ACL surgery is very important for better final outcomes after ACL reconstruction surgery (Eitzen *et al*. 2009; Keays *et al*. 2003; Kowalchuk *et al*. 2009). Especially full knee extension ROM, no or minimal effusion and quadriceps strength pre-operatively have all been considered predictors for better post-ACL-surgery functional outcomes (de Jong *et al*. 2007; Eitzen *et al*. 2009; Lewek *et al*. 2002; Reinold *et al*. 2006). As described in chapter 1, it is well known that after an ACL injury, an acute inflammation of the knee takes place, which takes 6 up to 12 weeks to settle down and motion to be restored (Mohtadi *et al*. 1991). Function and stability of the knee is impaired during this post-traumatic period; lag of extension ROM, effusion/swelling and weak quadriceps, all being related with poor functional outcomes as described above. Also, there have been studies showing that chances of arthrofibrosis are high when ACL reconstruction surgery is performed early during this post-traumatic inflammation period of first few weeks (Almekinders *et al*. 1995; Mayr *et al*. 2004; Shelbourne *et al*. 1991). So, the trend amongst clinicians for all the above reasons is to recommend waiting for this post-traumatic inflammation period to settle down before treating. But there is no clear time cut-off to follow.

This systematic review relied on 'low quality' evidence, that is, prospective cohort and retrospective studies for clinical outcomes (Ryan & Hill 2016). Nevertheless, these studies compared time intervals after injury, which were not short and close to the injury when this post-traumatic inflammation occurs. The earliest group was within 1 month for one study (Chen *et al*. 2015), or within 2 months for another (Kennedy *et al*. 2010). For the rest of the studies the early group was at least within 6 weeks, which is consistent with the trend in current clinical practice. So, in the main early, subacute and delayed ACL surgery were compared relying on data provided by these studies. The limitation that this confers is acknowledged, as the retrospective studies are low in the evidence hierarchy and they may have biases introduced by their design (Vassar & Holzmann 2013). These studies are prone to bias because of their retrospective nature, affecting the study participation and collection of information about exposures and outcomes (Tripepi *et al*. 2010). Since participants and data are identified retrospectively, selection may be dependent on the likelihood of having the outcome of interest (such as

meniscal tears or chondral injuries), resulting in an overestimate of the association of interest (Davies & Crombie 2000). Also, in these studies it is not known why there is a delay; it could be related to patient characteristics. For example, older age has been reported as a risk factor for chondral injuries after ACL reconstruction (Gupta *et al*. 2016; Kluczynski *et al*. 2013), and male sex has also been reported as a risk factor for more LM tears (Gupta *et a*l. 2016; Kluczynski *et al*. 2013). But also female sex and mid-aged adults (35-44 years old) have been related with more dynamic knee instability after ACL rupture (Hurd *et al*. 2008) and such instability has been considered as a predictor for worse functional outcomes post-operatively as explained above. So, these patients (e.g. older patients) do worse and this could lead again to overestimation of impact.

Other studies not eligible for this review because they used different timing criteria and/or different population (including children and adolescents), also suggest that delayed ACL reconstruction is associated with more meniscal and chondral injuries. Most of the studies have reported that delayed ACL reconstruction surgery results in increased rates of meniscal tears (especially MM tears) and chondral injuries in different timings (Demirağ *et al*. 2011, Ghodadra *et al*. 2013; Granan *et al*. 2009; Karlsson *et al*. 1999; Magnussen *et al*. 2013; Papastergiou *et al*. 2007; Røtterud *et al*. 2011; Sri-Ram *et al*. 2012). On the other hand, a few studies have shown no relationship between the length of time from injury to ACL surgery and meniscal tears (De-Roeck & Lang-Stevenson 2003; Ghodadra *et al*. 2013; Wasilewski *et al*. 1993). The majority of these studies were retrospective low quality, with no RCTs.

b. <u>Functional and patient-reported outcomes</u>

For functional outcomes and patient-reported outcomes, the overall conclusions that can be drawn are limited due to the sparsity of the available literature. Quality of evidence is also ‘low’ as per GRADE approach (Ryan & Hill
2016). For functional outcomes, one retrospective study though showed no difference between subacute and delayed ACL reconstruction groups in stability, laxity and ROM of the knee. However, this was a small series (n=61) with short follow-up (Ahlén & Lidén 2011). In contrast, one larger RCT followed-up patients for 2 and 5 years post-operatively and reported better stability and laxity of the ACL reconstructed knee in the

early surgery group as compared to the delayed group (Frobell *et al*. 2010; Frobell *et al*. 2013).

Patient-reported outcomes compared were: (i) Knee scores: Lysholm, KOOS (ii) Activity-related scales: TAS, Return to pre-injury activity level (iii) QoL measurements: SF-36, Knee related QoL. The RCT showed no difference in all the above outcomes comparing early and delayed ACL reconstruction (Frobell *et al*. 2010). The RCT findings conflict with evidence from the retrospective study which reported significantly better Lysholm and TAS scores in the subacute ACL surgery group as compared to the delayed group, showing a possible negative relationship of elapsed timing with these patient-reported outcomes (Ahlén & Lidén 2011).

But there are differences between these studies that may account for the conflicting findings. One difference was that in the RCT all patients in both early and delayed groups had structured rehabilitation with physiotherapy pre-operatively (Frobell *et al*. 2010); whereas in the retrospective study it is not clearly stated whether all patients in both subacute and delayed group had structured physiotherapy pre-operatively (Ahlén & Lidén 2011). This pre-operative physiotherapy may have helped the patients with better ROM, less swelling and stronger quadriceps which may have influenced the final functional and patient-reported outcomes (as explained above). Also, the follow-up in the RCT was longer up to 5 years (Frobell *et al*. 2013); whereas the retrospective study had a shorter mean follow-up of 25 months (Ahlén & Lidén 2011). This shorter follow-up may not have been enough to show the long-term effect of ACL surgery on the function of the knee and the patient-reported outcomes. The retrospective studies though, had additional issues which would introduce bias as highlighted above and by the risk of bias tool (see Table 2.20). These issues were that the patients were not consecutive, the retrospective collection of data, and the fact that different surgeons performed the ACL reconstructions in one study (Ahlén & Lidén 2011).

Other studies not eligible for this review have shown similar conflicting results regarding functional outcomes after early and delayed ACL reconstruction. Stability of the knee has been reported better after early (TFI $\leq$ 2 weeks) as compared to delayed (TFI > 3 months) ACL reconstruction in one RCT with a follow-up of 60 months (Marcacci *et al*. 1995). Also a retrospective study showed better stability and laxity (KT-1000 Arthrometry) after early as compared to delayed ACL reconstruction, reporting also that loss of meniscus appeared to affect these outcomes (Sgaglione *et al*.

1993). In contrast, stability and laxity of the knee have been reported to be similar after early and delayed ACL reconstruction in other studies. However, these studies used short time intervals close to the injury (time cut off at 2 or 3 weeks) which is not sufficient time to test the function of the knee as explained above (Bottoni *et al*. 2008; Raviraj *et al*. 2010; Hunter et al. 1996). ROM has been considered to be affected more having a bigger deficit after an acute or early ACL reconstruction, while there is still inflammation inside the knee, as described in section 1.2.2 (Harner *et al*. 1992; Mohtadi *et al*. 1991; Shelbourne *et al*. 1991; Sgaglione *et al*. 1993). But there is evidence showing that this effect on loss of ROM is short-term and there is no significant difference in the long-term in patients regaining the full ROM of the knee after either early or delayed ACL reconstruction observed in other studies (Hunter *et al*. 1996; Karlsson *et al*. 1991; Majors & Woodfin 1996; Meighan *et al*. 2003).

Similar conflicting findings have been reported from other studies not eligible for this review regarding patient-reported outcomes. One RCT showed no functional advantage of early versus delayed ACL reconstruction, measuring the TAS and IKDC scores 52 weeks post-operatively (Meighan *et al*. 2003). But the delayed group in this RCT was defined as 8 to 12 weeks from injury and the follow up is only for one year. Another RCT compared early (TFI $\leq$ 2 weeks) and delayed (TFI > 3 months) and showed similar Lysholm scores but poorer results of IKDC score for the delayed group at a follow up of 60 months which is longer (Marcacci *et al.* 1995). Another study reported similar Lysholm scores but significantly better TAS score and better desired level of activity for patients who had early ACL reconstruction (within 3 months) as compared to those who had delayed surgery (12 – 24 months from injury), but this study included patients less than 16 years old (Karlsson *et al*. 1999). It also reported that meniscal injuries were more frequent in the delayed group, suggesting that this may affected these outcomes.

Objective 2: To determine if patient characteristics are related to the timing of ACL reconstruction and whether timing has an impact on outcomes in different patient groups.

This systematic review identified some potentially important patient characteristics as risk factors related with outcomes overall but evidence about the relationship of these factors with timing was limited, so it cannot be suggested if a patient group would do better with early or subacute ACL surgery. Limited evidence suggests that older, male

and less active patients were related with more chondral and/or meniscal injuries after ACL surgery overall. In relation with timing, one study reported a higher incidence of MM tears and chondral injuries in athletes who had delayed ACL reconstruction as compared to those who had early ACL surgery (Joseph et al. 2008). This suggests that athletes did better with less meniscal and chondral injuries when they had early ACL surgery, although the same finding was reported for non-athletes.

Overall there is a suggestion from the studies included in this review that younger patients and female patients are treated earlier. So, surgeons in these studies seemed to prefer treating older and male patients with a delayed ACL surgery. It is not clear, though, if this was the surgeons' decision and what was the rationale behind this decision. Robust decision-making in clinical practice is important to deliver high quality healthcare, but since clinicians are involved, this is often susceptible to biases such as towards patient's age or gender (Marcum 2015). There has not been enough research on what patient factors influence clinicians' decision making, especially in Orthopaedics. In other areas like oncology and cardiovascular medicine there has been limited and controversial research implying that age and gender may have an impact on clinicians' decision, but the studies are limited and did not always support that these played a role in outcomes (especially age) (Adams *et al*. 2006; Marcum 2015; Yellen *et al*. 1994). One way used to investigate what influences decision-making has been vignette studies. Vignette studies describe hypothetical situations (vignettes) in order to elicit participants' knowledge, opinions or views according to how they would behave or respond in the situation described (Lanza 1990). Clinicians in a vignette survey for ACL injured patients, for example, might feel more comfortable to explain about their decisions as the vignette, being a hypothetical situation, gives them distance and space for interpretation within the context of the vignette (Barter & Reynold 2000). Vignette studies have been used in medicine and nursing research to obtain data and examine clinicians' attitudes and/or beliefs, for example in general practitioners' decision making (Bos-Touwen *et al*. 2017; Wainwright *et al*. 2010), decision-making in cardiothoracic surgery (Adams et al. 2006), quality of care in outpatient settings (Peabody *et al*. 2004), and, recently, in cancer awareness (Martins *et al*. 2015).

Importance of findings

On balance and based on available evidence, this review suggests that timing of ACL reconstruction influences medial meniscal and chondral injuries if delay is more than 6 months from injury. An early or a subacute ACL reconstruction up to 6 months from injury may not increase the risk for meniscal and chondral injuries, but any further delay after 6 months seems to increase this risk. This effect is even more apparent and worse when there was further delay > 12 months, with many studies defining delayed ACL reconstruction the one performed after 12 months from injury and the majority of them showing increased rates of MM and chondral injuries with that delay.

The biomechanical value of menisci and cartilage is well recognized and explained in section 1.1.1. Menisci are important performing different functions, such as contribution to stability and joint lubrication (Aagaard & Verdonk 1999). Cartilage is also important for smooth gliding of the bones over each other when the knee moves. The impact of meniscal and chondral injuries on the knee is to predispose to pain and impaired function and motion of an ACL-deficient knee leading to less cartilage inside the knee increasing the theoretical risk of OA as explained in section 1.1.2, although it is difficult to relate these injuries with OA in clinical practice and prove this relationship, as other parameters come to play, like ageing process or the severity of injury (Englund 2004; Englund *et al*. 2008; Englund *et al*. 2009b; Englund & Lohmander 2004). Evidence about the relationship between the development of OA after ACL reconstruction and anterior instability, justifying the benefit from ACL reconstruction in decreasing the risk of long term knee OA is controversial. There are numerous studies reporting that loss of meniscus and anterior instability in these ACL deficient knees induces OA (Almekinders *et al*. 2004; Culvenor *et al*. 2014; Eckstein *et al*. 2015; Englund 2004). In contrast, there are few reports supporting the opposite view: anterior instability is not related with OA in the knee, as they have detected degenerative (osteoarthritic) changes and increased rates of meniscal tears during long-term follow-up after ACL reconstruction which had restored the anterior stability of the knee (Barenius *et al*. 2014; Luc *et al*. 2014; Gillquist & Messner 1999). The majority of the available studies at the moment are low quality retrospective studies, with short follow-up insufficient to show the long-term effect on OA progression. In a middle-aged patient a long-term follow-up up to 10 or 20 years may be needed to establish this long-term effect.

However, this negative effect of timing of ACL surgery on outcomes was not consistently shown in studies measuring functional and patient-reported outcomes with

limited and conflicting evidence. One high quality RCT (amongst two studies) showed better early functional outcomes (maximum 5 years) after early ACL reconstruction as compared to delayed ACL reconstruction, but no difference in patient reported outcomes (Frobell *et al*. 2010; Frobell *et al*. 2013). The other retrospective study, with all its limitations, did not show any difference in functional outcomes between subacute and delayed groups, but reported better patient reported outcomes after subacute ACL reconstruction (Ahlén & Lidén 2011). This may mean that delay in ACL surgery may increase meniscal and chondral injuries, but this increase may not translate to worse functional outcomes, maybe because the effects of such injuries are more long term than these clinical studies have examined. So, the long-term effect on functional and patient-reported outcomes is not shown. Obviously, there is limited research so far looking into the long-term effect of MM and chondral injuries on functional and patient-reported outcomes after ACL reconstruction. Further long-term research seems necessary focusing on such outcomes and such research is suggested and described in section 2.5.3 below.

2.5.2 Strengths and limitations

This systematic review has its own strengths and limitations. An important strength is the extensive and structured literature search in five different electronic bibliographic databases (MEDLINE, EMBASE, CINAHL, AMED, CENTRAL) with a combination of multiple relevant key words. This search gave 5,556 records to go through and include all available evidence for timing of ACL surgery.

Another important strength is the fact that there were two reviewers assessing the search outputs independently at the same time using the pre-defined inclusion and exclusion criteria. Having two reviewers minimised the risk of missing any studies or over-including irrelevant studies.

There are a few important limitations to this systematic review as well. Firstly, there was a significant discrepancy and lack of agreement initially between two reviewers in the titles extracted for review. This was because the second reviewer was not clear of the inclusion and exclusion criteria initially and this was resolved by discussing the whole protocol again and agreeing about the titles, abstracts and papers to be reviewed.

Any disagreement was passed to one of two experienced reviewers to decide upon inclusion or exclusion. To avoid such a limitation next time, a face to face session of both reviewers to go through all inclusion and exclusion criteria and to do a pilot screening of up to 100 outputs of the search together would help.

One of the major limitations of this review was that there is not an accepted definition of early and delayed timing of ACL surgery. Studies had various definitions for timings. To try and reduce the complexity, timing from ACL injury to ACL surgery was defined for the purposes of this review as early, subacute and delayed with certain time intervals as described in section 2.3.2. The intention was to fit the studies into these three categories (early, subacute, delayed) but this was difficult because of variations. Some studies, defined as being within a specific time category, had patients whose ACL surgery was undertaken outside the range described for that category. So it was decided to include studies if the mean time from injury for groups fell within the limits of at least of the categories (early, subacute, delayed). This inevitably means that the findings may conflict with others in that time category.

Another limitation acknowledged was the age cut off at 16 years old which led to exclusion of 24 studies that included patients less than 16 years old. These studies had information about adult population as well and they might have been useful adding relevant data to our results, but data for adult population in these studies could not be extracted. Further information regarding the adult population of these studies could have been sought by asking the authors of these studies. But this was already done for authors of nine other studies asking to clarify about some data of their studies but only two replied, suggesting that asking and waiting for replies from 24 authors might have been difficult. Twenty-four is a big number suggesting potentially loss of lots of useful data, but on the other hand the paediatric population is different in physiology and anatomy to adult populations (Rang & Wegner 2006); and pooling data strictly about adult population may be more helpful for clinicians.

There is a potential limitation regarding the methodology followed to identify patient risk factors related to timing of ACL reconstruction, as this was only examined in the already eligible studies for the review. But there may be other studies looking into such patient factors and this relationship; this is something that could be the subject of a separate systematic review of the literature to assess all available evidence.

Lastly, only studies available in English language were included and this is a limitation. There may be studies in any other languages (such as French or German) that could have looked at the relationship of timing of ACL reconstruction with all these outcomes with useful data that may have been missed.

2.5.3 Research implications

Evidence was enough for the relationship of delay in surgery (>6 months) with clinical outcomes, but evidence was limited with conflicting findings about functional and patient reported outcomes. There was only limited evidence to suggest better early functional outcomes (maximum 5 years) after early ACL reconstruction (Frobell *et al*. 2013). It has been shown that meniscal tears can affect function of the knee and theoretical risk of further OA, although it is difficult to relate these injuries with OA in clinical practice as explained above (Englund 2004; Englund & Lohmander 2004; Fithian *et al*. 2002). But there is no strong evidence about the relationship of timing of ACL surgery with long-term functional and patient-reported outcomes and the relationship of meniscal tears and chondral injuries with these outcomes. For better interpretation in the future, this relationship must be established, and further research is needed on appropriate time intervals for ACL reconstruction surgery.

A robust study with long-term follow-up reporting on both meniscal tears and chondral injuries is needed, but focusing on functional outcomes and certain patient-reported outcomes after ACL reconstruction. Comparison of results after different timings of ACL reconstruction in relation to injury with strict time definitions is necessary. Such study should ideally be a large RCT or a large multi-center prospective cohort with long-term follow-up. The follow-up should be long for at least 10-20 years post-operatively to examine the long-term effect on these outcomes. There is a potential difficulty though in maintaining contact with trial or study participants, so the risk of losing participants to follow-up which may introduce significant bias must be acknowledged (Dettori 2011). Also, 20 years is long waiting time to get findings to inform clinical practice and by then, these findings may not be useful.

So, for that purpose alternatively a large retrospective cohort study may be more suitable and feasible. The sample size would need to be sufficiently large to ascertain clinically important differences between groups, such as different age groups, genders, different level of activity and different mechanisms of injury, and hence, it would have to be a multi-centre study to get a large enough sample-size. Patients who had ACL reconstruction surgery 10 to 20 years ago would need to be identified and this may be difficult if clinical records are not kept; in addition, core data items collected in a similar way would have to be available: e.g., time from injury to surgery; meniscal tears and chondral injuries and then current functional and patient-reported outcomes need to be collected prospectively. It should be acknowledged though that functional outcomes may be influenced by multiple factors, such as initial injury, patients' functional level, normal aging process, patient's motivation and changes in biomechanics conferred by ACL reconstruction (Bauer *et al*. 2014; Gobbi & Francisco 2006; Villa *et al*. 2016).

Regarding the range of functional and patient-reported outcomes that should be measured, the COMET (Core Outcome Measures in Effectiveness Trials) initiative has developed agreed standardised sets of outcomes for trials or any other research and a consensus has established 'successful outcomes' after ACL injury and reconstruction (Lynch *et al*. 2015). These are: (i) the absence of giving away, which can be measured with clinical tests for stability (such as Lachman and Pivot shift tests) and KT-1000 Arthrometry (for laxity), (ii) return to sports, which can be measured with an activity related scale (such as TAS), (iii) quadriceps and hamstrings' strength greater > 90% of the uninjured limb, (iv) not more than mild knee effusion/swelling, (v) no single patient-reported outcome (activity and participation related) achieved consensus, but thresholds of 85 – 90 were agreed (Lysholm core or KOOS score or IKDC score could be used). Outcomes can then be grouped according to time from injury and then compared to identify any possible relationship with timing. Based on the timings used in all the studies of this review and its results, the suggestion would be to group timings from injury to ACL surgery into 3 groups: (i) early within 3 months (ii) subacute 3 – 6 months (iii) delayed 6 – 12 months. Any ACL reconstruction performed after 12 months from injury should be excluded as the systematic review showed even worse clinical outcomes when the delay was > 12 months.

This systematic review also implied that age, gender and level of activity may have played a role in some studies for decision-making regarding the timing of ACL

reconstruction, but the evidence was limited. These factors seem to be related with outcomes (mainly chondral injuries and/or meniscal tears). Younger patients and female patients seem to have had earlier ACL surgery. This suggests that surgeons are taking these factors into consideration on treatment options. But these studies did not assess if these factors had an impact on outcomes in different timing with the exception of high levels of activity, albeit formal investigation was lacking in these studies. The evidence is low quality and very limited and needs further research to establish if patients with certain characteristics do better than others after early or delayed ACL surgery.

2.5.4 Clinical implications

Although there was heterogeneity in defining timings of ACL reconstruction in the included studies, there was enough evidence to suggest that delay of ACL surgery may influence clinical outcomes (MM tears and chondral injuries) and possibly functional outcomes if the delay is > 6 months. So, an early or subacute ACL surgery up to 6 months is justified. In public healthcare services one must prioritize in how funds are delivered, and commissioners need to recognize the importance of early/subacute ACL reconstruction when purchasing services. Based on this review, the recommendation would be to avoid delays more than six months in those patients who are suitable for ACL reconstruction surgery. Such a recommendation may be considered in national guidance provided by bodies such as British Association for Surgery of the Knee (BASK) or British Orthopaedic Association (BOA). A consensus meeting could be arranged by such national guidance bodies to agree for a recommendation to perform ACL surgery within six months from injury and give appropriate guidance about best clinical practice regarding patients who undergo an ACL reconstruction surgery. Similar recommendations/guidelines regarding timing of intervention for different orthopaedic conditions have been made after similar meetings, like the guidelines for management of open fractures issued after such a meeting by British Orthopaedic Association and British Association of Plastics, Reconstructive and Aesthetic Surgeons (Nanchahal *et al*. 2009).

So, the effect of delay of ACL reconstruction surgery on outcomes is shown, however, this does not mean that early or subacute ACL surgery should be offered to anyone. This review did not identify evidence examining specific subgroups of patients that

would benefit from early/subacute versus delayed ACL reconstruction with regards to the parameters examined. In the absence of such evidence, a consensus study of experts may be used to gather information with regards to this issue. This is a recognised approach for guiding clinical practice when other more robust evidence is lacking (Jones & Hunter 1995).

At the moment, there seem to be academic variation with no consensus regarding which patient factors each surgeon takes into consideration for decision making regarding ACL surgery and its timing. It is not shown whether this variation is translated to clinical practice. A study that would examine current variations in clinical practice regarding decision making for ACL reconstruction could set the grounds for the consensus study described above and determine which different patient factors surgeons actually take more often into consideration and why, as surgeons in practice influence the type of treatment selected for each patient. A method of collecting surgeons' views to identify variation in current clinical practice would be a type of survey amongst a sufficient number of experts on ACL surgery from different centres and countries to collect and synthesize their knowledge and views on different ACL injured patients' management. One way used to investigate what actually influences decision-making and identify the variation in clinical practice has been vignette studies as explained already in section 2.5.1. Such a vignette study could set the grounds for a consensus study and show which factors are taken into consideration from surgeons and why. A pilot for such a vignette study is presented in the next chapter.

2.5.5 Conclusions

The systematic review has shown that delays in ACL reconstruction surgery are influential at various frames post-injury and may adversely affect outcomes. This review had its own strengths and limitations, the main limitation being the heterogeneity in definition of timings amongst included studies. Evidence is enough though to suggest that delay of ACL surgery > 6 months may have a negative effect on clinical outcomes (further meniscal tears and chondral injuries). There is not consistent evidence about the effect of timing on functional and patient-reported outcomes and rigid conclusions cannot be drawn due to the sparsity and the low quality of evidence examining those parameters. Given the deleterious effect that meniscal and chondral injuries could have

on knee function, an early or subacute ACL reconstruction within 6 months can be recommended in those patients suitable for such surgery. This recommendation may be considered by national guidance bodies and established after a consensus meeting.

However, this thesis does not examine which patient should have an ACL reconstruction, and it is well recognized that certain patients may do well without knee ACL reconstruction. It simply examines the effect of timing on those who had ACL reconstruction. So, the suggestion to perform an early or subacute ACL reconstruction does not apply to anyone with an ACL injury. Therefore, it would be useful to know if any patient characteristics influence the effect of timing on meniscal and chondral injuries. In particular, whether certain patient sub-groups would be harmed more from a delayed ACL reconstruction. This systematic review could not assess this due to the sparsity of available evidence.

A future large cohort study may help resolve some of these outstanding issues, in particular the relationship between timing of ACL reconstruction and functional/patient-reported outcomes, as well as the influence of patient characteristics on the effect of timing. In the absence of strong evidence about these issues, a consensus study of experts may be used to collect relevant information. In the meantime, to help guide timing of ACL reconstruction in certain patient groups and to identify variation in current clinical practice, a vignette study may help shed further light.

CHAPTER 3: VIGNETTE-BASED PILOT STUDY

3.1 Background

Taking into account the results of the systematic review described in chapter 2, a surgeon should probably point towards an early or subacute ACL reconstruction within 6 months from injury, but there were limitations and significant heterogeneity as explained in section 2.4.2.2. There was also some evidence that outcome was related to patient characteristics including age, gender, pre-operative level of activity, mechanism of injury (Chen *et al*. 2015; Chhadia *et al*. 2011; Fok & Yau 2014; Joseph *et al*. 2008; Kennedy *et al*. 2010; Michalitsis *et al*. 2013; Yüksel *et al*. 2006); this may also influence surgeon's decision.

To understand the variation in current practice and its consistency with the literature and to identify the patient factors that influence surgeons' decision making and establish guidelines for the selection of patients based on these factors, a survey seemed helpful. The type of survey proposed was a vignette-based survey. Vignette surveys, though, are quite complex studies to do and there was insufficient time within the MSc to develop, pilot and then undertake a full vignette study; so in this MSc, the development and pilot study was performed, which could point out what needs to be done for a future full vignette study.

This chapter reports on the findings of such a pilot study to develop vignettes with a questionnaire tool and test the feasibility and acceptability of undertaking a vignette-based survey among orthopaedic surgeons.

3.2 Methodology

Vignettes are simulations of real events (Atzmüller & Steiner 2010; Forrester 1990). Vignette research studies describe hypothetical situations (vignettes) in order to elicit participants' knowledge, opinions or judgments according to how they say they would behave or respond in the hypothetical situation described (Lanza 1990). Vignettes are a good way of studying potentially sensitive topics which are otherwise difficult to approach. Responding to a hypothetical situation is easier than a direct question about

your experiences, views or judgments (Barter & Renold 2000; Forrester 1990). So, clinicians in a vignette survey for ACL injured patients might feel more comfortable to answer and explain about their decisions as the vignette, being a hypothetical situation, gives clinicians distance and space for interpretation within the context of the vignette before answering.

Vignette-studies are constructed with a certain method to be considered reliable and valid. Particularly important when developing and constructing vignettes is the content and face validity of the vignettes and the relevance and realism of the vignettes in the research encounter (Evans *et al*. 2015; Wilson & While 1998).

Content validity refers to what extent a vignette reflects and captures the topic of the research (Gould 1996). To address content validity, the vignettes should be constructed by combining the existing literature and previous research, researchers' and experts' personal and professional experience and individual experiences of the topic of research (Evans *et al.* 2015; Wilson & While 1998). The systematic review from chapter 2 provided evidence from the existing literature, which was combined with researchers' and one of the supervisors' personal and professional experience, to build up a first version of a vignette-based questionnaire which would be then tested and discussed by interviewing a small number of experts (see Methods below).

Face validity refers to the layout, understandability and comprehensiveness of the vignettes. Vignettes are usually piloted before application and professionals or researchers are asked to assess content and face validity of the vignettes to strengthen their validity and reliability (Gould 1996). Also, when vignettes attract participants' interest, are relevant to people's lives or everyday practice, and seem real, they are more likely to be effective and the quality of data is likely to increase (Wilson & While 1998).

The first step in designing a vignette is the construction of the population of different vignettes, which should be then presented to participants to ask for their opinion or judgement. There should be a framework to construct vignettes by systematically combining predictor variables/factors in order to assess their effect on dependent variables/factors (Evans *et al*. 2015). So, the population of vignettes is similar combining all relevant factors/characteristics, with a few characteristics varying

between the vignettes. The characteristics of vignettes consist of up to 3 different aspects: (i) experimental aspects: systematically manipulated to assess their effect on dependent variables, (ii) controlled aspects: consistent (identical or similar) in order to minimise additional variance, (iii) contextual aspects (in some vignettes): show some variation in order to be more realistic (in non-essential details) (Evans *et al*. 2015).

Using vignettes as research tools has its own advantages and disadvantages. Advantages include: the ability to collect large volumes of data simultaneously from a large number of participants with a good reported response rate (Evans *et al*. 2015); the ability to manipulate some variables in a vignette, in a way that is not possible in observational studies (Evans *et al*. 2015; Forrester 1990); absence of observer effect known as 'Hawthorne effect' as compared to observational studies (Endacott 1994) and avoiding many ethical dilemmas often encountered in observational or other clinical studies (like invading subjects' privacy, placing vulnerable patients at risk). Furthermore, by controlling some variables in vignettes, every participant responds to the same stimuli, giving more uniform data as compared to observational studies (Lanza 1990). Finally, vignette-methodology is more cost-effective and less time-consuming as compared to collection of clinical data by observation with less practical difficulties (Evans *et al*. 2015).

Disadvantages include the difficulty in establishing reliability and validity, which has been a major criticism in the past (Gould 1996; Hughes & Huby 2001; Spalding & Phillips 2007; Wallander 2009). The artificiality of vignettes is a problem, and the concern always is that their textual description and hypothetical behavior may not be sufficiently representative of the real-world situation, which raises concerns about the validity of any findings and conclusions based on the vignettes. The vignettes need to be carefully developed and constructed by addressing content and face validity with the approach described above. When trying to reach high levels of reliability when constructing a vignette, first a vignette should stimulate some aspects of real-world scenarios. Second, differences between vignettes should elicit the effect that is hypothesized to exist in the real world. Third, vignettes should give results that can generalize to real-world situations encountered by participants (Evans *et al*. 2015). In that way the vignettes can be considered more reliable, but when the vignettes are piloted the participants' views on the reliability of the vignettes will be asked.

As well as the vignettes, there need to be questions to elicit the participant's responses to the vignettes. There are a few basic principles and steps to develop a questionnaire (Boynton & Greenhalgh 2004). First, the research aims need to be defined after reviewing the relevant literature. The next step is to define the population and the sample. Population is all the members of the group of interest and the sample is the part of the population that is chosen, as access to the whole population is not usually possible (time, money, resources). The sample needs to be representative of the population. Often, the sample is chosen randomly from a list with all the members of the population ('sampling frame').

The next step is to decide how to collect replies, either directly with an interview or indirectly by post or e-mail. When indirectly, an information sheet or letter is needed to explain what the questionnaire and the survey is about. Next step is the design of the questionnaire which includes: a) determining the questions to be asked, b) selecting the question type for each question (open or closed questions, single or multiple responses) and the wording, c) designing the sequence of questions and the overall layout.

Next, the questionnaire needs to be piloted/tested on a small number of respondents before the actual survey. The overall aim of piloting the questionnaire is to predict any potential problems and correct these prior to the actual survey. Also, other points to examine are the understandability and acceptability of the questionnaire and if it is comprehensive enough. If respondents have space and time for comments, additional issues may be pointed. The variability of answers given can also be checked. Having completed the pilot of the questionnaire/survey, changes can be made in order to maximize the response rate and minimize errors. Finally, the actual survey is carried out by delivering the questionnaire with the selected method (directly or indirectly) to the participants/respondents identified. These principles and steps were followed in this vignette pilot study.

3.3 Aim and Objectives

3.3.1 Aim

To develop vignettes and a questionnaire tool regarding decision making for timing of ACL reconstruction and the factors influencing this.

3.3.2 Objective 1

To evaluate the face and content validity of the proposed vignettes and questionnaire tool.

3.3.3 Objective 2

To evaluate if the questionnaire is completed appropriately and demonstrate if there is variation in practice in line with what is expected.

3.3.4 Objective 3

To estimate the response rate to the vignette survey.

3.4 Methods

There were 4 components to this vignette-based pilot study:

1. Development of the vignettes and questionnaire tool
2. Think aloud interviews with surgeons to pilot vignettes and questionnaire tool and assess their face and content validity.
3. Revision of the vignettes and questionnaire tool
4. Pilot study of surgeons in Greece and UK to assess response rate and variation in practice

3.4.1 Development of vignettes and questionnaire tool

The systematic review in chapter 2 suggested that delay in ACL reconstruction surgery affects outcomes but it also identified limited evidence for potentially important patient risk factors which can affect outcomes which in turn might influence choice of timing of surgery for different subgroups of the population. These factors were: age, gender, pre-operative level of activity and mechanism of injury. So, an appropriate vignette-based survey could possibly identify the most important patient factors to consider for decision making, collecting clinicians' views on appropriate timing of ACL reconstruction for different vignettes and establishing guidelines for the selection of patients based on these factors.

These factors should be different amongst the vignettes to cover the majority of patients that surgeons face in clinical practice and assess how these factors influence their decision for each vignette. Equally, the description of each vignette should seem real and relevant to clinical practice and give enough details that surgeons may need to decide on treatment. These four factors should be different and manipulated (experimental aspects) and the rest of the characteristics of the vignettes should be consistent (identical or similar) to minimize additional variance (controlled aspects) (Evans *et al*. 2015). So, the vignettes should be more than one to accommodate all factors but not more than four as then they may not attract participants' interest and have an impact on surgeon's completing the survey and hence on response rate (Evans *et al*. 2015).

The decision was to have four vignettes as the different factors influencing outcome previously identified in the systematic review were four and after consideration of different combinations they were combined into four vignettes of different ages, genders, pre-operative level of activity/sports and mechanism of injury (contact or non-contact injury) as per table 3.1.

Table 3.1 Case-vignettes

	Age (years)	**Gender**	**Pre-operative level of activity/sports**	**Mechanism of injury**
Case 1	23	Male	Amateur football player	Contact knee injury
Case 2	28	Female	Amateur tennis player	Non-contact turning/twisting knee injury
Case 3	41	Female	Regular runner	Non-contact knee injury
Case 4	48	Male	Sedentary life/No sports	Non-contact knee injury

All other parameters in the description of the four vignettes were kept identical: immediate development of knee swelling, inability to walk, MRI next day confirming the ACL rupture, no other injury, assessment next day.

Then the questions asked for each vignette were determined. The questions were the same for all vignettes and followed each vignette. The decision was to ask simple questions with short possible answers to maximize the response rate. The first question was a straightforward question about the timing of ACL reconstruction that participants would perform in weeks. The second question was about the factors that would

influence their decision. The third question was about any other information they would want to know before making a decision. These questions are shown below:

1. How long after the injury would you operate on this patient in weeks?
2. What are the important factors which would influence your decision in this patient?
3. Is there any other information would you want to know before making a decision?

At the end of questionnaire there were 3 non-personalised demographic questions. One was about their qualifications, second was about their experience of assessing and /or treating ACL injuries in years. The third was about how many ACL reconstructions they perform/assist per year. The proposed questionnaire is presented in Appendix 3a.

3.4.2 Think aloud interviews

3.4.2.1 Objectives

To pilot the proposed vignettes and questionnaire tool and assess their content and face validity.

3.4.2.2 Setting

The setting was a convenient private setting mutually agreed in advance with each participant. These interviews were not undertaken inside a hospital or National Health Service (NHS) Trust.

3.4.2.3 Participants

Participants were Orthopaedic surgeons – researchers who had worked with the research student in the past and resided in UK. Their level was either at Senior Registrar or Consultant level and they had some experience in ACL injuries and research.

3.4.2.4 Recruitment

The participants were recruited after personal contact of the research student with them, either by phone or by email.

3.4.2.5 Study design

The study was performed as a pilot survey to test the proposed vignettes and questionnaire tool (see Appendix 3a). The questionnaire was distributed directly to the surgeons at the agreed place and time. The replies were collected by face to face interviews using the think aloud technique.

3.4.2.6 Interviews

After contacting the surgeons by phone or by email, the interviews were scheduled for a certain date and time at the mutually agreed private setting. For all surgeons/participants the same process was followed. Firstly, an information sheet was given to the participant to read through and then a written informed consent was obtained. The information sheet and the informed consent are presented in Appendix 3b and Appendix 3c respectively. The vignette-based questionnaire was then distributed to the surgeon. Then the surgeon was asked to think aloud while reading and answering the questionnaire. Surgeons raised points and had some comments on the questionnaire while thinking aloud and answering; so, at the end of the think aloud session, there was a small session to discuss their comments and feedback. A digital recorder was used to record the think aloud interviews for data collection. Then each interview was listened to again and participants' answers, comments or feedback and issues raised were noted.

Interview focus

More specifically, for content validity, surgeons were asked to consider the relevance of the vignettes to clinical practice, whether they were sufficiently different to engender different clinical decisions and what other information they felt should be included. To assess face validity, they were asked to consider the layout and understandability of the questionnaire and whether it was sufficiently comprehensive.

Analysis

All answers, comments or feedback and issues raised were collected for analysis to assess content and face validity of the vignettes and the questionnaire proposed. All comments and issues raised were noted and then reflected upon to consider what needed to be modified in the vignettes and the questionnaire. These were discussed with the

supervisors and a final vignette questionnaire tool created and used in the actual pilot survey (see results in section 3.4.2.9).

3.4.2.7 Ethics

Ethics approval was gained after an appropriate application to the relevant University of Central Lancashire (UCLAN) Ethics Committee (Ethics Approval letter is shown in Appendix 3d). The questionnaires were not distributed before getting the University's approval. Written informed consent was gained from the participants before starting the interviews (see Appendix 3c). No possible risk or inconvenience or harm was anticipated for participants and this was clearly stated in the information sheet (see Appendix 3b). Furthermore, it was clear that participation was voluntary and the participants could withdraw their participation at any time without penalty. Full contact details were given to participants for any questions and also for dissemination the results, should any participants be interested in this.

3.4.2.8 Data Protection

The interviews were recorded with a digital recorder. Recordings were converted to audio files after the interviews and immediately put onto the students' password protected area on the UCLAN server. The data on the tape recorder were then immediately destroyed. Recorded data from the interviews are in anonymised audio files in a single folder on the UCLAN password protected area of the research student; it will be deleted as soon as the MSc is completed. The consent forms were stored in a locked personal cabinet and then transferred to the University for storage. They will be destroyed in the University confidential waste at the completion of the MSc.

3.4.2.9 Results

Interviews

Three (3) participants agreed to participate and 3 "think aloud" interviews were conducted as described above in section 3.3 (Methods). One participant was an experienced Senior Orthopaedic Registrar with experience in assessing and referring ACL injuries; his interview lasted 14 minutes and 20 seconds. One participant was an experienced Consultant Orthopaedic Surgeon specializing in ACL injuries and ACL reconstructions; his interview was 15 minutes and 10 seconds long. The third participant was an experienced Consultant Orthopaedic Surgeon with experience in assessing and

referring ACL injuries but with no experience in ACL reconstructions; his interview lasted 14 minutes and 15 seconds.

Face and content validity – Issues raised

Face validity of the questionnaire was assessed by all 3 participants and they all thought that the layout was appropriate and simple, the questionnaire was clear and easy to understand, and it was comprehensive providing sufficient information overall. A comment was made on the questions following each case, highlighting that questions 2 and 3 were very similar and could be incorporated in one question.

Content validity was assessed in detail for all 4 vignettes and all questions. The 4 vignettes were considered relevant to clinical practice, presenting cases that a surgeon can often come across. But there were some comments. Two of the participants, the two Consultant Orthopaedic Surgeons, commented that other cases that they often see in clinical practice are younger patients (16-17 years old), professional athletes and patients with associated meniscal tear along with an ACL rupture.

With regards to the age groups of the vignettes, they suggested small changes to broaden the age group for the vignettes. They suggested to have one very young case (16-17 years old), one at mid-20s (or 20-30 years old), one at late 30s (or 30-40 years old) and one at late 40s (or 40-50 years old).

When they were asked whether the vignettes were different enough to engender different decision making with regards to ACL reconstruction surgery, they all said that cases 1 and 2 were very similar with regards to age and to level of sports and activity and cases 3 and 4 were very similar with regards to age and level of activity. They suggested to reconsider the age groups in all cases as described above and also the level of sports for cases 1 and 2 and level of activity for cases 3 and 4.

When they were asked what other information they felt that should be included they made the following comments:

- it would be helpful to state the past medical history of each case and whether they are fit for anaesthesia/surgery
- they would like to know the job of each patient

- for athletes, it would be helpful to state whether it is an amateur or a professional athlete
- it should be clear in the description that the MRI did not show any other associated meniscal and chondral injuries.

3.4.3 Revision of the vignettes and questionnaire tool

All comments and issues raised by the 3 participants described above were reflected upon; changes and add-ons were noted and incorporated in a new vignette questionnaire tool which was used as the final questionnaire tool for the pilot study.

The basic principles for vignette methodology were applied and also the fact that this is a pilot study and not a final consensus study led to the following considerations. There should be a framework to create vignettes by systematically combining predictor variables in order to assess their effect on dependent variables as described already above in 3.3.1 (Evans *et al*. 2015). So, combining the limited evidence identified in the systematic review (Chapter 2) and considering the comments and issues raised by participants described above, the revised experimental aspects (variables) that differed in the final 4 vignettes were:

- Age
- Gender
- Pre-operative level of activity / sports
- Mechanism of injury

The revised controlled (consistent) variables in the 4 vignettes were:

- Insignificant past medical history of the patient
- Fitness for anaesthesia/surgery
- Immediate development of swelling and inability to walk
- Assessment a few days after the injury
- Findings of MRI which will show no other associated meniscal, chondral or ligamentous injury.

So, the revised factors that differed between vignettes were changed as per table 3.2.

Table 3.2 Revised case-vignettes

	Age (years)	Gender	Pre-operative level of activity/sports	Mechanism of injury
Case 1	18	Male	Amateur footballer	Contact knee injury
Case 2	24	Male	Amateur footballer	Contact knee injury
Case 3	39	Male	Heavy manual job, kneeling, running	Non-contact knee injury
Case 4	49	Female	Office work, no sports	Non-contact knee injury

The questions after each vignette were increased to five and changed slightly. The first question was changed to be clear enough and have clear answers. So, first it asked if participants would recommend ACL reconstruction surgery for the patient (Yes/No); and then as a second question: "If yes, at what time-frame (in weeks) would you recommend having the ACL reconstruction surgery?". The questions 2 *(What are the important factors which would influence your decision in this patient?)* and 3 *(Is there any other information would you want to know before making a decision?)* from the proposed questionnaire were found to be very similar by the interviewees, so they were incorporated in one question asking: "What are the important factors which would influence your decision in this patient?". Two questions were added. A fourth question about what the participants would recommend if the patient had a different pre-operative level of activity. A fifth question about what they would recommend if there were extra MRI findings (meniscal tear or early signs of osteoarthritis).

Lastly, another question was added at the end of the questionnaire along with the 3 non-personalised demographic questions, asking the participants to evaluate the questions following the vignettes, giving 4 options to choose: Well stated and understandable, Ambiguous, Not well stated and not understandable, Other (please specify). The purpose of this question was to get some more comments from the participants after filling the questionnaire with regards to its understandability, trying to evaluate the questionnaire whilst piloting it.

The final version of the vignette questionnaire for the pilot survey after incorporating all the above is shown in Appendix 3e.

3.4.4 Pilot study

3.4.4.1 Objectives

To evaluate if the vignette questionnaire developed is completed appropriately, assess the response rate and demonstrate if there is variation in practice in line with what is expected.

3.4.4.2 Setting

The pilot study was conducted as a web survey via email using an online web tool.

3.4.4.3 Participants

Participants were orthopaedic surgeons from Greece and UK. Two countries were chosen as national bodies and training may influence management. Only Orthopaedic surgeons specializing in knee arthroscopies or with experience in ACL injuries were included. Consultant Orthopaedic Surgeons and junior trainees with no experience in ACL injuries were excluded as their views and knowledge on management of such patients would not be based on experience and would not necessarily be up to date. Amongst trainees, only senior trainees or registrars with some experience in ACL injuries and/or knee arthroscopies were included, so that their answers and views on management of such patients would be based on experience and not only on academic knowledge. All participants spoke English, even those from Greece.

3.4.4.4 Recruitment

The participants were identified using one of the following ways:

1. Orthopaedic surgeon members of the Panhellenic Arthroscopic Society in Greece were identified through the director and secretary of the society. After getting approval from the society, contact details (email addresses) of members in alphabetical order were obtained.
2. Whilst participating in Orthopaedic conferences and seminars, Orthopaedic surgeon delegates were approached and were informed about the survey. If they were happy to participate after reading the information sheet, their email address was noted in order to participate in the web survey. The conferences were: 37th SICOT Orthopaedic World Congress in Rome, Italy (September 2016) and the 72nd Annual Panhellenic Orthopaedic Conference of the Hellenic Association of Orthopaedic Surgery & Traumatology in Athens, Greece (October 2016). The seminar was: "Arthroscopic Surgery of the Knee" of the Panhellenic Arthroscopic Society in Larissa, Greece (April 2016).

3. UK Orthopaedic surgeon authors of papers on ACL reconstruction were identified through a search of an online database (MEDLINE) and email addresses of contacting authors were obtained.
4. Other Orthopaedic surgeons specialising in knee arthroscopies and ACL reconstruction in both UK and Greece who had worked with the research student in the past; these were approached via email or phone.

3.4.4.5 Study design

The web survey was performed using the final revised vignette questionnaire tool created from the previous study (see section 3.3.3 and Appendix 3e. This questionnaire tool was anonymous and distributed via email accompanied by an information sheet (see Appendix 3f). Survey responses were collected online using the "Survey Monkey" web tool.

3.4.4.6 Survey administration

The participants identified were approached initially via an email, inviting their participation in a pilot survey about timing of ACL reconstruction with an attached detailed information sheet (see Appendix 3f). This email had a clear headline-subject line: "Timing of ACL reconstruction Vignette-based survey". The email had a link at the end leading to the questionnaire for the survey. Implied consent was used; as long as participants read the attached information sheet and they were happy to participate, they were able to click on the link provided leading to the above questionnaire along with the vignettes to fill in. The text in the email invitation is shown in Appendix 3g. There were two separate email invitations with the online web tool, one for UK surgeons and one for Greek surgeons. Since the web survey was anonymous, a named personal reminder notice could not be sent. So, a reminder notice was sent to all UK and Greek surgeons initially identified. The survey run for a total of 4 weeks with 3 reminder notices sent in between.

3.4.4.7 Analysis

Responses were collected and analyzed focusing on the following:

Response rate overall and also by vignette and by question. After waiting for 4 weeks in total, with reminder notices sent in between, the overall response rate was defined as the number of the surgeons who completed the questionnaire divided by the number of all the invited participants as a percentage. Vignette and vignette question response rates

were defined as the number of the surgeons who answered the questions in each vignette divided by the number of all surgeons (14) who completed the questionnaire as a percentage.

Answers to the questions for each vignette were aggregated to evaluate if surgeons agree in their decision regarding the timing of ACL reconstruction and if their clinical practice was consistent with evidence in literature as reported in the systematic review in Chapter 2. The factors that influenced surgeons' decision regarding timing of ACL reconstruction were also analysed.

Reviewing all the above data and analysis, an assessment was made as to whether the vignette questionnaire could be used as a tool to inform guidelines on timing of ACL reconstruction and the factors influencing decisions.

3.4.4.8 Sample size

There is limited evidence regarding how large a pilot study should be. There are studies that recommend approximately 10 participants (Julious 2005; Nieswiadomy 2002; van Belle 2002). Others suggest 10 – 30 participants (Isaac & Michael 1995; Hill 1998). Others recommend that a pilot study sample should have 10% of the final study estimated size (Connelly 2008; Lackey & Wingate 1998). Finally, another study, often cited from statisticians to justify the recommended sample size for a pilot study, recommends a sample size of 30 (Lancaster *et al*. 2004). Considering this evidence, it was decided to invite the maximum recommended number of 30 participants. Assuming at least a 50% response rate, which has been considered adequate for a reliable questionnaire (Harrison & Draugalis 1997), this would give at least 15 responses to the questionnaire. Because of the problem one of the participants encountered when trying to complete the questionnaire which resulted in them leaving most of the questions unanswered (described in detail below in results), another surgeon was invited as well, so the final number of invited participants was 31 Orthopaedic surgeons.

3.4.4.9 Ethics

Ethics approval was gained with an appropriate application to the relevant UCLAN Ethics Committee (Approval letter is shown in Appendix 3d). With regards to orthopaedic surgeons identified and recruited through the Panhellenic Arthroscopic Society in Greece, permission was sought and obtained to get in touch with their

members. Complying with UCLAN Ethical guidelines, implied consent was used by attaching a detailed information sheet (see Appendix 3f) in the email sent for the web survey. After getting UCLAN Ethics approval, another ethics approval was not needed for electronic distribution of the questionnaires both in UK and Greece. Full contact details were given to participants for any questions and also for dissemination of the results, should any participants be interested in this. The same information sheets and questionnaire in English were used both for UK and Greek participants and there was no need for special language communication or translation.

3.4.4.10 Data protection

No personal details were collected to comply with the Data Protection Act (1998), as this study did not require any further contact after the primary data collection. The web survey was voluntary, and participants completed the questionnaire with their implied consent. They were aware that the questionnaires and all data provided were anonymous and will only be used for the purpose of this research and future publications related to this study. Email addresses were deleted from the email system as soon as the data collection period was complete.

Survey responses were collected online using a web-based tool, utilising an encrypted internet server ("Survey Monkey"). Anonymised data were downloaded to a password protected folder to allow analysis. The data were uploaded onto the student's password protected area of the University server in a form of an MS-excel spread sheet along with a separate PDF file with the individual responses of each participant and then all emails from the web survey were deleted. This data will be stored for the duration of the research project and will be transferred to the Director of Studies at the end of MSc. Data will be kept for 5 years following completion of the study to allow write-up and publication. Only the principal researcher and the research team will have access to the raw data.

3.4.4.11 Results

Invitations-Reminders

Two email invitations for the web survey were sent with the online web tool ("Survey Monkey") at the same time (11 November 2016). One to 10 UK Orthopaedic surgeons (Invitation UK) and one to 21 Greek Orthopaedic surgeons (Invitation GR). So, in total

31 email invitations were sent. Three reminders followed: first within a few days (15/11/2016) and then another two (29/11/2016, 6/12/2016). The survey was open for 4 weeks.

Participants

Email invitations for the survey were sent to 31 participants in total. All participants were qualified consultant orthopaedic surgeons with experience in either treating and operating or assessing and managing ACL injuries. They were identified using the different ways described in section 3.3.4.4.

Specifically, amongst the 21 Greek participants, there were 19 participants identified though the records of Panhellenic Arthroscopic Society after getting approval from the society. Two more were orthopaedic surgeons who had worked with the research student in the past and they were recruited after direct contact via email. Amongst the 10 UK participants, 2 were identified again through the records of the Panhellenic Arthroscopic Society as they were honorary members; these were consultant orthopaedic surgeons practicing inside UK NHS Trusts. One participant was approached and identified at an international Orthopaedic congress (37th SICOT World Congress) when he agreed to participate and shared his contact details. One was identified from a paper on timing of ACL reconstruction cited in MEDLINE database. Lastly, six orthopaedic surgeons who had worked in the past with the research student in UK NHS Trusts were approached.

Response rate

Fourteen (14) out of the 31 invited participants-surgeons responded and completed the questionnaire overall, so the overall response rate was 45% (95%CI 19% to 71%). Amongst UK participants (Invitation UK) the response rate was 50% and amongst Greek participants (Invitation GR) the response rate was 43%. Four of the 14 participants (29%) who responded, returned the questionnaire in the first few days before any reminder notice was sent. Seven respondents (50%) returned the questionnaire after the first reminder notice and 3 respondents (21%) after the third reminder.

Amongst Greek respondents, there were 5 Academic (PhD) and 4 Non-Academic (Qualified Consultant Orthopaedic Surgeons with no academic title). Amongst UK respondents there were 2 Academic (PhD) and 3 Non-academic (Qualified Consultant

Orthopaedic Surgeons with no academic title). With regards to the experience of the respondents, 12 had at least ten years of experience assessing and referring or treating ACL injuries with two of them having 20 and 25 years of experience. Only two respondents had less than 10 years of experience (1 Greek, 1 UK). Almost all respondents performed/assisted at least 10 ACL reconstructions per year, with 3 of them performing more than 100. Only one was not performing any ACL reconstructions, but managed over 200 patients with ACL injury through rehabilitation.

Amongst the participants that did not respond, one UK participant opted out and declined to participate. Initially, the survey was designed in a way that the participants could not change their answers once they left a survey page. In the beginning of the survey, one Greek participant started to fill in the questionnaire but then once he left a survey page without answering, he could not go back. So, this issue was flagged up by him as he left lots of questions unanswered and it was corrected immediately so that participants could change their answers even after they completed the survey.

Findings per vignette

Vignette 1

"An 18-year-old male had a contact knee injury while playing football. Knee swelling developed immediately and he could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other meniscal, chondral or ligamentous injury. He was then referred to you for assessment and you see him a few days later. He is an amateur football player and he wants to continue playing regular football at least at an amateur level. He is a student with no medical problems and he is fit for anaesthesia."

The response rate to each question of vignette one was 100%. The responses and the answers per question vignette one are shown below:

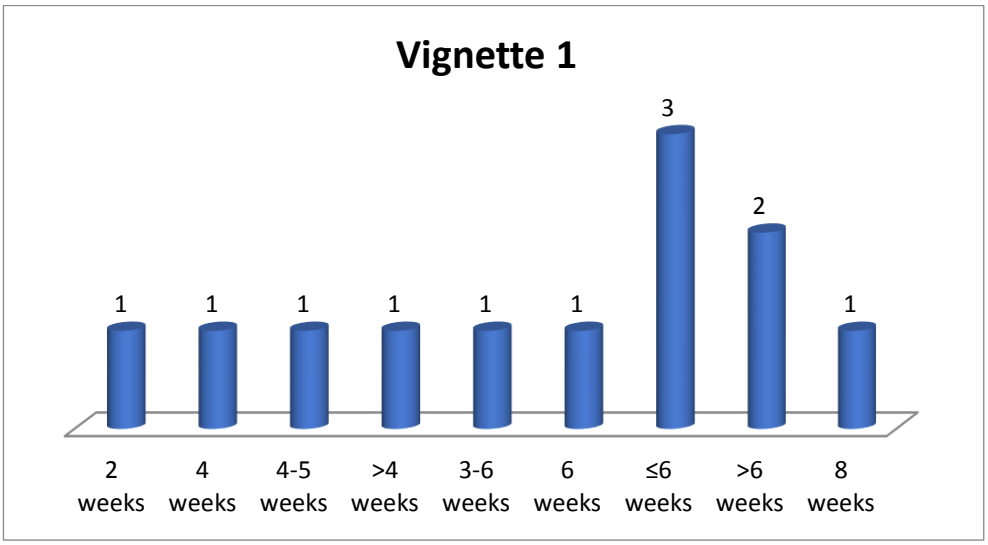
Question 1: *"Would you recommend ACL reconstruction surgery for this patient? Yes/No"*

13/14 respondents (93%) would recommend ACL reconstruction surgery for this vignette. Only one respondent would not recommend ACL surgery.

Question 2: *"If yes, at what time-frame (in weeks) would you recommend having the ACL reconstruction surgery?"*

Different time-frames were recommended from the 13 respondents who recommended ACL reconstruction. One surgeon just answered soon without specifying the exact time-frame. The time-frames suggested from the remaining 12 respondents are shown in the bar chart below (Figure 3.1). They varied from 2 up to more than 6 weeks, with three surgeons recommending ACL reconstruction within six weeks (early), and three recommending after 6 weeks. All other surgeons recommended different time-frames with no agreement, but all were within 8 weeks.

Figure 3.1 Recommended time-frame for ACL reconstruction surgery for vignette 1



Question 3: *"What are the important factors which would influence your decision in this patient?"*

Seven respondents (50%) answered that level of activity and/or level of sports would influence their decision for vignette one towards ACL reconstruction, with four of them focusing on the desired level of sports post-operatively. Six respondents (43%) said that (young) age would influence their decision towards ACL reconstruction. Other less popular factors that would influence respondents' decision for vignette one were: effusion (29%), ROM (21%), knee instability or laxity pre-operatively (14%), associated injuries (7%) and growth plate status (14%).

Question 4: *"What would you recommend if this patient was a professional footballer?"*
Four (29%) surgeons answered that they would perform an earlier or even an immediate ACL reconstruction if vignette 1 was a professional footballer (and not an amateur footballer). The rest of the respondents (71%) would not change their decision and management.

Question 5: *"What would you recommend if the MRI showed a potentially repairable meniscal tear?"*
Only two (14%) respondents answered to that question giving an answer related to the timing and said that they would perform an earlier ACL reconstruction with a meniscal repair at the same time. The rest of the respondents did not comment on the time-frame within which they would operate and ten of them focused on the meniscal tears saying that they would do a meniscal repair without giving any information on the different time-frames for the ACL reconstruction.

Vignette 2

"A 24-year-old male had a contact knee injury while playing football. Knee swelling developed immediately and he could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other meniscal, chondral or ligamentous injury. He was then referred to you for assessment and you see him a few days later. Past medical history is insignificant and he is fit for anaesthesia. He is an amateur football player and he wants to continue playing regular football."

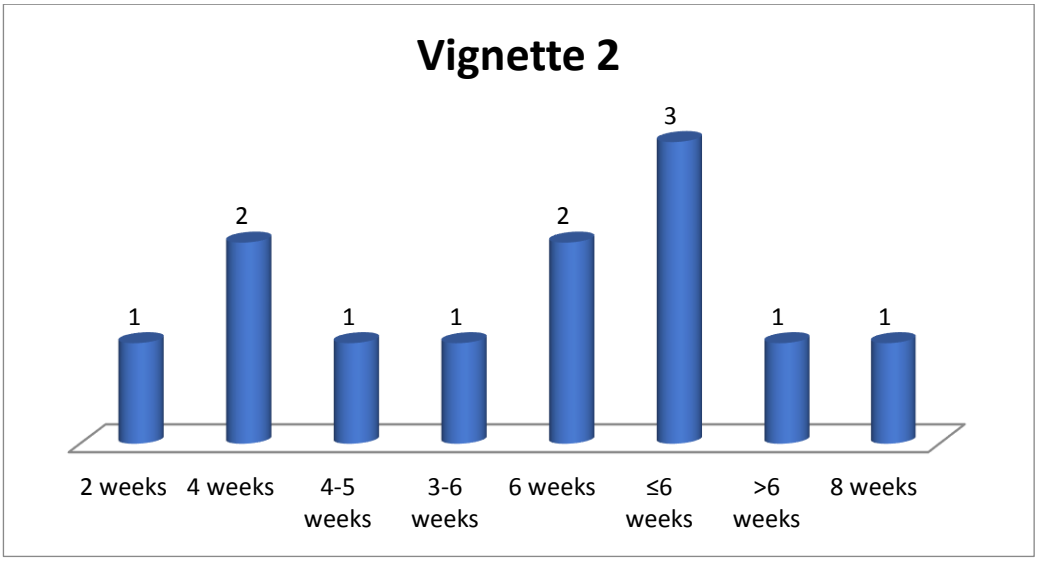
The response rate to each question of vignette two was 100%. The responses per question for vignette two are shown below:

Question 1: "*Would you recommend ACL reconstruction surgery for this patient? Yes/No"*
13/14 respondents (93%) would recommend ACL reconstruction surgery for this vignette. Only one respondent would not recommend ACL surgery.

Question 2: *"If yes, at what time-frame (in weeks) would you recommend having the ACL reconstruction surgery?"*

Different time-frames were recommended again. One surgeon just answered soon without specifying the exact time-frame. The time-frames suggested from the rest 12 respondents are shown in the bar chart below (Figure 3.2). They varied again from 2 up to more than 6 weeks and they were almost the same as per vignette one. Three surgeons recommended ACL reconstruction within six weeks (early). Two surgeons recommended ACL reconstruction after six weeks.

Figure 3.2 Recommended time-frame for ACL reconstruction surgery for vignette 2



Question 3: *"What are the important factors which would influence your decision in this patient?"*

Answers to that question were the same as per vignette one, with one more respondent (57%) saying that level of activity and/or level of sports would influence their decision. For age it was again six respondents (43%) who said that age was an important factor and other factors were the same as above: effusion (29%), ROM (21%), knee instability or laxity pre-operatively (14%), associated injuries (7%) and growth plate status (14%).

Question 4: *"What would you recommend if this patient was a professional footballer?"*

Answers to that question were exactly the same as per vignette one.

Question 5: *"What would you recommend if the MRI showed a potentially repairable meniscal tear?"*

Answers were exactly the same as per vignette 1, with most of them not commenting on the time-frame they would operate but focusing on the meniscal tears and suggesting a meniscal repair.

Vignette 3

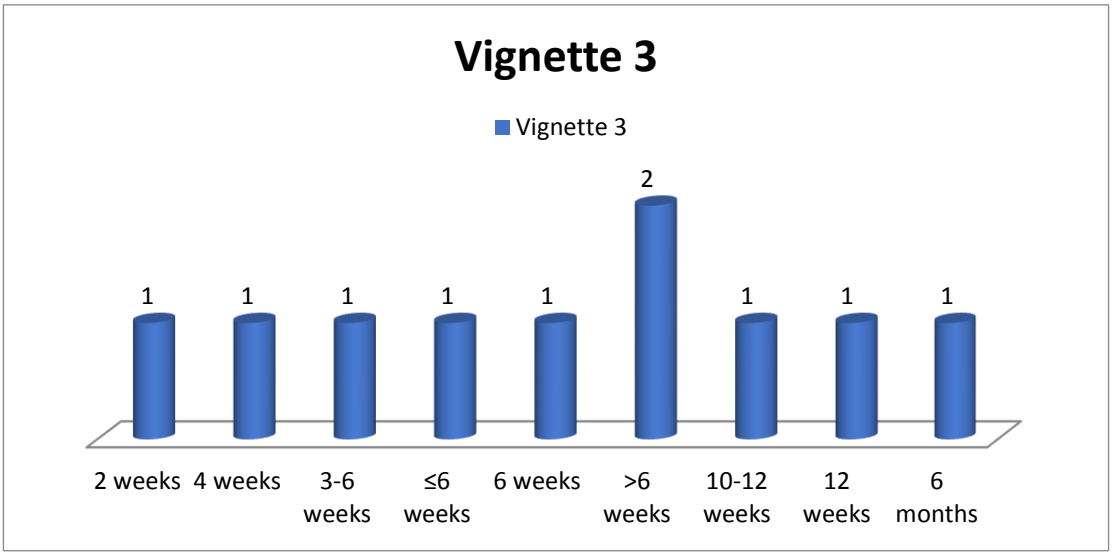
"A 39-year-old male had a non-contact knee injury while running. Knee swelling developed immediately and he could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other meniscal, chondral or ligamentous injury. He was then referred to you for assessment and you see him a few days later. He is doing a heavy manual job with lots of kneeling and is doing low demand sports (like running). Past medical history is insignificant and he is fit for anesthesia."

Response rate for vignette three was 93% (13/14). The one participant that did not answer all the questions on vignette three was the Greek participant who stopped answering halfway through and was unable to return to answer the remaining questions because of how the survey was set up at the beginning. The responses per question for vignette three are shown below:

Question 1: *"Would you recommend ACL reconstruction surgery for this patient? Yes/No".*
11/13 (85%) respondents would recommend ACL reconstruction surgery for vignette three. One respondent answered yes and no.

Question 2: *"If yes, at what time-frame (in weeks) would you recommend having the ACL reconstruction surgery?"*
Different time-frames were recommended from the 10 surgeons that recommended ACL surgery. The time-frames varied from 2 weeks up to 6 months. Most respondents gave a different time-frame, most of them suggesting ACL surgery within three months (early). One surgeon recommended surgery at six months. Two surgeons said that they would recommend physiotherapy first, and then they would offer ACL surgery; one giving a time-frame of 6 weeks, but the other not clarifying the time-frame and he was the one who answered yes and no at the first question. All the time-frames suggested for vignette 3 are shown in figure 3.3 below.

Figure 3.3 Recommended time-frame for ACL reconstruction surgery for vignette 3



Question 3: "*What are the important factors which would influence your decision in this patient?"*

Four respondents (29%) answered that age would influence their decision for vignette 3 towards ACL reconstruction. Three respondents (21%) said that level of activity or sports would influence their decision, with two of them recommending ACL reconstruction and one recommending no ACL surgery. Two surgeons (14%) said that ROM was an important factor and another two (14%) said that effusion would influence their decision. Other less popular factors amongst surgeons for vignette three were: knee instability pre-operatively (7%), body habitus (7%), motivation (7%), associated injuries (7%), pivoting activity (7%) and whether the patient was likely to comply with physiotherapy protocols (7%).

Question 4: *"What would you recommend if this patient was an office worker?"*

Three respondents (21%) said that they would change their decision to conservative management, two (14%) said that they would change to management to physiotherapy and perform ACL reconstruction only if there was instability and one respondent (7%) said that he would change to a "wait and see" approach without further clarifying what he meant.

Question 5: *"What would you recommend if the MRI showed a potentially repairable meniscal tear?"*

No respondent commented on the time-frame within which they would operate if MRI showed a potentially meniscal tear and all of them focused on what they would do for the meniscal tear. Three said they would do ACL reconstruction combined with meniscal repair, one said he would do ACL reconstruction combined with meniscectomy, five just said that they would do meniscal repair and two just said they would meniscectomy.

Vignette 4

"A 49-year-old female had a non-contact knee injury at work after falling. Her knee became swollen immediately. She could not walk after the injury and she could not go to work. MRI performed the next day showed an ACL rupture with no other meniscal, chondral or ligamentous injury. She is referred to you for assessment and you see her a few days later. She is an office worker (secretary) doing no sports. She has no medical problems and she is fit for anaesthesia."

The response rate for vignette four was again 93% (13/14). The one participant that did not answer all the questions following vignette four was the same Greek participant.

Question 1: *"Would you recommend ACL reconstruction surgery for this patient? Yes/No"*

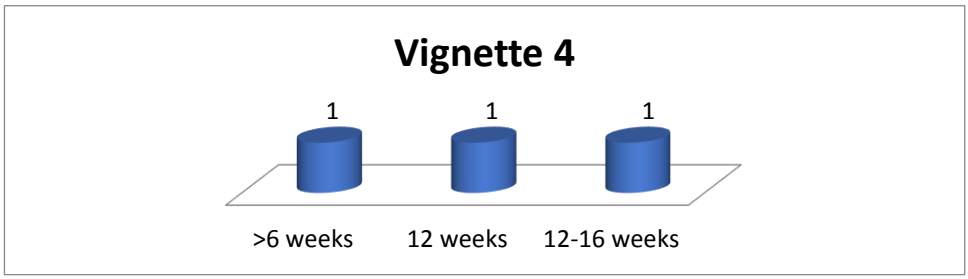
Only three respondents (23%) would recommend ACL reconstruction for vignette four. But one said that he would recommend ACL surgery if the patient was symptomatic and the second said that he would try conservative management first. Only one of the three surgeons would recommend ACL reconstruction surgery from the beginning. The remaining ten respondents (77%) would not recommend ACL reconstruction surgery for this vignette.

Question 2: "*If yes, at what time-frame (in weeks) would you recommend having the ACL reconstruction surgery?"*

This question was answered only from the three respondents who answered yes to question 1 suggesting ACL reconstruction surgery. The three surgeons recommended different time-frames, but all recommending a longer time period to perform ACL reconstruction surgery than for previous scenarios. One recommended more than 6

weeks and the other two recommended 12 weeks (early) or 12-16 weeks (subacute) (see Figure 3.4).

Figure 3.4 Recommended time-frame for ACL reconstruction surgery for vignette 4



Question 3: *"What are the important factors which would influence your decision in this patient?"*

Nine respondents (64%) answered that level of activity or sporting activities would influence their decision for vignette four towards non-operative management. One commented more specifically that it would be important for him to know about the lack of sporting ambition from the patient. Eight surgeons (57%) said that age would influence their decision for this vignette, with seven of them recommending no ACL surgery and only one recommending ACL reconstruction in 12-16 weeks. Two surgeons (14%) said that knee instability pre-operatively would be an important factor for their decision. Other less popular factors amongst surgeons for vignette 4 were: work (7%), motivation (7%), associated meniscal tears (7%) and patient's weight (7%).

Question 4: *"What would you recommend if this patient was older (mid-50s)?"*

Eleven respondents (79%) would recommend conservative management if this patient was older, with two of them focusing on physiotherapy. One would recommend ACL reconstruction if the patient was symptomatic and another surgeon would discuss the situation with the patient and try conservative management first. Amongst the three surgeons who would recommend ACL surgery for vignette four, as described above, one said that he would change his mind if the patient was older and would recommend conservative management focusing on physiotherapy.

Question 5: *"What would you recommend if MRI showed early signs of osteoarthritis?"*

Apart from the Greek participant who could not answer the questions for this vignette, there was one other surgeon who did not answer that question. Amongst the remaining 12 respondents who answered this question there were:

- seven (50%) surgeons who would recommend conservative management,
- two (14%) would recommend diagnostic arthroscopy and high tibial osteotomy,
- one would recommend high tibial osteotomy (if tibia vara) or arthroscopy and micro-fractures,
- one said that he would recommend treatment for OA without clarifying what treatment, and
- one who would recommend ACL reconstruction surgery if there was knee laxity.

Amongst the three surgeons that recommended ACL surgery for vignette four, all three would change their decision if MRI showed early signs of OA; one would recommend conservative management considering also Platelet-Rich Plasma (PRP) and stem cell injections, the second would recommend conservative management and one would recommend high tibial osteotomy.

Evaluation of the tool

At the end of the questionnaire, there was a question aiming to evaluate the questionnaire tool, asking the participants the following:
"How would you evaluate the questions following the case-vignettes? Options: Well stated and understandable – Ambiguous – Not well stated and not understandable – Other (please specify)".

8 (57%) answered well stated and understandable.
4 (28.6%) answered ambiguous.
1 (7%) answered not well stated and not understandable.

Only one respondent justified his evaluation saying that he found the questions ambiguous as he thought that questions were biased towards a surgical answer. One participant did not answer that question and that was the Greek participant who could not go back to answer some of the questions. All the other respondents (12) did not provide any further comment to justify their answer.

3.4 Discussion – Summary of findings

The first objective of the pilot study was to evaluate if the vignette questionnaire was completed appropriately, assess the response rate and review if there is variation in practice in line with what is expected. An understanding of these issues would help the researcher determine if a large-scale survey is feasible and would contribute to knowledge about decision-making in clinical practice.

Response rate to the survey

The response rate for the questionnaire tool was 45% overall, with a slightly higher rate amongst UK participants. This was despite numerous reminders. Generally, the higher the response rate, the lower the likelihood of response bias or non-response error (Harrison & Draugalis 1997). Non-response error is when a significant number of participants do not respond to the survey potentially influencing the results, impairing the reliability and validity of the survey findings (Harrison & Draugalis 1997). That means that there is a significant difference between respondents and non-respondents which potentially introduces bias; non-respondents may have a completely different opinion from respondents making the results invalid as they do not reflect the 'target population's opinion overall. For surveys among clinicians, medical journals have recommended response rates of at least 60% to minimize the response bias (Burns *et al*. 2008; JAMA 2012). However, research has shown that response rates in surveys among clinicians tend to be lower than surveys in general population, with rates averaging about 10% points lower than general surveys (Asch *et al*. 1997; Cummings *et al*. 2001). There are different reasons that could explain this lower response rate among clinicians, some being their demanding work schedules with minimal free time to devote to participate in a survey or the high frequency that they are approached for surveys, making them reluctant to participate (Flanigan *et al*. 2008).

Although high response rates are always desirable, research indicates that surveys among clinicians are more resilient to the effects of non-response than other types of surveys, as most non-response clinical studies have reported no or minimal response bias (Kellerman & Herold 2001; Cull *et al*. 2005; McFarlane *et al*. 2007). So, non-response bias might be introduced with our low response rate, but this may be less of a

concern in a clinical survey like this as just explained and much more could not be expected given the group of participants were clinicians (surgeons).

Taken into consideration our response rate of 45%, in a future full vignette study among surgeons based on this pilot study, there should not be expected more than half of the participants responding. So, to get at least 100 respondents, the invited participants must be at least 200.

Appropriate completion of questions

The response rate by vignette and by question was very high 93-100%. This might suggest that the proposed vignette-based questionnaire tool was well understandable and acceptable overall. However, this was not reflected in the answers to the question about the clarity of the questions, with only 60% saying that it was clear and understandable.

The main issue appeared to be the question: "What would you recommend if the MRI showed a potentially repairable meniscal tear?" which was asked for the first three vignettes. A meniscal repair combined with ACL reconstruction in patients who have ACL injury and associated meniscal tear is increasingly preferred over meniscectomy, trying to preserve as much meniscal tissue possible (Shelbourne & Dersam 2004; Toman *et al*. 2009). The trend reported in literature is to try to repair these meniscal tears early along with an ACL reconstruction, as the complexity of these tears increase in the chronic stage, and they are less amenable to repair as time passes (Fok & Yau 2013; Keene *et al*. 1993). In that context, it was considered useful to ask this question aiming to see if a meniscal tear would change participants' decision with regards to timing of ACL reconstruction. The answers though focused on management of the meniscal tears and did not comment on timing of ACL reconstruction. Therefore, the clinicians did not consider it important to answer this question in relation to timing of ACL reconstruction, probably because they would do ACL surgery anyway for the first three vignettes and most of them would do a meniscal repair. Whereas for vignette 4 where most of them did not recommend ACL reconstruction, a meniscal tear may have influenced their decision. For vignette 4 though only three surgeons would do ACL surgery, but this question was not asked. So, there is potentially a problem with the structure of the question which needs to be more specific and clear as to whether a

potentially repairable meniscal tear on MRI would change their planned management and in what way. Also, this question should probably be asked in all scenarios.

Another important observation was that vignettes 1 and 2 gave almost identical responses. This would imply that the characteristics of these two patients are similar leading to similar decisions and that including both provides no additional information. Therefore, there is no need for two separate vignettes and the patient characteristics could be merged, for example, the case could be one of a young male amateur football player.

Variation in clinical practice

There was obvious variation in practice in the timing of ACL reconstruction and decisions being for various patient factors.

ACL reconstruction:

One issue that came up was that not all surgeons would recommend an ACL reconstruction, and this was most prominent for the cases which were of older patients and particularly the case that was non-active (vignette 4), in which 10/13 said they would not undertake a reconstruction and this trend was among both UK surgeons (3/5) and Greek surgeons (7/8). For the case which was active but doing heavy manual job and only low demand sports (vignette 3), the majority of the surgeons (11/13) would recommend ACL reconstruction and this was for both UK surgeons (4/5) and Greek surgeons (7/8). Nine of them said that they would do an ACL reconstruction anyway but within different time-frames. Two of them said that they would recommend physiotherapy first. On the other hand, almost all surgeons (13/14) would recommend ACL reconstruction as first line for the younger and active patients (vignettes 1 and 2). Only one surgeon would not recommend ACL reconstruction for these younger and active patients, and this was one UK surgeon that would not recommend ACL reconstruction for all the patients, as they practiced rehabilitation.

Time-frames:

Within each of the vignettes there was some variation between participants in the times given for ACL reconstruction. However, for the younger patients in vignettes 1 and 2 the timings were all under 8 weeks, with the majority being ≤ 6 weeks. For the older but

active patient in vignette 3 the timings were longer with more timings (6/10) being more than 6 weeks and up to 3 or 6 months. For the older and inactive patient in vignette 4, there were only three surgeons who would recommend ACL surgery suggesting three different time-frames from 6 up to 16 weeks.

The systematic review reported in the previous chapter showed similar heterogeneity in time-frames for ACL reconstruction surgery in available literature, with time intervals varying from 6 weeks for early ACL surgery but going up to 24 months for delayed ACL surgery (Chhadia *et al*. 2011; Church & Keating 2005; Fok & Yau 2014; Frobell *et al*. 2010; Kennedy *et al*. 2010; Yüksel *et al*. 2006). None of the surgeons in this study would appear to recommend delayed surgery.

Patient factors:

Gender and mechanism of injury did not seem to influence participants' decision with regards to timing of ACL reconstruction, but age and level of activity did influence decisions.

Particularly, age was an important factor that influenced participants' decision towards ACL reconstruction in 43% of the respondents for the young patients in vignettes one and two. These respondents suggested ACL reconstruction for these two vignettes in rather early different time-frames but mainly within six weeks. For the older (39-year-old) patient in vignette three, for 29% of the respondents, age influenced their decision generally towards later ACL reconstruction, with five suggesting time-frames of six weeks or more. Although one suggested a time-frame of 6 months, none suggested delayed (more than six months) surgery. For the older (49-year-old) patient in vignette four, age influenced whether surgery was recommended, with 62% of the respondents leaning towards no ACL surgery.

Pre-operative but also desired post-operative level of activity and/or level of sports were the other important patient factors that influenced the participants' decision. For the active patients in vignettes one and two, 50% of the respondents said that the level of activity and/or level of sports influenced their decision towards ACL reconstruction, suggesting early time-frames within eight weeks and only one suggesting a longer time-frame of more than six weeks. For the older but active patient in vignette three, the level of activity was an important factor to influence the decision for 21% of the respondents,

with two of them suggesting ACL reconstruction and one suggesting no ACL surgery. For the older and inactive patient in vignette four, level of activity and/or level of sports influenced the decision for 64% of respondents suggesting no ACL surgery for this patient.

The systematic review reported in the previous chapter examined the limited evidence for these factors and implied that age may have played a role for decision-making regarding the timing of ACL reconstruction. There was no evidence to suggest that level of activity may have played a role in decision-making, although athletes who had early ACL surgery had less meniscal and chondral injuries than other athletes who had delayed surgery (Joseph et al. 2008). None of these studies investigated though whether younger or more active patients did better overall with early or subacute ACL surgery. They only assessed the effect of these patient characteristics overall.

Limited evidence reported suggests that increased age is associated with increased risk of chondral injury in ACL deficient knees, but no relationship has been reported between age and meniscal tears or even more important with functional outcomes (Chhadia *et al*. 2011; Fok & Yau 2014; Kennedy *et al*. 2010; Yüksel *et al*. 2006). Evidence is limited and conflicting about the relationship of pre-operative level of activity with rates of chondral or meniscal tears in an ACL deficient knee, with studies reporting both positive and negative relationships (Chen *et al*. 2015; Joseph *et al*. 2008; Michalitsis *et al*. 2013). Evidence focuses on pre-operative level of activity, but surgeons considered also the desired post-operative level of activity of the patient to help them make decision, although, this is often related to the pre-operative activities of the patient.

For patients in vignette one and two, being a professional footballer instead of an amateur footballer, changed the decision of relatively few of the respondents (29%) with regards to timing of ACL surgery, recommending an even earlier ACL reconstruction. It has been suggested to perform an early ACL reconstruction in competitive athletes to prevent any further episode of instability, any secondary pathology inside the ACL deficient knee and for an earlier return to training and competition, which is a big challenge for such athletes (Kennedy *et al*. 2010; Schneider 2014). This rationale is not reflected among the responding surgeons, as 71% of them did not consider performing an earlier ACL reconstruction. This may be because the

surgeons treat this group of patients (competitive athletes), like professional footballers, with early ACL reconstruction anyway or maybe some of the respondents did not have experience with elite or competitive athletes.

The survey suggested that there were other (less popular) factors which influenced the participants' decision about timing of ACL reconstruction. These included: knee instability (pre-operatively), ROM and effusion inside the knee, other associated injuries (like meniscal tears), weight of the patient and compliance of the patient. This is important as it points to some factors that are being considered from the perspectives of surgeons. The systematic review reported in the previous chapter did not examine the evidence for these factors; although, there have been reports in the past relating pre-operative swelling (effusion), ROM and obesity with outcomes after ACL reconstruction surgery (Eitzen *et al*. 2009; Keays *et al*. 2003; Kowalchuk *et al*. 2009; Mayr *et al*. 2004). Mayr *et al*. (2004) reported that limited pre-operative ROM and swelling was associated with increased risk for arthrofibrosis after ACL reconstruction and poor functional outcomes, needing surgical intervention (either arthrolysis or revision ACL surgery). Kowalchuk *et al*. (2009) showed that obesity (BMI>30) and smoking were associated with poor patient-reported outcomes after ACL reconstruction. Eitzen *et al*. (2009) showed that pre-operative quadriceps muscle strength deficits were associated with poor long-term functional outcomes after ACL reconstruction, and suggested that ACL reconstruction should not be performed before quadriceps muscle strength deficits of the injured limb is less than 20% of the uninjured limb. A similar relationship of pre-operative quadriceps muscle strength deficits with poor functional stability after ACL reconstruction was supported by one more study (Keays et al. 2003). Such patient factors were not examined in the systematic review and were not incorporated in any of the vignette cases. Since there is room for one more vignette for a future study, one more case could be one of a young obese smoker. Also, a question added to all vignettes about "whether swelling or limited pre-operative ROM would change their planned management and in what way" could add useful information about surgeons' decision-making.

Strengths and limitations

The main strengths of this pilot study were first the three reminders sent to the participants during the survey, which got the response rate to 45%, as 71% of the

respondents answered after at least one reminder, highlighting the significance of sending reminders. Second was that the participants were recruited from two different countries to prevent the impact of possible national biases towards particular management strategies.

The main limitation was the low response rate of 45%, due to which although the study started off with an acceptable number for a pilot study, it ended up with only 14 answers. Given the small sample size, the confidence interval is wide, and the response could be as low as 19%. It might have been better to estimate the number needed to target for estimating a 50% response rate with +/- 5% margin with 95% confidence. The low response rate may introduce bias as explained above, but it appeared to be enough to demonstrate there is clinical variation albeit that this was mainly about whether surgery would be undertaken and the variation in time-frames was limited mainly to within the early group as previously defined in the systematic review.

Research implications

The pilot study accomplished its objective of highlighting a number of issues with the survey that would need to be addressed before proceeding to a larger study. These included the following:

(i) Sample size: A future larger study must assume that the response rate will be low. The sample size based on this pilot study must be estimated as the number needed to target for estimating a 50% response rate with +/- 5% margin with 95% confidence.

(ii) Vignettes: The cases for vignettes one and two, with the young footballers, were considered similar giving identical responses and leading to similar decisions. Therefore, the patient characteristics of these two cases should be merged in one case of a young male amateur footballer. Considering the factors that the respondents reported as influential for their decisions and also the available literature, one case vignette should be added which should be an obese and smoker young patient.

(iii) Questions: The question: “What would you recommend if the MRI showed a potentially repairable meniscal tear?” for the first three vignettes, should be more specific and stated in a different way, such as: “Would a potentially

repairable meniscal tear in the MRI change your planned management and in what way?". This question should probably be asked for all vignettes. One question that should be added to all vignettes is about pre-operative swelling and restricted ROM asking: "Would pre-operative swelling/effusion or restricted ROM change your planned management and in what way?".

However, the pilot study has shown that the research is feasible and provided information which could inform a sample size, in particular the variation in clinical practice and the response rate. Such a study could be helpful in further understanding of the factors which are considered important for clinical decision making, with regards to whether ACL reconstruction is recommended as first line or at all and the timing of ACL reconstruction. It will also show how much variation there is in current clinical practice with regards to surgeons' decision making for ACL reconstruction about different patient groups. These findings would help to demonstrate that there may still be uncertainties about the timing of ACL reconstruction in clinical practice, although from the findings of this study, these might be limited to shorter time-frames than those that have been historically investigated in the academic literature. It would also reinforce that further research is required to provide better guidance for clinicians on access to and timing of ACL reconstruction for different sub-groups of patients.

Clinical implications

The results from the pilot survey cannot lead to any clinical conclusion or recommendation on the timing of ACL reconstruction surgery due to the small number of participants. Such recommendation may be possible after a full vignette survey amongst a larger sample of experts. However, the current pilot study does suggest that some surgeons may be delaying ACL surgery for older patients beyond six weeks but up to six months. The effectiveness of these timings is still supported by the systematic review findings.

CHAPTER 4: DISCUSSION AND CONCLUSIONS

ACL is a crucial knee stabilizer which is commonly ruptured especially in younger and active populations (Giannotti *et al*. 2009). ACL ruptures lead to knee instability, which leads to meniscal tears and chondral damage, which is thought to subsequently lead to poor function and OA (Lohmander *et al*. 2007; Oiestad *et al*. 2009). Management of ACL injuries and decision making with regards to operative treatment with ACL reconstruction surgery is challenging as there are a lot of controversies regarding ACL reconstruction surgery and timing of the surgery.

This thesis described and highlighted these controversies in management of ACL injuries with regards to timing of ACL reconstruction surgery in chapter 1. In chapter 2, it presented the findings of a systematic review of studies which compared clinical, functional and patient-reported outcomes between early, subacute and delayed ACL surgery and on patient factors which may influence these outcomes. Chapter 3 reported on the development and piloting of a vignette questionnaire on clinicians' views of timing of ACL reconstruction surgery and the factors that could influence this decision for different patient sub-groups.

It must be noted that this thesis was not focused on which patient should have an ACL reconstruction, but was focused on the effect of timing of surgery on those who had ACL reconstruction. The systematic review showed that there is an effect of timing of ACL reconstruction on outcomes. It showed that there does not appear to be much difference in outcomes between early and subacute ACL reconstruction, but there is significant difference in delayed ACL reconstruction, with delay more than 6 months from injury associated with more medial meniscal tears and chondral injuries. Nevertheless, the importance of this increase in meniscal and chondral injuries has not yet clearly been established. The evidence is limited and not consistent about the effect of timing on functional and patient-reported outcomes. But given the detrimental effect that meniscal and chondral injuries may have on knee function, based on the available evidence, delays more than 6 months from injury in those patients deemed suitable for ACL reconstruction should not be recommended.

Even though there is evidence to guide as to which patients would benefit from ACL reconstruction in general, there is limited and 'low quality' evidence as to which

patients would benefit specifically from early or subacute ACL reconstruction. Therefore, it would be useful to know if any patient factors influence the effect of timing on clinical outcomes and, particularly, whether any patient sub-groups would benefit from early or subacute ACL surgery or be harmed from a more delayed ACL surgery. This systematic review could not provide any conclusion on this due to the sparsity of available evidence, within the eligible studies.

The pilot vignette study, although small, suggests that such a delay in ACL surgery, as defined in the systematic review, appears to be avoided in clinical practice for younger and more active people anyway, and most surgeons would recommend surgery within six weeks. This is maybe because young and active people with an ACL injury present usually with the main complain of 'giving way', being keen to go back to their sport related activities as soon as possible (Dye *et al*. 1999; Makhmalbaf 2013). Giving way is a sign of knee instability which the surgeons need to restore as soon as possible, otherwise the patient cannot go back to his activities and sports soon and even if he does return to sports activities without restoring the instability, the risk of re-injury and/or associated injuries is high, increasing also the theoretical risk of secondary osteoarthritis (Eckstein *et al*. 2015; Fithian *et al*. 2002; Nebelung &Wuschech 2005). So, the main goal of the ACL reconstruction is to restore the knee stability and consequently the function of the knee, allowing the patient to return to normal and even high demand activities, including sports (Dye *et al*. 1999; Makhmalbaf 2013). This may be why the surgeons in the pilot study recommended an early ACL reconstruction for the young and active case vignettes.

Whereas for older and less active people with an ACL injury, where the return to sports or high demand activities is not usually desired, non-operative treatment has traditionally been recommended and good results have been reported (Andersson *et* al. 1991; Buss *et al*. 1995; Herrington & Foler 2006; Strehl & Eggi 2007). In that context, the surgeons in the pilot study may have decided to recommend non-operative management of such a patient or they offered less early ACL reconstruction than younger patients, although none were delayed as defined in the systematic review.

Therefore, there seem to be two groups of patients that research need to focus in the future. First the young and active patients with an ACL injury to whom a large long-term cohort study like the one described in detail in chapter 2 should probably focus,

comparing clinical but mainly functional/patient-reported outcomes after early and subacute ACL reconstruction in such patients. The aim would be to identify if early or subacute ACL reconstruction is related with better long-term functional and/or patient-reported outcomes and at what early time-frame such a surgery would make significant difference for these patients.

Second the older and less active patients with an ACL injury, for whom we need to understand whether the delay in ACL surgery is important. So, it would be valuable in a large cohort study to compare functional/patient-reported outcomes between subacute and delayed ACL reconstruction for this group of patients, aiming to establish whether a delay makes significant difference for this patient group and if yes, then what time-frame should be recommended for those suitable for ACL surgery. In the meantime, a consensus study among experts could collect their views trying to identify any certain factors among this patient group that may influence the effect of timing of ACL surgery on outcomes.

Whilst a large cohort study is awaited, a vignette study amongst experienced orthopaedic surgeons based on the pilot vignette study presented in chapter 3, may shed further light to help guide timing in these patient groups, incorporating these patient factors in different (both young and old) case vignettes.

Conclusions

Delay in ACL reconstruction surgery more than 6 months from injury may adversely affect medial meniscal tears and chondral injuries. Based on these findings and given the potential deleterious effects that such injuries may have on knee function, we recommend that delays of more than 6 months for ACL reconstruction in those patients who are deemed suitable to have one, are avoided. This recommendation should be considered by national guidance bodies. Further research may further evaluate the effect of timing of ACL surgery on functional and patient-reported outcomes, for which the available evidence is very limited, is inconsistent and of low quality.

However, the suggestion to perform an early or subacute ACL reconstruction in less than 6 months from injury does not apply to anyone with an ACL injury. This

systematic review could not assess whether certain patient sub-groups may benefit more from an early/subacute or may be harmed more from a delayed ACL reconstruction due to the sparsity of available evidence. So, further research is needed to establish if any patient characteristics influence the effect of timing on clinical and/or functional/patient-reported outcomes after ACL reconstruction surgery.

A future large and long-term cohort study may help resolve some of these issues, in particular the relationship of timing of ACL reconstruction and functional/patient reported outcomes and the influence of patient factors on the effect of timing. Such a cohort study should probably focus on young and active patients to compare those outcomes after early and subacute ACL reconstruction to identify what time-frame would make significant difference for these young patients. Second this cohort study should compare subacute and delayed ACL reconstruction for older and less active patients suitable for such surgery, in order to establish whether a delay makes significant difference for such patients and if yes, what time-frame should be recommended.

In the absence of strong evidence and whilst is awaited, a consensus study of experts may be used to collect relevant information and possibly agree for a consensus. In the meantime, to help guide timing of ACL reconstruction in different patient groups and to identify the variation in current clinical practice, a vignette study based on the pilot vignette study described in Chapter 3 may shed further light.

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Appendices

Appendix 1: PROSPERO database registered record

PROSPERO International prospective register of systematic reviews

Timing of anterior cruciate ligament reconstruction

Apostolos Prodromidis, Nasri Zreik, Charalambos Charalambous, Maria Paola Dey

Citation

Apostolos Prodromidis, Nasri Zreik, Charalambos Charalambous, Maria Paola Dey. Timing of anterior cruciate ligament reconstruction.
PROSPERO 2016:CRD42016032846 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016032846

Review question

Is there a relation between timing from ACL rupture to ACL reconstruction surgery and a) development of further meniscal tears and chondral injuries b) functional and/or patient reported outcomes?

If a relation does exist, is it influenced by patient characteristics and does timing have an impact on outcomes in different patient groups?

Searches

The following electronic bibliographic databases to be searched:

MEDLINE (1946 to present) – Interface: EBSCOhost; EMBASE (1974 to present) – Interface: Ovidsp; CINAHL (1961 to present) – Interface: EBSCOhost; AMED (1995 to present) – Interface: EBSCOhost; CENTRAL (1988 to present) – Interface: Cochrane Library

Additional sources to be searched: Archives of clinical trials.

Restrictions:

There will be language limitations. Only studies available in English language will be included.

Age was set as a limit to the search because of the difficulty of setting specific search terms, but all titles and abstracts about children (age < 16 years) were excluded whilst screening.

Types of study to be included

Any comparative study design was eligible. This included randomised controlled trials (RCTs), prospective cohort studies, case control studies, and retrospective comparative studies. Excluded study designs included case reports, reviews, editorials, personal opinions, surveys and case series.

Condition or domain being studied

Orthopaedics. ACL injury and ACL reconstruction.

Participants/population

Adults with a complete ACL rupture. Adults with partial ACL tear were excluded, because these patients are most often treated non-operatively. Also, studies of re-ruptures of a previously repaired or reconstructed ACL were excluded. Only skeletally mature patients were included. Skeletal maturity is normally achieved around 16 years old, so the age group of interest will be > 16 years old.

Intervention(s), exposure(s)

Primary ACL reconstruction for ACL rupture at a given time from ACL injury. Only arthroscopic primary ACL surgery was included and any study with open ACL surgery was excluded, because the arthroscopic technique is the most commonly performed.

Comparator(s)/control

Different timings to intervention were compared: (i) Early treatment: any intervention performed within 12 weeks (3 months) from injury, including the first 72 hours from injury. (ii) Subacute treatment: any intervention performed between 12th week (3 months) and 24th week (6 months) from injury. (iii) Delayed treatment: any intervention performed between 6th and 36th month from injury.

Primary outcome(s)

Meniscal tears and chondral injuries: any type of meniscal tear and/or any type of chondral injury graded by any system.

Secondary outcome(s)

Functional (objective) outcomes and patient-reported (subjective) outcomes.

Data extraction (selection and coding)

Data was extracted from the included studies by two reviewers independently using a standardised data extraction form developed by one reviewer and inputted onto an appropriate Excel spreadsheet to record results. The results from each reviewer's data extraction form for each study were compared and any discrepancies were reviewed. Data that were extracted are:

• Demographics of each study (country/setting, number of patients, age group, sex);

• Patients' factors that might affect outcome (e.g. gender, age group, level of activity, mechanism of injury);

• Timing from injury till intervention (ACL reconstruction);

• Types and rates of further meniscal tears;

• Types, grading system and rates of further chondral injuries;

• Functional and/or patient-reported outcomes.

Risk of bias (quality) assessment

The following will be applied:

The Cochrane risk of bias tool for randomized controlled trials.

The Methodological Index for Non-Randomised (comparative and non-comparative) Studies – MINORS criteria.

Newcastle-Ottawa scale for observational comparative (cohort) studies.

Strategy for data synthesis

If the data is sufficiently homogenous, a meta-analysis would also be performed using a random-effects model. Meniscal tears and cartilage/chondral injuries will be the primary outcomes of the study. Summary risk ratios and 95% confidence intervals (CIs) will be calculated and reported for each outcome.

If data is not homogenous, the studies in the overview would be summarised narratively using tables, figures and text.

Analysis of subgroups or subsets

If the included studies are of different design, they would be analysed separately according to the study design and a subgroup analyses would be performed.

Contact details for further information

Apostolos Prodromidis

a.prodromidis@hotmail.com

Organisational affiliation of the review

University of Central Lancashire

Review team members and their organisational affiliations

Dr Apostolos Prodromidis. University of Central Lancashire
Mr Nasri Zreik. University of Central Lancashire
Professor Charalambos Charalambous. University of Central Lancashire, Blackpool Victoria Hospital
Professor Maria Paola Dey. University of Central Lancashire

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Anterior Cruciate Ligament; Anterior Cruciate Ligament Reconstruction; Humans; Knee; Knee Injuries; Treatment Outcome

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Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Appendix 2: Other tables

a. Full electronic search strategies with results for databases EMBASE, CINAHL, AMED, CENTRAL

Table 1. Full electronic search strategy with results for EMBASE database

#	Query	Limiters/Expanders	Last Run Via	Results
S1	anterior cruciate ligament	English language; Human.	Interface – Ovidsp Database – EMBASE	13,089
S2	ACL	Same as S1	Same as S1	10,348
S3	menisc*	Same as S1	Same as S1	9,907
S4	chondral	Same as S1	Same as S1	2,120
S5	cartilag*	Same as S1	Same as S1	55,141
S6	function*	Same as S1	Same as S1	1,940,961
S7	outcome*	Same as S1	Same as S1	1,702,168
S8	pain	Same as S1	Same as S1	653,524
S9	scor*	Same as S1	Same as S1	742,916
S10	delay*	Same as S1	Same as S1	269,742
S11	earl*	Same as S1	Same as S1	1,014,501
S12	tim*	Same as S1	Same as S1	2,107,789
S13	surgery	Same as S1	Same as S1	1,198,531
S14	reconstruct*	Same as S1	Same as S1	176,171
S15	S1 OR S2	Search modes: Boolean/Phrase	Same as S1	16,053
S16	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Search modes: Boolean/Phrase	Same as S1	4,146,547
S17	S10 OR S11 OR S12	Search modes: Boolean/Phrase	Same as S1	2,992,240
S18	S13 OR S14	Search modes: Boolean/Phrase	Same as S1	1,290,216
S19	**S15 AND S16 AND S17 AND S18**	**Search modes: Boolean/Phrase**	**Same as S1**	**2,541**

Table 2. Full electronic search strategy with results for CINAHL database

#	Query	Limiters/Expanders	Last Run Via	Results
S1	anterior cruciate ligament	English language; Human.	Interface – EBSCOhost Database – CINAHL complete	3,938
S2	ACL	Same as S1	Same as S1	1,434
S3	menisc*	Same as S1	Same as S1	1,379
S4	chondral	Same as S1	Same as S1	242
S5	cartilag*	Same as S1	Same as S1	3,826
S6	function*	Same as S1	Same as S1	130,123
S7	outcome*	Same as S1	Same as S1	288,989
S8	pain	Same as S1	Same as S1	77,840
S9	scor*	Same as S1	Same as S1	103,638
S10	delay*	Same as S1	Same as S1	23,503
S11	earl*	Same as S1	Same as S1	79,705
S12	tim*	Same as S1	Same as S1	233,370
S13	surgery	Same as S1	Same as S1	130,357
S14	reconstruct*	Same as S1	Same as S1	11,280
S15	S1 OR S2	Search modes: Boolean/Phrase	Same as S1	4,076
S16	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Search modes: Boolean/Phrase	Same as S1	467,909
S17	S10 OR S11 OR S12	Search modes: Boolean/Phrase	Same as S1	300,639
S18	S13 OR S14	Search modes: Boolean/Phrase	Same as S1	133,257
S19	**S15 AND S16 AND S17 AND S18**	**Search modes: Boolean/Phrase**	**Same as S1**	**552**

Table 3. Full electronic search strategy with results for AMED database

#	Query	Limiters/Expanders	Last Run Via	Results
S1	anterior cruciate ligament	English language.	Interface – EBSCOhost Database – AMED	1,606
S2	ACL	Same as S1	Same as S1	719
S3	menisc*	Same as S1	Same as S1	295
S4	chondral	Same as S1	Same as S1	74
S5	cartilag*	Same as S1	Same as S1	1,076
S6	function*	Same as S1	Same as S1	29,636
S7	outcome*	Same as S1	Same as S1	33,022
S8	pain	Same as S1	Same as S1	25,552
S9	scor*	Same as S1	Same as S1	14,358
S10	delay*	Same as S1	Same as S1	2,487
S11	earl*	Same as S1	Same as S1	8,238
S12	tim*	Same as S1	Same as S1	27,596
S13	surgery	Same as S1	Same as S1	11,895
S14	reconstruct*	Same as S1	Same as S1	2,196
S15	S1 OR S2	Search modes: Boolean/Phrase	Same as S1	1,650
S16	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Search modes: Boolean/Phrase	Same as S1	74,793
S17	S10 OR S11 OR S12	Search modes: Boolean/Phrase	Same as S1	35,297
S18	S13 OR S14	Search modes: Boolean/Phrase	Same as S1	12,881
S19	**S15 AND S16 AND S17 AND S18**	**Search modes: Boolean/Phrase**	**Same as S1**	**189**

Table 4. Full electronic search strategy with results for CENTRAL database

#	**Query**	**Limiters/Expanders**	**Last Run Via**	**Results**
S1	anterior cruciate ligament	Trials	Interface – Cochrane Library Database – Cochrane	1220
S2	ACL	Same as S1	Same as S1	838
S3	menisc*	Same as S1	Same as S1	541
S4	chondral	Same as S1	Same as S1	52
S5	cartilag*	Same as S1	Same as S1	1,047
S6	function*	Same as S1	Same as S1	107,820
S7	outcome*	Same as S1	Same as S1	195,063
S8	pain	Same as S1	Same as S1	76,855
S9	scor*	Same as S1	Same as S1	100,548
S10	delay*	Same as S1	Same as S1	23,618
S11	earl*	Same as S1	Same as S1	61,767
S12	tim*	Same as S1	Same as S1	212,862
S13	surgery	Same as S1	Same as S1	78,610
S14	reconstruct*	Same as S1	Same as S1	4,241
S15	S1 OR S2	Search modes: Boolean/Phrase	Same as S1	1,458
S16	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Search modes: Boolean/Phrase	Same as S1	341,847
S17	S10 OR S11 OR S12	Search modes: Boolean/Phrase	Same as S1	262,120
S18	S13 OR S14	Search modes: Boolean/Phrase	Same as S1	80,846
S19	**S15 AND S16 AND S17 AND S18**	**Search modes: Boolean/Phrase**	**Same as S1**	**315**

b. Details of studies excluded from the systematic review

Table 1. Details of studies excluded from the systematic review

Study **Author (Year)** **Study design**	**Journal**	**Reason for exclusion**
Barenius et al. (2011) Retrospective	Arthroscopy. 2011 Oct;27(10), e247-e248	Range of age: 5-67 years. Data for adults not extractable.
Daniel et al. (1994) Prospective cohort	Am J Sports Med. 1994; 22(5), pp. 632-644	Range of age: 15-44 years. Data for adults not extractable.
Fetto & Marshall (1980) Not stated (Retrospective)	Clin Orthop Relat Res. 1980 Mar-Apr;147, pp. 29-38	Range of age: 13-73 years. Data for adults not extractable.
Foster et al. (2005) Retrospective	Knee. 2005 Jan;12(1), pp. 33-35	Range of age: 12-51 years. Data for adults not extractable.
Ghodadra et al. (2013) Retrospective	J Knee Surg. 2013 Jun;26(3), pp. 185-193	Range of age: 11-61 years. Data for adults not extractable.
Karlsson et al. (1999) Retrospective	Knee Surg Sports Traumatol Arthrosc. 1999;7(3), pp. 146-151	Range of age: 13-40 years. Data for adults not extractable.
Kluczynski et al. (2013) Prospective cohort	Am J Sports Med. 2013 Dec;41(12), pp. 2759-65	Range of age: 7-62 years. Data for adults not extractable.
Magnussen et al. (2013) Retrospective	Knee Surg Sports Traumatol Arthrosc. 2013 Sep;21(9), pp. 2029-34	Range of age: 13-59 years. Data for adults not extractable.
Majors & Woodfin (1996) Retrospective	Am J Sports Med. 1996 May-Jun;24(3), pp. 350-355	Range of age: 14-51 years. Data for adults not extractable.
Marcacci et al. (1995) Not clearly stated. (Retrospective)	Am J Sports Med. 1995 Nov;23(6), pp. 690-693	Range of age: 14-38 years. Data for adults not extractable.
Meighan et al. (2003) RCT	J Bone Joint Surg Br. 2003 May;85(4), pp. 521-524	Range of age: 15-35 years. Data for adults not extractable.
Murrel et al. (2001) Cross-sectional	Am J Sports Med. 2001 Jan-Feb;29(1), pp. 9-14	Range of age: 14-67 years. Data for adults not extractable.
O'Connor et al. (2005) Retrospective case series	Arthroscopy. 2005 April;21(4), pp. 431-438	Range of age: < 15 up to ≥ 50 years. Data for adults not extractable.

ACL: Anterior cruciate ligament, **TFI:** time from injury, **RCT:** Randomised clinical trial

Table 1. Details of studies excluded from the systematic review (continued)

Study **Author (Year)** **Study design**	**Journal**	**Reason for exclusion**
Papastergiou et al. (2007) Retrospective	Knee Surg Sports Traumatol Arthrosc. 2007 Dec;15(12), pp. 1438-44	Range of age: 14-52 years. Data for adults not extractable.
Quelard et al. (2010) Prospective cohort	Am J Sports Med. 2010 Oct;38(10), pp. 2034-9	Range of age: 14-62 years. Data for adults not extractable.
Raviraj et al. (2010) RCT	J Bone Joint Surg Br. 2010 Apr;92-B(4), pp. 521-6	It compared two groups of early ACL reconstruction (≤2 weeks and 4-6 weeks)
Røtterud et al. (2011) Prospective cohort	Am J Sports Med. 2011 Jul;39(7), pp. 1387-94	Range of age: 9-69 years. Data for adults not extractable.
Shelbourne et al. (1991) Retrospective	Am J Sports Med. 1991 Jul-Aug;19(4), pp. 332-336	Range of age: 13-46 years. Data for adults not extractable.
Slauterbeck et al. (2009) Retrospective	J Bone Joint Surg Am. 2009 Sep;91(9), pp. 2094-2103	Range of age: 12-56 years. Data for adults not extractable.
Sri-Ram et al. (2012) Prospective cohort	Bone Joint J. 2013 Jan;95-B(1), pp. 59-64	Included children < 17 years. Data for adults not extractable.
Sterrett et al. (2003) Not stated (Retrospective)	Orthopedics. 2003 Feb;26(2), pp. 151-154	Range of age: 14-50 years. Data for adults not extractable.
Tandogan et al. (2004) Retrospective	Knee Surg Sports Traumatol Arthrosc. 2004 Jul;12(4), pp. 262-270	Range of age: 14-59 years. Data for adults not extractable.
Wasilewski et al. (1993) Retrospective	Am J Sports Med. 1993 May-Jun;21(3), pp. 338-342	Range of age: 13-52 years. Data for adults not extractable.
Zamber et al. (1989) Prospective cohort	Arthroscopy. 1989;5(4), pp. 258-28	Range of age: 14-63 years. Data for adults not extractable.
Zhou et al. (2008) Retrospective	Chin Med J (Engl). 2008 Nov;121(22), pp. 224-228	Range of age: 15-40 years. Data for adults not extractable.
Dimmond et al. (1998) Retrospective	Am J Knee Surg. 1998;11(3), pp. 153-159	Inclusion of chronic ACL tears up to 9.9 years. Data per appropriate TFI not extractable.
Potter et al. (2012) Prospective cohort	Am J Sports Med. 2012 Feb;40(2), pp. 276-85	Inclusion only of chronic ACL tears.

ACL: Anterior cruciate ligament, **TFI:** time from injury, **RCT:** Randomised clinical trial

Table 1. Details of studies excluded from the systematic review (continued)

Study **Author (Year)** **Study design**	**Journal**	**Reason for exclusion**
Bray & Dandy (1989) Not stated. (Retrospective)	J Bone Joint Surg Am. 1989 Jan;71-B(1), pp. 128-130	Inclusion only of chronic ACL tears.
Irvine & Glasgow (1992) Not stated	J Bone Joint Surg [Br]. 1992;74-B, pp. 403-405	Inclusion of chronic ACL tears up to 240 months. Data per appropriate TFI not extractable.
Maffuli et al. (2003) Prospective case series	Arthroscopy. 2003 Sep;19(7), pp. 685-690	Inclusion of chronic ACL tears up to 16 years. Data per appropriate TFI not extractable.
Moon (2011) RCT	Am Fam Physiciam. 2011;83(7), pp. 842-844	Inclusion of chronic ACL tears up to >2 years. Data per appropriate TFI not extractable.
Vasara et al. (2005) Cross-sectional	Am J Sports Med. 2005 Mar;33(3), pp. 408-414	Inclusion of chronic ACL tears up to 401 months. Data per appropriate TFI not extractable.
Bottoni et al. (2008) RCT	Am J Sports Med. 2008; 36(4), pp. 656-662	Did not group patients and/or results so as could be grouped by TFI into early, subacute and/or delayed groups.
De Roeck & Lang-Stevenson (2003) Not stated (Retrospective)	Injury. 2003;34, pp. 343-345	
Granan et al. (2009) Prospective cohort	Am J Sports Med. 2009 May;37(5), pp. 955-961	
Tayton et al. (2009) Retrospective	Knee Surg Sports Traumatol Arthrosc. 2009 Jan;17(1), pp. 30-34	
Yoo et al. (2009) Retrospective	Am J Sports Med. 2009 Aug;37(8), pp. 1478-83	
Church & Keating (2005) Retrospective	J Bone Joint Surg Br. 2005 Dec;87(12), pp. 1639–1642	
Fok & Yau (2013) Retrospective	Knee Surg Sports Traumatol Arthrosc. 2013 Apr;21(4), pp.928-933	
Tambe et al. (2006) Retrospective	Int Orthop. 2006 Apr;30(2), pp. 104–109.	
Keene et al. (1993) Retrospective	Am J Sports Med. 1993 Sep-Oct;21(5), pp. 672-9	Did not clarify range of age. Did not respond to email sent for clarification.

ACL: Anterior cruciate ligament, **TFI:** time from injury, **RCT:** Randomised clinical trial

Table 1. Details of studies excluded from the systematic review (continued)

Study **Author (Year)** **Study design**	**Journal**	**Reason for exclusion**
Hunter et al. (1996) Prospective cohort	Arthroscopy. 1996 Dec;12(6), pp. 667-674	Did not clarify range of age. Did not respond to email sent for clarification.
Kilcoyne et al. (2012) Prospective cohort	Orthopedics. 2012 Mar;35(3), pp. 208-212	
Tatari & Guliyev (2014)	Orthop J Sports Med. 2014 Nov; 2(11)(3 Suppl)	Not clear data about groups of patients. Did not clarify range of TFI per group of patients.
Melikoglu et al. (2008) Prospective cohort	J Back Musculoskelet Rehabil. 2008 Apr;21(1), pp. 23-28	Appropriate data not extractable from text and figures. Did respond to email sent for clarification.
Demirağ et al. (2011) Retrospective	Acta Orthop Traumatol Turc 2011;45(5), pp. 348-352	Appropriate data not extractable from text and figures. Did respond to email sent for clarification.
Fithian et al. (2005) Prospective non-randomised controlled clinical trial	Am J Sports Med. 2005 Mar;33(3), pp. 335-346	Appropriate data not extractable from text and figures. Did not respond to email sent for clarification.
Fithian et al. (2005) Prospective non-randomised controlled clinical trial	Am J Sports Med. 2005 Mar;33(3), pp. 335-346	Appropriate data not extractable from text and figures. Did not respond to email sent for clarification.
Dunn et al. (2015) Prospective cohort	J Bone Joint Surg Am. 2015 Apr;97(7), pp. 551-7	No correlation of outcomes with TFI.
Puddu et al. (1984) Prospective cohort	Am J Sports Med. 1984 May-Jun;12(3), pp. 196-198	No correlation of outcomes with TFI.
Reider (2015)	Am J Sports Med. 2015;43(2), pp. 273-4	Ineligible study design. Editorial.
Rosenberg & Sherman (1992)	Sports Medicine. 1992;13(6):423-432	Ineligible study design. Review.
Cordasco (2014)	Clin Orthop Relat Res. 2014 Mar;472(3):998-1000	Ineligible study design. Review
Shelbourne & Patel (1995)	Knee Surg Sports Traumatol Arthrosc. 1995;3(3):148-156	Ineligible study design. Review with case studies.
Bernstein (2011)	J Bone Joint Surg Am. 2011;93:e48(1-5)	Ineligible study design. Study analyzing and commenting on the RCT included in the analysis (Frobell et al. 2010).

ACL: Anterior cruciate ligament, **TFI:** time from injury, **RCT:** Randomised clinical trial, **ACLR:** Anterior cruciate ligament reconstruction, **OA:** osteoarthritis

Table 1. Details of studies excluded from the systematic review (continued)

Study **Author (Year)** **Study design**	**Journal**	**Reason for exclusion**
Harris et al. (2015)	Journal of Athletic Training. 2015;50(1):110-112	Ineligible study design. Study analyzing and commenting on the RCT included in the analysis (Frobell et al. 2010).
Levy (2010)	N Engl J Med. 2010 Jul;363(4):386-388	Ineligible study design. Editorial analyzing and commenting on other study (RCT) included in the analysis (Frobell et al. 2010).
Shelbourne et al. (1990) Retrospective	Am J Sports Med. 1991;19(4):332-336	Full paper unavailable. Cannot extract relevant data from the abstract.
Cabaud & Rodkey (1985) Not stated	Clin Sports Med. 1985 Apr;4(2):313-324	Full paper unavailable. Cannot extract relevant data from the abstract.
Finsterbush et al. (1990)		Included partial ACL tears.
Graf et al. (1994) Retrospective	Orthopedics. 1994 Oct;17(10):909-912	Included open ACL surgery.
Frobell et al. (2009) RCT	Osteoarthritis and Cartilage. 2009;17(2):161-167	Study which compared early/acute ACLR with conservative (non-operative) management.
Dare & Rodeo (2014) Prospective observational	Curr Rheumatol Rep. 2014;16:448	Ineligible outcome: factors that contribute in ACL deficient knees to development of OA.
Meunier et al. (2006) RCT	Scan J Med Sci Sports. 2007 Jun;17(3):230-237	Ineligible outcomes: Radiological OA changes 15 years post treatment for ACL rupture (both surgical and non-surgical).

ACL: Anterior cruciate ligament, **TFI:** time from injury, **RCT:** Randomised clinical trial, **ACLR:** Anterior cruciate ligament reconstruction, **OA:** Osteoarthritis

c. Demographic characteristics of all included studies in the systematic review

Table 1. Demographic characteristics of all included studies in the systematic review

Author (Year)	Country / Setting	Gender	Age (years)	Level of activity before ACL injury
Frobell et al. (2010)	Sweden, Denmark/ Helsingborg hospital and Lund University hospital	89 males 32 females	Range: 18-35 Mean: 26	TAS: 7-9
Michalitsis et al. (2013)	Greece/ University Hospital of Larissa	96 males 13 females	Mean: 26.4	Not stated
Chhadia et al. (2011)	USA/ 3 different institutions	Not stated	Group 1: Mean age: 24.4 Group 2: Mean age: 26.6 Group 3: Mean age: 27.0 Group 4: Mean age: 29.8	Not stated. General community population.
Church & Keating (2005)	Scotland/ Edinburgh Royal Infirmary	135 males 48 females	Range: 16-40 Mean: 27	Not stated. Young adult patients.
Yüksel et al. (2006)	Turkey/ Etimesgut Military Hospital	Males	Range: 19-50 Mean: 28.1 +/- 7.0	Military personnel. Not stated.
Tambe et al. (2006)	United Kingdom/ University hospital of Leicester	Not stated	Range: 17-47	TAS > 7 (competitive athletes)
Joseph et al. (2008)	India/ GKNM hospital	1130 males 245 females	Range: 16-48	Athletes (competitive sports or regular recreational sports). Non-athletes.

ACL: Anterior cruciate ligament, **TAS:** Tegner-Activity Scale

Table 1. Demographic characteristics of all included studies in the systematic review (continued)

Kennedy et al. (2010)	Ireland/ Santry hospital, Sports surgery clinic	237 males 63 females	Group 1: Mean: 22.9 +/- 6.4 Group 2: Mean: 25.4 +/- 6.6	Not stated
Author (Year)	**Country / Setting**	**Gender**	**Age (years)**	**Level of activity before ACL injury**
Anstey et al. (2012)	USA/ Massachusetts General Hospital	115 males 80 females	Range: 16 -60 Mean: 33.7	Not stated. Included older patients.
Fok & Yau (2014)	China/ University of Hong Kong, Queen Mary Hospital	129 males 21 females	Range: 13 – 48 Mean: 26.3	Not stated clearly. Included both athletes and non-sports patients.
Chen et al. (2015)	China/ West China hospital, Sichuan University	228 males 65 females	Range: 18 – 40 Mean : 28.6	Active patients (high-intensity sports) and inactive patients (mild-exercise or no exercise).
Ahlén & Lidén (2011)	Sweden/ NU-Hospital Organisation	34 males 37 females	Group 1: Mean 26 +/- 9 Group 2: Mean 27 +/- 6	TAS: 4 – 10
Jacob & Oommen (2012)	India/ Christian Medical College, Vellore	124 males 5 females	Mean: 30.62 +/- 9.5	Not stated

ACL: Anterior cruciate ligament, **TAS:** Tegner-Activity Scale

Appendix 3: Other documents

a. Proposed Questionnaire for think aloud interviews

Case 1: A 23-year-old male had a contact knee injury while playing football. Knee swelling developed immediately and he could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other injury. He was then referred to you for assessment the next day. He is an amateur football player playing regularly only football.

1. How long after the injury would you operate on this patient in weeks?
2. What are the important factors which would influence your decision in this patient?
3. Is there any other information would you want to know before making a decision?

Case 2: A 28-year-old female had a non-contact knee injury while playing tennis. Knee swelling developed immediately and she could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other injury. She was then referred to you for assessment the next day. She is an amateur tennis player playing regularly only tennis.

1. How long after the injury would you operate on this patient in weeks?
2. What are the important factors which would influence your decision in this patient?
3. Is there any other information would you want to know before making a decision?

Case 3: A 41-year-old female had a non-contact knee injury while running. Knee swelling developed immediately and she could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other injury. She was then referred to you for assessment the next day. She is a regular runner but he does not do any other sports.

1. How long after the injury would you operate on this patient in weeks?
2. What are the important factors which would influence your decision in this patient?
3. Is there any other information would you want to know before making a decision?

Case 4: A 48-year-old male had a non-contact knee injury at work after falling. His knee got swollen immediately. He could not walk after the injury and he could not go to work, MRI performed the next day showed an ACL rupture with no other injury. He is referred to you for assessment the next day. He is living a sedentary life and he does not do any sports.

1. How long after the injury would you operate on this patient in weeks?
2. What are the important factors which would influence your decision in this patient?
3. Is there any other information would you want to know before making a decision?

Please complete the following:
a. What are your qualifications (academic or non-academic):
b. How many years of experience of assessing and treating ACL injuries do you have?
c. Approximately how many ACL reconstructions do you perform/assist per year?

b. Information sheet for think aloud interviews

Participant Information Sheet

Study title: Timing of Anterior Cruciate Ligament (ACL) Reconstruction
Vignette based study – Think aloud interview

Dear participant:
My name is Apostolos Prodromidis and I am a graduate student at the University of Central Lancashire undertaking an MSc by research. For my thesis, I am examining the relation of timing of ACL reconstruction with clinical outcomes (meniscal tears and chondral injuries) and patient reported outcomes. Because you know about ACL reconstruction, I am inviting you to participate in this pilot study by completing the attached questionnaire.

I have performed a systematic review on timing of ACL reconstruction and am now interested to know what the important considerations for consultant surgeons are when deciding on when to operate. I am developing a vignette-based questionnaire tool on what and how surgeons decide the timing of ACL surgery in different types of patients in clinical practice. At this stage I am interested in what a small number of surgeons (about 3) think about the survey before I pilot it. I would be grateful if you would like to participate at this phase of the study.

Your participation is strictly voluntary. If you agree to take part, I will ask you to complete the survey which includes answering a few questions on 4 different vignettes (cases) and as you fill it in to give feedback on the structure, understandability and relevance of the proposed vignettes and questionnaire. This will be done as a think aloud interview which will be digitally recorded. This should take about 20 minutes of your time and can be undertaken at your convenience. You can stop the interview at any time if you no longer want to take part. The recorded interviews will be anonymous, stored in my password-secure area on the university server and/or and encrypted pen stick and will be destroyed after completion of my thesis. Since this the interview is anonymous, data cannot be withdrawn after the data has been deleted off the recorder and stored. No data presented in the thesis or other presentation or publication will identify you. Your participation is strictly voluntary.

If you would like to take part in this pilot study, I will ask you to sign the consent form attached. Thank you for taking the time to assist me in my educational endeavours. The data collected with this interview will provide useful information to develop a vignette-based questionnaire tool upon timing of ACL reconstruction and selection of patients, which will be distributed as a

web survey. It will be used for my thesis, subsequent publications in peer reviewed journals and presentations.

If you would like additional information on this study or have questions, please feel free to contact me or my supervisors. 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.

Sincerely.

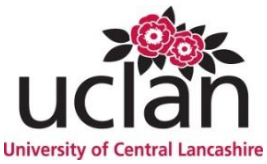
Dr. Apostolos Prodromidis
aprodromidis@uclan.ac.uk
Research MSc student
School of Medicine, University of Central Lancashire, UK
Orthopaedic Registrar, (South Tyneside NHS Trust)

Supervisors:
Prof Waqar Ahmed
WAhmed4@uclan.ac.uk
School of Medicine, College of Clinical and Biomedical Sciences
University of Central Lancashire, UK.

Mr Charalambos C. Charalambous
Ccharalambous@uclan.ac.uk

Honorary Visiting Professor at University of Central Lancashire
Consultant Orthopaedic Surgeon at Blackpool Victoria Hospital, UK

c. Informed consent of participants for think aloud interviews



Timing of Anterior Cruciate Ligament (ACL) reconstruction – Vignette based study
CONSENT FORM – INDIVIDUAL "THINK ALOUD" INTERVIEW
Please tick in the boxes provided to indicate 'YES' to the following statements:

I have read and understood the information sheet and I have had the opportunity to ask questions.	☐
I agree to the interview being audio-recorded and/or written notes being undertaken.	☐
I understand that my participation is strictly voluntary, and I may refuse to participate. I am also free to stop the interview at any point.	☐
I understand it will not be possible for me to withdraw my data from the transcripts and analysis once the main pilot survey has started.	☐
I understand that my participation will be anonymous and there will be no connection to me in the results and in any future publication of the results (reports or other publications).	☐
I agree to take part in the interview.	☐

Name (PRINT):	Date:
Signature:	
Name of researcher taking consent:	Apostolos Prodromidis
Signature:	Date:

d. Ethics approval letter

26th September 2016

Waqar Ahmed/Apostolos Prodromidis

School of Medicine

University of Central Lancashire

Dear Waqar/Apostolos,

Re: STEMH Ethics Committee Application

Unique Reference Number: **STEMH 531**

The STEMH ethics committee has granted approval of your proposal application 'Timing of Anterior Cruciate Ligament (ACL) reconstruction'. Approval is granted up to the end of project date* or for 5 years from the date of this letter, whichever is the longer.

It is your responsibility to ensure that:

- the project is carried out in line with the information provided in the forms you have submitted
- you regularly re-consider the ethical issues that may be raised in generating and analysing your data
- any proposed amendments/changes to the project are raised with, and approved, by Committee
- you notify roffice@uclan.ac.uk if the end date changes or the project does not start
- serious adverse events that occur from the project are reported to Committee
- a closure report is submitted to complete the ethics governance procedures (Existing paperwork can be used for this purposes e.g. funder's end of grant report; abstract for student award or NRES final report. If none of these are available use e-Ethics Closure Report Proforma).

Yours sincerely,

Kevin Butt

Vice Chair

STEMH Ethics Committee

* for research degree students this will be the final lapse date

NB - Ethical approval is contingent on any health and safety checklists having been completed, and necessary approvals as a result of gained.

e. Revised questionnaire for pilot study

QUESTIONNAIRE

Vignette 1: An 18-year-old male had a contact knee injury while playing football. Knee swelling developed immediately and he could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other meniscal, chondral or ligamentous injury. He was then referred to you for assessment and you see him a few days later. He is an amateur football player and he wants to continue playing regular football at least at an amateur level. He is a student with no medical problems and he is fit for anaesthesia.

1. Would you recommend ACL reconstruction surgery for this patient? Yes/No
2. If yes, at what time-frame (in weeks) would you recommend having the ACL reconstruction surgery?
3. What are the important factors which would influence your decision in this patient?
4. What would you recommend if this patient was a professional footballer?
5. What would you recommend if the MRI showed a potentially repairable meniscal tear?

Vignette 2: A 24-year-old male had a contact knee injury while playing football. Knee swelling developed immediately and he could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other meniscal, chondral or ligamentous injury. He was then referred to you for assessment and you see him a few days later. Past medical history is insignificant and he is fit for anaesthesia. He is an amateur football player and he wants to continue playing regular football.

1. Would you recommend ACL reconstruction surgery for this patient? Yes/No
2. If yes, at what time-frame in weeks would you recommend having the ACL reconstruction surgery?
3. What are the important factors which would influence your decision in this patient?
4. What would you recommend if this patient was a professional footballer?
5. What would you recommend if the MRI showed a lateral meniscal tear?

Vignette 3: A 39-year-old male had a non-contact knee injury while running. Knee swelling developed immediately and he could not walk after the injury. MRI performed the next day confirmed an ACL rupture with no other meniscal, chondral or ligamentous injury. He was then referred to you for assessment and you see him a few days later. He is doing a heavy manual job with lots of kneeling and is doing low demand sports (like running). Past medical history is insignificant and he is fit for anesthesia.

1. Would you recommend ACL reconstruction surgery for this patient? Yes/No
2. If yes, at what time-frame in weeks would you recommend having the ACL reconstruction surgery?
3. What are the important factors which would influence your decision in this patient?
4. What would you recommend if this patient was an office worker?
5. What would you recommend if MRI showed a lateral meniscal tear?

Vignette 4: A 49-year-old female had a non-contact knee injury at work after falling. Her knee became swollen immediately. She could not walk after the injury and she could not go to work. MRI performed the next day showed an ACL rupture with no other meniscal, chondral or ligamentous injury. She is referred to you for assessment and you see her a few days later. She is an office worker (secretary) doing no sports. She has no medical problems and she is fit for anaesthesia.

1. Would you recommend ACL reconstruction surgery for this patient? Yes/No
2. If yes, at what time-frame in weeks would you recommend having the ACL reconstruction surgery?
3. What are the important factors which would influence your decision in this patient?
4. What would you recommend if this patient was older (mid-50s)?
5. What would you recommend if MRI showed early signs of osteoarthritis?

Question 5. How would you evaluate the questions following the case-vignettes?
Options: Well stated and understandable – Ambiguous – Not well stated and not understandable – Other (please specify)

Question 6. What are your qualifications (academic or non-academic)?

Question 7. How many years of experience of assessing and referring or treating ACL injuries do you have?

Question 8. Approximately how many ACL reconstructions do you perform/assist per year?

f. Information sheet for pilot study (web survey)

Participant Information Sheet

Study title: Timing of Anterior Cruciate Ligament (ACL) Reconstruction

Dear participant:

My name is Apostolos Prodromidis and I am a graduate student at the University of Central Lancashire. For my thesis, I am examining the relation of timing of ACL reconstruction with clinical outcomes (meniscal tears and chondral injuries) and patient reported outcomes. Because you are an expert on ACL reconstruction, I am inviting you to participate in this research study by completing the attached survey. I am approaching about 20 surgeons.

I have performed a systematic review on timing of ACL reconstruction. We are performing a vignette-based pilot survey to develop a vignette-based questionnaire tool on what and how surgeons decide for timing of ACL surgery in different patients in clinical practice and if this is consistent with evidence in literature. I would be grateful if you would like to participate in this pilot study. Your answers and feedback is really important.

What will my participation involve? This project involves completing a few questions on 4 different vignettes (cases) regarding your decision for treating each patient-vignette.

How long will participation take? The questionnaire will require 5-10 minutes to complete.

The questionnaire is anonymised. In order to ensure this, please do not include your name or other information that would identify you personally. No personal data will be stored.
If you choose to participate in this survey, please answer all questions as honestly as possible. Your participation is voluntary. By completing this survey, you are consenting to take part in the study. Since this is an anonymous survey, your data cannot be withdrawn once it is collected.

Thank you for taking the time to assist me in my educational endeavours. The anonymous data collected with this survey will provide useful information on what and how surgeons decide for timing of ACL surgery and will help to develop a vignette-based questionnaire tool upon timing

of ACL reconstruction and selection of patients. It will be used for my thesis, subsequent publications in peer reviewed journals and presentations.

If you would like additional information on this study or have questions, please feel free to contact me or my supervisors. 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.

Sincerely.

Dr. Apostolos Prodromidis
aprodromidis@uclan.ac.uk
Research MSc student
School of Medicine, University of Central Lancashire, UK
Orthopaedic Registrar, (South Tyneside NHS Trust)

Supervisors:
Prof Waqar Ahmed
WAhmed4@uclan.ac.uk
School of Medicine, College of Clinical and Biomedical Sciences
University of Central Lancashire, UK.

Mr Charalambos C. Charalambous
Ccharalambous@uclan.ac.uk
Honorary Visiting Professor at University of Central Lancashire
Consultant Orthopaedic Surgeon at Blackpool Victoria Hospital, UK

g. Email invitation text for pilot study

“Dear participant:
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Sincerely.

Dr. Apostolos Prodromidis
aprodromidis@uclan.ac.uk
Research MSc student
School of Medicine, University of Central Lancashire, UK
Orthopaedic Registrar, (South Tyneside NHS Trust)

Supervisors:
Prof Waqar Ahmed
WAhmed4@uclan.ac.uk
School of Medicine, College of Clinical and Biomedical Sciences
University of Central Lancashire, UK.

Mr Charalambos C. Charalambous
Ccharalambous@uclan.ac.uk
Honorary Visiting Professor at University of Central Lancashire
Consultant Orthopaedic Surgeon at Blackpool Victoria Hospital, UK."