Pre-surgery exercise-conditioning (P–SEC) in patients waiting for Total Knee Arthroplasty

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Queen Margaret University
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Declaration

I declare that this thesis was composed by myself and that the work contained therein is my own, except where explicitly stated otherwise in the text.

(Anna Maria Risso)
This thesis is dedicated to all the little girls in the world. No dream is too big to achieve! Never stop dreaming, never stop believing.
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“Investing in human capital to create more opportunities and promote the well-being of society”.

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Abstract

Using a randomised controlled trial to assess efficacy, a ‘novel’ pre-surgical exercise-conditioning (P–SEC) programme was investigated in this thesis addressing the knowledge gap in the literature regarding pre-surgical conditioning for improving objective measures of physical performance (neuromuscular and sensorimotor) and self-reported outcomes in patients waiting to undergo total knee arthroplasty (TKA) surgery. Cross-education (CE) effects measured in the untrained limb following the P–SEC intervention were also investigated. A single-centre, assessor-blinded randomised controlled study was conducted over an 11-month period. Forty-six participants waiting to undergo TKA surgery were enrolled and randomised into one of three groups (two intervention groups (P–SEC_{IPSI} (n = 15) and P–SEC_{CONTRA} (n = 17), in which the knee extensors of the leg awaiting surgery and the non-surgical leg, respectively, were trained) and one control group (n = 14), which received usual care practice of no training). Seventeen participants (out of 46) had been lost-to-follow-up. Participants underwent evaluation at four pre-surgery assessments: ≈12 weeks (T1), 2 weeks (T2), 1 week (T3) pre-surgery, week of surgery (T4) and at 6 weeks post surgery (T5). Objective measures of neuromuscular (electromechanical delay (EMD), rate of force development (RFD), peak force (PF)) and sensorimotor (force error (FE)) performance outcomes revealed statistically significant group x time x leg interactions with moderate to large gains (12% – 37%; ES = 2.0; p < 0.05) in the respective outcomes. No statistically significant (p > 0.05) group x time interactions were found for the patient reported outcomes as measured by the Oxford Knee Score (OKS), Knee injury and Osteoarthritis Score (KOOS), 36-Item Short Form Health Survey (SF-36v2™), Pain Self Efficacy Questionnaire (PSEQ), Performance Profile (PP) and International Physical Activity Questionnaire (IPAQ). Small but approaching moderate (4% – 11%; ES = 0.1 – 0.4; p < 0.05) CE-related improvements in the physical performance outcomes (EMD, RFD, PF and FE) were also reported in the untrained limb.

This thesis provides evidence that a novel approach to P–SEC which elicited statistically significant improvements in physical performance outcomes (neuromuscular and sensorimotor) in patients waiting for TKA surgery compared to a usual care control group. Furthermore, this study is the first of its kind to evaluate and confirm the presence of CE in this cohort of patients. The novel characteristics of P–SEC highlight the importance for revisiting contemporary pre-surgical conditioning. Limitations to the study included sample size attrition, with the potential for bias and inflated rates of Type II error. The thesis presents possible directions into the use of this ‘novel’ intervention in clinical practices and in other joint related conditions.

Keywords: arthroplasty, sensorimotor, knee osteoarthritis, pre-surgical, neuromuscular, cross-education

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“Above all, don’t fear difficult moments. The best comes from them.”
Rita Levi-Montalcini (Neurobiologist)
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8.1 The figure above is a visual representation of the different aspects underpinning the hypotheses of the thesis and their respective relationships. The dashed lines represent the relationships that were unknown or not clearly defined in the literature prior at the start of the thesis. The solid lines represent the clearly-defined relationships that are reported within the literature and that have been discussed within the literature review (Chapter 2).
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- EMD - electromechanical delay; RF - rectus femoris muscle; VL - vastus lateralis muscle; P–SEC\textsubscript{IPSI} - surgical leg; P–SEC\textsubscript{CONTRA} - non-surgical leg; RFD - rate of force development; PF - peak force; FE - force error.

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Publications arising from or related to this thesis

Journal publications:


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List of Abbreviations

1 RM – One Repetition Maximum

ACL – Anterior cruciate ligament
ACLr – Anterior cruciate ligament reconstruction
ACSM – American College of Sports Medicine
ADL – Activities of Daily Living
AMI – Arthrogenic Muscle Inhibition
ANOVA – Analysis of Variance

BMI – Body Mass Index

CE – Cross-Education
CONSORT – Consolidated Standards of Reporting Trials
CG – Control Group
C.I. – Chief investigator
CI – Confidence Interval
COP – Centre of Pressure
CT – Clinical Trial

EMD – Electromechanical Delay
EMD$_{RF}$ – Electromechanical Delay in Rectus Femoris muscle
EMD$_{VL}$ – Electromechanical Delay in Vastus Lateralis muscle
EMG – Electromyography
EQ-5D – EuroQoL Five Dimensions Questionnaire
ES – Effect Size

FE – Force Error

IPAQ – International Physical Activity Questionnaire
IAP – Intra-Articular Pressure
IASP – International Association for the Study of Pain
ICC – Interclass Correlation Coefficient
IQR – Interquartile Range

KOOS – The Knee Injury and Osteoarthritis Score
KSS – Knee Society Score

M – Motor
MCID – Minimal Clinically Important Difference
MDC – Minimal Detectable Change
MET – Metabolic Equivalent
MC – Mental Component
MN – Motor Neuron
MRK™ – Medial Rotation Knee™
MU – Motor Unit

N – Newton
N/s – Newton per second
NHP – Nottingham Health Profile
NJR – National Joint Registry
Nm – Newton-Meter
NHS – National Health Service
NS – Non-Significant

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OA – Osteoarthritis
OKS – Oxford Knee Score
OSI – Overall Stability Index

PA – Physical Activity
PC – Physical Component
PEDro – Physiotherapy Evidence Database score
PF – Peak Force
PP – Performance Profile
PRISMA – Preferred Reporting of Systematic Reviews and Meta-Analysis
PROs – Patient-Reported Outcomes
PSEQ – Pain Self Efficacy Questionnaire
P–SEC – Pre-Surgery Exercise-Conditioning
P–SECIPSI – Pre-Surgery Exercise-Conditioning Ipsilateral
P–SECIPSI-CE – Pre-Surgery Exercise-Conditioning Ipsilateral Cross-Education (Cross-education in the Surgical leg)
P–SECCONTRA – Pre-Surgery Exercise-Conditioning Contralateral
P–SECCONTRA-CE – Pre-Surgery Exercise-Conditioning Contralateral Cross-Education (Cross-education in the Non-Surgical leg)
PT – Peak Torque

QoL – Quality of Life

RCT – Randomised Controlled Trial
RFD – Rate of Force Development
RJAH NHS Trust – Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Trust Foundation
ROM – Range of Motion
RPE – Rate of Perceived Exertion
RTD – Rate of Torque Development
SEC – Series Elastic Component
SEM – Standard Error of the Mean
SIP – Sickness Impact Profile
SM – Sensorimotor
SF – Short Form
SF-12 – 12-Item Short Form Health Survey
SF-36v2™ – 36-Item Short Form Health Questionnaire version 2
SPSS – Statistical Package for the Social Sciences

TKA – Total Knee Arthroplasty

UK – United Kingdom

VAS – Visual Analogue Scale

WMD – Weighted Mean Difference
WOMAC – The Western Ontario and McMaster Universities Osteoarthritis Index
Chapter 1

Introduction

Total knee arthroplasty surgery (TKA) is one of the most common and successful joint surgeries in the UK with figures of TKA surgeries reaching over 100,000 in a year (National Joint Registry Annual Report 14th Edition 2018). TKA is the treatment of choice for patients suffering from severe pain and functional limitations caused by osteoarthritis (OA) of the knee joint’s surfaces (Magee et al. 2015). Rehabilitation following surgery is essential for recovery and with TKA this is crucial in regaining movement, function and joint stability. Current rehabilitation focus is primarily on post-surgery rehabilitation with the aim of increasing range of motion (ROM) and strength for a quick return to functional independence. Although the majority of the patients report decreased pain and improved function after surgery (Anderson et al. 1996), research has shown that patients still continue to experience reduced capacities in balance capabilities up to a year following TKA surgery (Silva et al. 2003, Moutzouri et al. 2017). A decrease in balance capabilities is often measured as a decline in neuromuscular and sensorimotor responses that are required for quick knee joint reactions and overall stability (Piva et al. 2010, Rätsepsoo et al. 2011) and is often also present in both knees regardless of which one is undergoing surgery (Berth et al. 2002). A deficit in an individual’s knee joint stability, together with impaired muscular strength that is often found in these patients, can contribute to injury (Lephart et al. 1997) and a greater risk of falls (Swinkels et al. 2008, Bade et al. 2010, Rätsepsoo et al. 2011). The National Institute for Health and Clinical Excellence (NICE) considers balance impairments and muscle weakness as the most prevalent risk factors to falls that in turn have been linked
to an increased risk of morbidity and mortality in the older adult population. Therefore, it is of prime importance that these deficits in joint stability are addressed early on in the rehabilitation process. However, time-constraints within the health-care system, whose primary focus in rehabilitation is to decrease pain and improve general function following TKA surgery, has sometimes been to the detriment of other aspects of rehabilitation. Pre-habilitation (pre-surgery rehabilitation) involving physical exercise has been an area of increased research interest in more recent years and uses the period when patients are waiting for surgery and often do not undergo any specific conditioning. Pre-surgery rehabilitation aims to improve rehabilitation outcomes and potentiate patients’ early and later rehabilitation progress and status following knee surgery (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015).

A. Pre-surgery exercise-conditioning

Utilising pre-habilitation to potentially improve recovery times following surgery, may seem an obvious and easy choice to many but uncertainties remain regarding the benefits of pre-surgery exercise programmes and as a result the benefits may not always outweigh the additional ‘costs’. The patterns of patients’ adaptations to the generic exercise stimuli used within pre-surgery studies, has not shown the gains that had been expected by physiological dose-response relationships (Wang et al. 2016, Chesham & Shanmugam 2017), and ultimately questioned the efficacy of using pre-habilitation for effective gains in long-term outcomes. Furthermore, recent systematic reviews (Wang et al. 2016, Chesham & Shanmugam 2017) suggested that although evidence does exist supporting the use of pre-habilitation in improving early post-operative pain and function, the effects are far too small and short-termed to be considered clinically important at this stage, and further research is required. Nevertheless, the concept of achieving early gains to conditioning status that might potentiate patients’ later rehabilitation processes and status, remains attractive in sports performance and rehabilitation (Crowe & Henderson 2003, Huber et al. 2015, Calatayud et al. 2017). Therefore, there is currently a gap in the literature regarding the efficacy of a pre-surgical programme that addresses these deficiencies in performance capacities (neuromuscular and sensorimotor function) in patients electing to undergo TKA surgery but without overly
increasing the already considerable rehabilitation time and costs.

B. Conditioning programmes: Sensorimotor training

Conditioning for enhanced sensorimotor performance has been consistently endorsed in the sports medicine (Mandelbaum et al. 2005, Hübscher et al. 2010) and clinical literature (Granacher et al. 2006, Tsao & Hodges 2007) for its causal relationship to reduced likelihood of injury and improved physical function. Parameters for sensorimotor training (SMT), where the combined sensory and motor input is included during the intervention, are much less reported in the literature. On the other hand, enhancing motor performance by means of exercise that resist the effects of gravity or externally-applied loading to a joint system, has established physiological underpinnings as it aims to improve motor (strength) performance and indirectly affects sensorimotor responses (Gür et al. 2002, Vikne et al. 2006, Moran & Wallace 2007). However, these conditioning programmes still do not fully address the underlying issues of reduced capacities in balance capabilities. Clinically, the challenge has been to formulate a suitably pragmatic programme of conditioning that will accommodate the time- and cost-pressures (shorter without an increase in equipment demand) associated with contemporary care practice while simultaneously offering efficacy when delivered prior to surgery as a pre-habilitative intervention. Rehabilitative and prophylactic conditioning programmes used in current studies for enhanced neuromuscular and sensorimotor performance, have typically been delivered in a duration of 6 –12 weeks (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015, Calatayud et al. 2017), which is also similar to strength based conditioning programmes for improving muscular performance (Suchomel et al. 2018). This has commanded a substantive logistical burden to elicit expected gains and formulate a suitable programme of conditioning in the pre-surgery phase.

C. Novel approach to conditioning

A novel formulation of conditioning that could condense the pattern of delivery of physiologically-effective, dose-related stimuli, while simultaneously maintaining the greatest proportion of potential gains in performance, would offer advantages to patients and
clinicians for logistical versatility with which a package of conditioning might be de-

livered. This would be especially important within the relatively short period of time
(11 – 12 weeks) between the patients electing for surgery and the surgical procedure,
if pre-habilitation were to be incorporated effectively within care pathways. Recent
randomised controlled studies (RCTs), where the delivery of contemporary rehabilita-
tive conditioning has been modified to incorporate physiological principles, have shown
pronounced gains in functional and neuromuscular performance capabilities (Bailey
et al. 2014, Moutzouri 2018), but not necessarily under other conditions (Wang et al.
2016, Chesham & Shanmugam 2017), despite established conceptual underpinnings
(Gür et al. 2002, Vikne et al. 2006, Moran & Wallace 2007). Furthermore, recent pilot
work (Peer & Gleeson 2018) has shown potential and micro-cyclical management of
the mode of exercise-conditioning is undertaken. Together with careful patterning of
exercise intensity and work/recovery ratios and progression of increasing physiological
stimuli for adaptation, it is possible to deliver gains in neuromuscular performance
within a programme lasting 2 – 3 weeks (Peer & Gleeson 2018). These gains would
match 70% of the effects expected from longer programmes (Peer & Gleeson 2018).
Additional adaptations to this intervention model would have to be taken into consid-
eration in order to counteract arthrogenic and autogenic sources of inhibition (AMI)
associated with long-term disease conditions such as OA (Rice & McNair 2010, Rice
et al. 2014) that limit neuromuscular and sensorimotor performance and condition-
ing gains by the intrusion of nociceptive stimuli, such as an increase in intra-articular
joint pressure (Palmieri et al. 2005, Palmieri-Smith et al. 2007). Further, inflammatory
episodes associated with OA and severe pain may preclude routine conditioning. Under
such circumstances, the capability to condition the contralateral leg and to reasonably
expect meaningful gains in the affected or ipsilateral leg would be attractive clinically.
Therefore, a ‘novel’ conditioning programme would also aim to utilise cross-education
effects for addressing the reduced physical capabilities that is often present in both legs
of patients undergoing TKA surgery (Berth et al. 2002, Palmieri-Smith et al. 2007,
Maffiuletti et al. 2010).

Considering the prevalence of knee OA, the likelihood of increasing numbers over the
coming years, overall costs and burden on the NHS (National Joint Registry Annual Report 14th Edition 2018), research within the field of arthritis is of prime importance. Therefore, the purpose of this thesis has been to address some of the questions whether a novel formulation of pre-surgical conditioning is capable of counteracting diminished capabilities for functional and physical performance that has routinely been observed in patients electing TKA surgery. Information from this thesis will help identify whether a ‘novel’ approach to conditioning can achieve significant improvements in neuromuscular and sensorimotor performance capabilities of patients electing to undergo TKA. Overall the aim of this research would be to critically evaluate the literature to establish and confirm the gaps in evidence that had been alluded to in this introduction, especially in relation to an appreciation of the optimal characteristics of exercise-based sensorimotor training, and use the findings to wherever possible, inform or refine the development of a pre-surgical exercise-conditioning programme (P–SEC). Ultimately, the thesis’ aim will be to undertake a controlled investigation of the efficacy of a ‘novel’ formulation of the P–SEC programme on objectively measured and patient-perceived performance capabilities in patients waiting to undergo TKA surgery. Other important aims will be to investigate supplementary strategies for using the P–SEC such as cross-education (CE) effects, and whether any potential gains in physical performance capabilities calibrate with patients’ perceptions.
Chapter 2

Literature review

The scope of this chapter is to critically evaluate and discuss the literature pertaining to the rationale behind the research reported in this thesis. This chapter also introduces and describes the main key terms used in this study. Towards the end of the chapter, a short summary can be found followed by the leading research questions and hypotheses of the study.

This chapter includes the description of the following main key terms and the critical evaluation of the following literature:

- Definition of total knee arthroplasty (TKA) surgery and its epidemiology in the UK and Scotland in particular (refer to Section 2.1.1);

- Definition of terms including the sensorimotor system and the knee joint system (refer to Section 2.1);

- An overview of the physiological mechanisms of neuromuscular and sensorimotor performance in the knee affected by end stage OA and the influence of exercise on these respective performance capabilities (refer to Sections 2.2 and 2.3);

- Physiological basis behind the P-SEC protocol (refer to Section 2.4);

- An overview on the use of neuromuscular and sensorimotor outcome measures, their psychometric properties and use within this clinical population (refer to Section 2.5);
• A review of patient reported outcome measurements of pain and physical performance capabilities used in TKA patients (refer to Section 2.6);

• A review of the evidence and the role of cross-education (CE) in rehabilitation (refer to Section 2.7);

• Aims, objectives, research questions and hypotheses (refer to Sections 2.9, 2.10 and 2.11).

2.1 Definition of terms

2.1.1 Epidemiology

Osteoarthritis (OA) is one of the most common musculoskeletal problems and is experienced by 29% (17.8 million) of UK’s population, with knee OA (16.6%) ranking the highest (Arthritis research UK 2018) (Figure 2.1). In Scotland 15.6% of the population suffer from knee OA of which a staggering > 100,000 undergo knee replacement surgery each year (Arthritis research UK 2018, National Joint Registry Annual Report 14th Edition 2018, Scottish Arthroplasty Project 2018). The likelihood of this number increasing over the coming years is thought to be fairly high due to the ageing population. The increase in number of patients requiring surgery means further increased demands on the national health service (NHS), which is estimated to reach £118.6 billion over the next ten years (Arthritis research UK 2018). Furthermore, an increase in patients requiring surgery translates to an increase in surgery waiting time due to limited resources. Waiting times for hip and knee joint replacement surgeries are approximately \( \approx 15 \text{ weeks} \) [105.4 days] (UK, based on 2015 values) (Arthritis research UK 2018). Longer waiting times may further increase patients’ already existing pain and functional disability that may impact recovery following surgery (Garbuz et al. 2006, Desmeules et al. 2010). Therefore, measures for decreasing waiting times is of current importance within the NHS and pre-surgery rehabilitative programmes have been one of the main research interests in rehabilitation for utilising a period of time leading up to surgery with the aim of improving patients pre-surgical state for early post-surgery recovery times and a decrease length of stay (LOS).
2.1.2 Total Knee Arthroplasty (TKA) surgery

Total knee arthroplasty (TKA), also commonly referred to as total knee reconstruction (TKR) or total knee replacement surgery, is one of the two most common joint surgeries performed in the UK (National Joint Registry Annual Report 14th Edition 2018). The surgery involves the replacement of two or more articular components of the knee joint that have been diseased with severe OA (Magee et al. 2015, National Joint Registry Annual Report 14th Edition 2018) as shown in Figure 2.2. These articular components are replaced with a tibial and femoral artificial insert that are made out of metal alloys and polyethylene inserts (National Joint Registry Annual Report 14th Edition 2018). Monobloc all-polyethylene tibial components have become the favoured and reported implant of choice (National Joint Registry Annual Report 14th Edition 2018).
In fact, all the participants who took part in the thesis’ study have been fitted with an MRM implant (Figure 2.3). Once the diseased tissue is replaced by the implant, symmetry, stability and full mobilisation is restored.

Figure 2.3: MRM implant as shown in the official leaflet on their website (Medial Rotation Knee orthopaedic website 2018).

Despite the overall surgery’s success, research has shown that patients undergoing TKA still continue to experience reduced capacities in neuromuscular and sensorimotor responses which are required for quick knee joint reactions, stability and proprioception, up a year following TKA surgery (Silva et al. 2003, Moutzouri et al. 2017). A deficit in an individual’s knee joint proprioception (synonymously referred to as a deficit in sensorimotor performance), together with impaired strength, can lead to reduced functional balance capabilities and movement control (Piva et al. 2010, Rätsepsoo et al. 2011) and can also contribute to injury (Leiphart et al. 1997) and a greater risk of falls (Swinkels et al. 2008, Bade et al. 2010, Rätsepsoo et al. 2011).
2.1.3 The Sensorimotor system (SMS)

The sensorimotor system (SMS) is a complex system combining the sensory and the motor control of the body’s joint complex. Schematically shown in Figure 2.4, the SMS combines a complex array of processes between the sensory and the motor control systems. Figure 2.4 also describes the mechanisms involved from the acquisition of the sensory (afferent) stimulus to the translation of the stimulus into a neural signal and ultimately the motor (efferent) response at the muscular tissue level (Lephart & Fu 2000). The transmission process between the afferent input and the efferent motor output is executed by various structures in the body that collectively fall under the sensorimotor system (Lephart & Fu 2000, Reimann 2002a,b) (Figure 2.4). The main peripheral structures that make up the sensorimotor system are composed of joint, skin and muscular receptors amongst which are the golgi tendon organs (GTOs), pacinian corpuscles (PC) and the muscle spindles (MS) (Lephart & Fu 2000). The receiving end of the input from the periphery arrives in the posterior horn of spinal cord (SC), specifically on Lamina V where signals are then transmitted to ascending (spino-cerebellar) pathways to the central nervous system in the brain (Lephart & Fu 2000, Solomonow & Krogsgaard 2001). Following processing, the efferent result then travels back down through the SC via the descending (cortico-spinal) pathways onto the ventral horn of the SC, where a motor-neurone (MN) synapse occurs resulting in the final motor action. Although the afferent signal is received and processed in the motor cortex, inputs from the associated areas such as the basal ganglia, cerebellum and visual cortex alter the resultant efferent output. A more direct output from the SC can also occur through a simple process such as a reflex action. During this reaction, a stimulation through the tendon hammer is received from the receptors in the tendon and joint’s structure. This impulse travels on directly to the SC where synapses occur, causing an immediate reaction of an efferent output on to the motor neurones resulting in a jerk reaction. Synaptic connections at the SC level are known to occur at different cord segments simultaneously, to allow for multiple muscular input crossing the joint (Solomonow & Krogsgaard 2001). Simply put, the role of the SM system is to incorporate all the afferent, efferent and central integration processing components that are involved with
maintaining functional joint stability.

Figure 2.4: A graphic representation of the sensorimotor system and the major intricate components that make up the system from stimulation to execution. The main areas in the brain for processing and execution of movement are the supplementary motor area (SMA), pre-motor cortex (PMC), motor cortex (M1) along with the associate areas for vision (visual cortex), co-ordination and control (basal ganglia (BG) and the cerebellum). The brainstem is the main connection between the periphery and the central processing areas that include the ascending and descending tracts.

2.1.4 Sensorimotor control of the knee joint’s stability

Early studies, have described the knee joint stability to originate solely from the anatomical structures of the joint, such as the articular boney surfaces and the ligamentous tissue surrounding the joint (Hurley et al. 1997, Hurley & Scott 1998). Over the years further research into muscular patterns and force-displacement relationships
during joint stability have allowed for a more broader function of the role of the muscular tissue on joint’ stability (Solomonow & Krogsgaard 2001, Reimann 2002a). Muscular tissue around the joint structure has since been described as the dynamic control of joint stability that is results from muscular contraction patterns (Lephart & Fu 2000, Solomonow & Krogsgaard 2001, Reimann 2002a, Clark & Lephart 2015). These muscular patterns are regulated by motor-neurones (α and γ) (Lephart & Fu 2000, Solomonow & Krogsgaard 2001, Reimann 2002a) that are found and govern the extrafusal and intrafusal muscle fibres of the involved musculature around the joint (Reimann 2002a). Research has shown that changes in muscle tension during muscular contractions is stimulated by the activity of these MNs (Lephart & Fu 2000, Reimann 2002a,b), which on the other hand are also regulated by stimulation through muscle and joint receptors that affect the efferent output (Clark & Lephart 2015, Lephart & Fu 2000). This allows for synergistic muscle contractions and the production of dynamic joint stability (Lephart & Fu 2000). Several early and more recent studies have confirmed the presence of this synergistic muscle co-activation (Solomonow et al. 1987, Baratta et al. 1988, Solomonow & Krogsgaard 2001) and its role is simply to decrease joint laxity when force is applied by producing the muscular contractions and activity required as quickly and efficiently as possible. This capability for stability and quick muscular reactions is required for example, during everyday functions such as when a person comes to a quick halt at the end of the pavement in preparation for crossing a road. An even quicker reaction is required when a person standing on a moving bus reacts to a sudden break-and-halt action. All these movements require a symphony of co-ordinated afferent inputs and efferent outputs to provide what is simply known to us as joint stability. It is important to note, the complexity of the SM system that allows for a multitude of reactions from various structures to provide the function the joint requires.

2.2 Changes in neuromuscular and sensorimotor performance in the knee with Osteoarthritis (OA)

Although OA essentially affects the joint articular surfaces, it has been established that altered muscular activation (neuromuscular), strength and sensorimotor function occurs
in the knee joints of patients affected by OA (Hurley et al. 1997, Hurley & Scott 1998, Rice & McNair 2010, Pietrosimone et al. 2011). When compared to healthy controls, patients suffering from knee OA produced statistically significant ($p < 0.001$) decreases in quadriceps strength and activation (100N less force and 20% less activation) and sensorimotor function (decreased JPS by $1.28^\circ$ - proprioceptive acuity) (Hurley et al. 1997). Changes in neuromuscular and sensorimotor outcomes have been linked to changes in physiological mechanisms that are altered in patients suffering from an ongoing inflammatory condition such as OA (Palmieri-Smith et al. 2007, Hart et al. 2010, Pietrosimone et al. 2011, Rice & McNair 2010). The resultant inflammation from articular damage results in an increase in pain and swelling that contribute to decrease joint stability and physical performance outcomes due to an ongoing inhibitory mechanism referred to as arthrogenic muscle inhibition (AMI) (Rice & McNair 2010, Pietrosimone et al. 2011, Calatayud et al. 2017). Studies have shown that AMI is a protective ongoing reflex mechanism that occurs following joint pathology or injury (Palmieri et al. 2004, 2005, Hart et al. 2010) and is very common in patients suffering from knee OA. In the presence of AMI, full voluntary muscle activation is inhibited due to a decrease in $\alpha$ MN excitability influenced by peripheral (reflexive) (Palmieri et al. 2004, 2005) and central (cortical) (Héroux & Tremblay 2006, Rice et al. 2014) inputs. Pain and joint effusion are generally but not always (Hurley et al. 1997, Hurley & Scott 1998, Hart et al. 2010, Rice et al. 2014) the main cause heading the ongoing inhibitory MN activity (Hurley et al. 1997, Hurley & Scott 1998). As described in Section 2.1.4 above, MN activity influences dynamic joint stability, therefore a decrease in MN activity will result in an altered (decline) neuromuscular (motor) and sensorimotor performance as measured by the respective outcomes. Furthermore, joint effusion (swelling) has been closely linked to altered gait patterns (Torry et al. 2000) that if prolonged leads to abnormal peripheral joint adaptations and persistent neuromuscular and sensorimotor inhibition. This persistent inhibition has been reported to last up to a year following TKA surgery (Palmieri-Smith et al. 2007). Therefore, if not addressed, it can contribute to injury (Lephart et al. 1997), greater risk of falls (Swinkels et al. 2008, Bade et al. 2010, Rätsepsoo et al. 2011) and overall lack of confidence in physical performance capabilities that has been linked to an increased risk of disability (Hurley et al. 1997, Hurley &
Scott 1998). Current literature suggests that an understanding of the potential long term effects of AMI and the mechanisms behind it could help target the appropriate rehabilitation, prevent further joint injuries and subsequent degeneration (Hart et al. 2010).

2.3 The influence of exercise for improving neuromuscular and sensorimotor performance capabilities

Conditioning programmes that have looked at improving aspects of neuromuscular and sensorimotor outcomes have been primarily and more commonly aimed at injury prevention in sports (Zech et al. 2009, 2010, Hübscher et al. 2010, Steib et al. 2017, Bonato et al. 2017) but have also been included in rehabilitation (Pohl et al. 2015, Moutzouri et al. 2016, Peer & Gleson 2018, Moutzouri 2018) and less often in pre-surgical programmes (Bitterli et al. 2011, Calatayud et al. 2017). The literature reports a large variation amongst the selected modalities used for improving aspects of neuromuscular and sensorimotor performance capabilities including: exercise (refer to Chapter 3), exergaming (Tarakci et al. 2013, Fu et al. 2015), neuromuscular electrical stimulation (Benavent-Caballer et al. 2014), or group classes such as pilates and Thai Chi (Chen et al. 2011, Liu et al. 2012). Conditioning programmes where exercise was used to elicit improvements in both physical performance outcomes have been amongst the most common due to its minimal use of equipment and ease of application (Hurley & Scott 1998, Sekir & Gur 2005, McKeon et al. 2008, Bonacci et al. 2011, Gusi et al. 2012, Huang et al. 2014, Bennell et al. 2014, Cruz-Diaz et al. 2015, Avelar et al. 2016, Cuğ & Wikstrom 2016, Shih et al. 2018). Common types of conditioning used to elicit neuromuscular and sensorimotor performance (refer to Chapter 3) include motor-based (strength training) conditioning programmes (Mandelbaum et al. 2005, Granacher et al. 2006, Tsao & Hodges 2007, Hübscher et al. 2010, Suchomel et al. 2018). Their focus has been on the physiological specificity of using exercise to elicit increased morphological size. Other conditioning programmes also include a more varied type of conditioning stimuli for improving neuromuscular performance with emphasis on speed-of-movement (time-limited movements) such as those experienced during ballistic, plyometric and related
challenges to motor performance (Suchomel et al. 2018). The latter type of conditioning is often referred to as sensorimotor training (SMT), a training method first developed for chronic musculoskeletal conditions in the mid 1900s by Dr. Vladimir Janda (Page 2006, Page & Frank 2007). The concept behind it lies in creating an increase in afferent input through different joints in the body. It is believed that increasing this afferent input will attain homeostasis (Reimann 2002a) within the joint structures involved, that have become physiologically “unstable” due to an underlying condition such as: swelling, injury and muscle dysfunction (Page & Frank 2007). The altered function is believed to occur within the complex sensorimotor system. This often results in altered proprioception, muscle inhibition manifesting itself as altered postural stability, kine-matics and kinetics during functional movements (Clark & Lephart 2015). Research on SMT is popular but the optimal parameters for clinical efficacy of SMT is currently not known and the systematic review in Chapter 3 has been undertaken to answer this gap in the literature.

2.4 Pre-surgery training and the P–SEC protocol

Moderate evidence exists on the effectiveness of exercise in the management of OA (Jessep et al. 2009, Fransen et al. 2015) with recent reviews and studies indicating that many rehabilitative conditioning programmes for OA’ treatment (Moutzouri et al. 2016, 2017, Peer et al. 2017) or for pre-habilitation prior to TKA (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015) lack robust physiological training principles. The latter, pre-habilitation (pre-surgery) is often a training intervention delivered to patients waiting to undergo TKA surgery with the aim of improving post-surgical outcomes (Ackerman & Bennell 2004, Peer et al. 2017). Studies have investigated the effects of pre-surgery exercise-based conditioning programmes (interventions) on neuromuscular and sensorimotor performance deficits, present in patients with chronic pain and inflammation such as those waiting to undergo TKA. Their aim has been to utilise a period of time pre-surgery, where little to no conditioning is being administered in NHS practices and improve patients’ physical performance.
outcomes (neuromuscular and sensorimotor function) (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015, Calatayud et al. 2017). By doing so, researchers endeavour to achieve an increase in post-surgical physical performance. However, the patterns of patients’ adaptations to the generic exercise stimuli used within these studies, has not shown the gains that had been expected in physical performance outcomes to be considered clinically effective, and ultimately questioned the efficacy of using pre-habilitation for effective gains in long-term outcomes (Gill & McBurney 2013, Silkman & McKeon 2012, Wang et al. 2016, Chesham & Shanmugam 2017).

A sensorimotor-focused (SM) type of conditioning, is often utilised in order to address the underlying impairments in physical function capabilities that lead to decreased joint stability and balance performance (deficits in neuromuscular and sensorimotor function) in people with OA (Silva et al. 2003, Piva et al. 2010, Rätsepsoo et al. 2011). Conditioning for enhanced neuromuscular and sensorimotor performance has been consistently endorsed in the field of sports-medicine (Mandelbaum et al. 2005, Zech et al. 2009, Hübscher et al. 2010) and clinical literature (Granacher et al. 2006, Tsao & Hodges 2007) for its causal relationship to reduce likelihood of injury and its capability to improve physical performance. A recent SR (Moutzouri et al. 2016) revealed that SM-focused exercise-programme offers an acceptable, safe, well-tolerated and targeted intervention to improve aspects neuromuscular and sensorimotor performance (such as balance) in patients undergoing TKA. However, despite these encouraging findings, the evidence used in the review is only based on six papers and overall is not sufficiently robust evidentially (moderate PEDro scoring 5-7) to be implemented and considered for use in clinical practice. Reasons for the latter included: small sample sizes, consistent lack of design sensitivity to compute and report sample size prior to data collection and unclear blinding procedures that ultimately lead to increased Type II error rates in the included studies (Moutzouri et al. 2016). Therefore, further research is required to identify the appropriate efficacious conditioning parameters for a SM-focused exercise-intervention in TKA. Furthermore, the studies included within this review (Moutzouri et al. 2016), looked at a SM-focused intervention delivered during the post-surgery phase, a period of time where a complex array of interactions
(e.g. physiological healing, post-surgery contemporary rehabilitation) may have also contributed to extra variability to the overall results.

Thus far, there have only been four studies that investigated the effects of a pre-surgical SM-focused intervention in patients undergoing TKA surgery (Gstoettner et al. 2011, Huber et al. 2015, Pohl et al. 2015, Calatayud et al. 2017). In all four studies, the SM-focused conditioning was aimed at improving aspects of neuromuscular and sensorimotor performance (such as balance). Significant within-group improvements for the selected performance outcome measures were reported within all four studies during the pre-surgery phase, however the SM-focused intervention was not always significantly preferred over the control (no conditioning) parameters especially post-operatively (Gstoettner et al. 2011, Huber et al. 2015, Pohl et al. 2015). Furthermore, the conditioning parameters for the delivery of the selected SM-focused pre-surgical intervention has more often commanded a long-duration and substantial sessional (6-12 weeks; 18-60 sessions) (Huber et al. 2015, Pohl et al. 2015, Calatayud et al. 2017) delivery, similar to previous generic pre-surgical studies (Silkman & McKeon 2012, Wang et al. 2016, Chesham & Shanmugam 2017), whose effects have not always been sufficiently effective and often too short-lived to be considered for use in clinical practices (Silkman & McKeon 2012, Wang et al. 2016, Chesham & Shanmugam 2017). Nevertheless, the concept of achieving early gains in conditioning status that might potentiate patients’ early\(^1\) and later rehabilitation processes and status, remains attractive to both the patient (Huber et al. 2015, Calatayud et al. 2017) and the NHS (Crowe & Henderson 2003).

The first gap identified within the literature, is the lack of appropriate and efficacious SM-focused conditioning parameters for use in clinical practice (Moutzouri et al. 2016). Therefore, the systematic review in Chapter 3 aims to identify the efficacy of using a sensorimotor-based exercise-conditioning (SMT) training programme and to characterise the physiological parameters for use in clinical practices. However, motor-\(^1\)By decreasing length of stay in early rehabilitation (Silkman & McKeon 2012, Calatayud et al. 2017)
based exercise interventions that resist the effects of gravity or an externally-applied loading to a joint system (strength based conditioning) has been well established in the literature for improving neuromuscular performance and indirectly affecting sensorimotor responses (Gür et al. 2002, Vikne et al. 2006, Moran & Wallace 2007). The challenge in a clinical environment has been to formulate a suitably pragmatic programme of conditioning that would accommodate the time- and cost-pressures associated with contemporary care practices while simultaneously offering efficacy when delivered prior to surgery as a pre-habilitative intervention. Both pre-surgical and motor-based conditioning programmes of conditioning have typically been delivered over a period of 6 – 12 weeks for enhanced neuromuscular and sensorimotor performance (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015, Calatayud et al. 2017, Suchomel et al. 2018). This has commanded substantive logistical difficulties to elicit expected gains. Therefore, there is a need to develop a novel formulation of conditioning that could condense the pattern of delivery of physiologically-effective, doses of stimuli, while simultaneously maintaining the vast proportion of potential gains in outcomes of physical performance and that it would offer advantages to patients and clinicians for logistical versatility with which a package of conditioning might be delivered. This would be especially important within the relatively short (11 – 12 weeks) period of time between the patients electing for surgery after clinical consultation and a surgical procedure, if pre-habilitation were to be incorporated effectively within care pathways.

Recent pilot work has shown that with careful periodisation and micro-cyclical management of the mode of exercise-conditioning, patterning of exercise intensity and work/recovery ratios, and progression of increasing physiological stimuli for adaptation, it is possible to deliver gains in neuromuscular performance within a programme lasting 2 – 3 weeks (pre-surgery) and which matches 70% of the effects expected during longer programmes (Peer & Gleeson 2018), showing its potential for efficacy. However, this novel approach to exercise conditioning has not yet been verified within hospital-based care pathways, and would require further additional adaptations to this intervention model to counteract arthrogenic and autogenic sources of inhibition (AMI) associated
with long-term disease conditions such as OA (Rice & McNair 2010), limiting neuromuscular performance and conditioning gains by the intrusion of nociceptive stimuli such as an increase in intra-articular joint pressure (Palmieri-Smith et al. 2007). Furthermore, recent RCTs have shown pronounced gains in functional and neuromuscular performance capabilities, where the delivery of the contemporary rehabilitative conditioning has been modified to incorporate physiological principles (Bailey et al. 2014, Moutzouri 2018). Despite the potential implications, both studies (Bailey et al. 2014, Moutzouri 2018) investigated the effects of the intervention during the post-surgery phase rather than pre-surgery, which might have also influenced the overall results. Furthermore, one of the RCTs (Moutzouri 2018) utilised a home-based SM-focused intervention with no real control of the actual dose-intensities delivered during their HEP. Therefore, there is a further gap in the literature for developing and investigating the effects of a well-controlled, physiologically-principled and efficacious (moderate to large effects sizes) SM-focused exercise-programme to be delivered during the pre-surgery phase of patients electing for TKA.

The novel conditioning programme such as the one being offered in this thesis (P-SEC), could offer increased cost-effectiveness due to its brevity, versatility and potential application to other related surgical procedures and temporal needs for conditioning, and the capacity for preparing patients physically for surgery. Furthermore, recent research has shown that rehabilitation delivered during the end-phase of rehabilitation (> 24 weeks post surgery) often offer limited gains in performance post surgery (Bailey et al. 2014). Therefore, the novel packaging of conditioning should aim to be delivered over a time-period (e.g. 1 week) equal to that utilised during the end-phase of rehabilitation, in order to offer a ‘cost-neutral’ delivery of the conditioning programme where a period of time post-surgery is sacrificed in favour to an equivalent time-period of conditioning prior to surgery. Figure 2.5 shows a diagrammatic representation of the proposed cost-neutral effect for a novel pre-surgery exercise-conditioning programme being offered in this thesis (P-SEC).
2.5 Objective measurements of neuromuscular and sensorimotor performance capabilities

A sophisticated array of outcomes are required in order to quantify the effects of complex interventions and diverse conditioning stimuli on neuromuscular and sensorimotor performance in patients waiting for TKA surgery (Reimann 2002b, Peer 2017). An early review (Riemann et al. 2002) on which subsequent research outcomes have been based, describe neuromuscular and sensorimotor outcome measures as falling under the following categories: sensorimotor (i.e. proprioception), neuromuscular and functional performance. Proprioception (sensorimotor) is often described as the afferent information acquired from peripheral receptors found in joints and muscles (Reimann 2002a,b, Herrington et al. 2008, Benjaminse et al. 2009, Suprak et al. 2016) and is measured in the following variables: the individual’s capacity to identify joint position in space (JPS), the ability to detect passive movement (Kinaesthesia - TTDPM) and the individual’s ability to regulate levels of force associated with joint stability or movement.
and is measured in a number of variables including force error (FE), force sense (FS) and velocity sense (VS) (Reimann 2002a,b, Riemann et al. 2002, Herrington et al. 2008, Benjaminse et al. 2009, Keenan et al. 2017). Neuromuscular performance includes the measurement of both the affarent input (sensory input) (through stimulated/evoked potentials (Minshull et al. 2007, 2011, Gleeson et al. 2013)) and efferent (muscular output) (Sterner et al. 1998, Wilderman et al. 2009, Hinman et al. 2003, Di Giminiani et al. 2014, Bailey et al. 2014) and is calculated from data obtained from electromyography (EMG) and dynamometry equipment. Lastly, functional performance includes non-sophisticated measurements of joint stability and control measured in variables of time or distance using OMs such as star excursion balance test (SEBT), functional reach test (FRT) and timed-up and go test (TUGT) (Riemann et al. 2002, Harkey et al. 2014, Ni et al. 2014, Hall et al. 2015). In addition, agility, speed and co-ordination are also essential components of central and peripheral integrated control (Riemann et al. 2002, Pasanen et al. 2009, Fu et al. 2013, Bailey et al. 2014, Baldon et al. 2014) and therefore used for the measurement of functional performance. Choosing the right outcome measure and methodologies can be challenging, but understanding mechanisms behind each available outcome and their respective psychometric properties allows for appropriate selection.

Literature recommends a combination of outcome measures that would be able to measure both aspects of neuromuscular and sensorimotor performance capabilities that are suitable in the respective cohort of patients (undergoing knee surgery) and sensitive to changes following an intervention (Reimann 2002b, Riemann et al. 2002, Peer 2017). The following sections will include an in-depth evaluation of the outcomes selected in this thesis for measuring neuromuscular (electromechanical delay (EMD), rate of force development (RFD) and peak force (PF)) and sensorimotor (force error (FE)\(^2\)) performance capabilities in patients awaiting TKA.

\(^2\)COP was the first outcome measure of choice for measuring sensorimotor function, but due to an uncontrollable fault occurring during data capture in the force plate system, the data was unreliable for analysis. Therefore, FE was regarded as the sole sensorimotor outcome for the study’s thesis.
A. Electromechanical delay (EMD)

EMD is described as the time delay between the onset of muscle activity and the detection of force measured in milliseconds (ms) (Enoka 1988, Cavanagh & Komi 1979, Minshull et al. 2007, 2009, Costa et al. 2013, Hannah et al. 2012). The causes behind this delay is stipulated to be multifactorial including muscle dysfunction, joint laxity and tissue stiffness (Cavanagh & Komi 1979, Costa et al. 2013, Hannah et al. 2012, Minshull et al. 2007, Smith et al. 2016). The series-elastic component (SEC) (Enoka 1988) of the joint musculo-tendinous area and the excitation-contraction coupling (ECC) (Cavanagh & Komi 1979) are also thought to contribute to changes in this latency period, but to date, this has not been physiologically proven. EMD along with other performance outcome measures such as RFD and PF are important factors during rapid skills when fast muscular action is required such as reacting to an unstable surface to avoid tripping or during explosive actions in sports. Generally, EMD values range from about 30 – 100 ms with an average of 49.5 ms in healthy individuals (Cavanagh & Komi 1979, Conchola et al. 2015). A longer EMD and a decrease in muscle force production result in slower muscular activity that have been linked to an increase risk of injuries (Aagaard et al. 2002, Hart et al. 2010, Rice & McNair 2010, Conchola et al. 2013). EMD is influenced by various factors including age, gender, physical activity and underlying joint pathologies (Cavanagh & Komi 1979, Zhou et al. 1995, Smith et al. 2016, Zhou 1995). The latter (effects of joint pathologies) is considered to be a more important aspect in affecting EMD in this thesis because of the underlying AMI caused by OA (refer to Section 2.2). Although a randomised controlled study means that a selection of different ages and gender will be included at random within the groups, previous literature on EMD for differences between individuals with different age and gender identities did not report any significant effect (Yavuz et al. 2010, Conchola et al. 2015, Hannah et al. 2012). Therefore, this is expected to be the same for the individuals included in this thesis.

Literature has shown that EMD has been a successful outcome measure of choice in identify improvements or otherwise in neuromuscular performance in healthy (Howat-
son 2010, Conchola et al. 2013, Gleeson et al. 2013, Conchola et al. 2015, Hannah et al. 2015) and disease affected individuals (Smith et al. 2016, Bailey et al. 2014, Peer 2017). Furthermore, successful use of EMD has also been reported in situations where an exercise intervention has been applied in order to identify the effects of the intervention on neuromuscular performance (Howatson 2010, Tillin et al. 2010, Costa et al. 2013, Conchola et al. 2013, Gleeson et al. 2013, Conchola et al. 2015, Hannah et al. 2015, Jenkins et al. 2016, Andrade et al. 2016). The results of the individual studies have not always reported a statistical significant effect or magnitude of results when compared to other outcomes of neuromuscular performance such as PF (Zhou et al. 1995, Aagaard et al. 2002, Tillin et al. 2010, Costa et al. 2013, Jenkins et al. 2016, Andrade et al. 2016). For example, training interventions whose delivery was aimed at increasing morphological aspects of muscular strength (Jenkins et al. 2016, Andrade et al. 2016, Costa et al. 2013) revealed a larger significant effect for force (PF) as opposed to EMD. The neuronal derived mechanism governing EMD may be the driving factor for these results and would explain the difference in reported outcomes (Enoka 1988, Cavanagh & Komi 1979, Aagaard et al. 2002). As described above, EMD is a measure of time-delay between onset of muscle activity that is detected as electrical activity in an EMG and the force reproduced, that is measured by an apparatus such as a dynamometer (Enoka 1988, Cavanagh & Komi 1979, Minshull et al. 2007, Howatson et al. 2009, Minshull et al. 2009, Costa et al. 2013, Hannah et al. 2012). Activity in the muscle is dependent on neural input from the periphery therefore any alteration in this neural activity would preferentially improve the time delay of muscular activity as measured by the EMD. Therefore, training that has a time element to it such as quick muscular actions performed during activities like ballistic or plyometric training, should be used in order to affect aspects of neuromuscular performance such as EMD. The P–SEC intervention being investigated in this thesis has been developed on quick (time-limited) eccentric-concentric muscular reactions that aim to overcome the underlying neuromuscular inhibition by eliciting an increase in neuronal pool that would preferentially improve neurally derived aspects of neuromuscular performance such as EMD. For this reason, EMD was chosen as the primary outcome measure of choice in the thesis’ studies.
Psychometrically, several research papers investigating the reliability and reproducibility of EMD have reported very good test-retest reliability for use in lower limbs (ICC range from 0.7 – 0.9) with specific use in the knee joint (Minshull et al. 2009, Jenkins et al. 2016). Intra- and inter-day-session reliability, in particular for the knee extensor musculature, has also shown moderate-to-high reliability with ICC values being at 0.8 ±0.1 (Coefficient of variation - CV% = 10.1% ±3.4) and 0.6 ±0.1 (CV% = 14.5% ±5.5) (Minshull et al. 2009) and reproducibility (V% = 4% – 5%; (Viitasalo 1980, Minshull et al. 2009)) further supporting the use of EMD as an outcome measure of choice in measuring changes in neuromuscular performance. The literature reports other outcome measures used to measure neurally derived muscular activity such as central activation ratio (CAR) (Staehli et al. 2010), root mean square (RMS) (Arroyo-Morales et al. 2008, Di Giminiani et al. 2014), evoked/twitch/doublet interpolation of EMG activity (Gleeson et al. 2008, Minshull et al. 2009, Staehli et al. 2010) are amongst the most common. All outcomes measure different aspects of muscular activation patterns and psychometrically exhibit similar (CAR = ICC range 0.7 – 0.8, CV% = 1.5% – 3.1% (Staehli et al. 2010); RMS = ICC 0.7 – 0.80 (Arroyo-Morales et al. 2008, Di Giminiani et al. 2014)) and lower (Evoked/twitch/doublet = ICC > 0.64 CV% = 5.0% – 20.5% (Gleeson et al. 2008, Minshull et al. 2009, Staehli et al. 2010)) properties for reliability and reproducibility in comparison to EMD. Furthermore, although psychometric properties have not been examined in patients undergoing TKA surgery, it has been successfully employed in identifying changes in neuromuscular performance in patients waiting for and undergoing TKA surgery (Peer 2017, Moutzouri 2018) supporting the use of EMD as an outcome measure of choice in this cohort of patients.

B. Peak force (PF)

PF is generally described as the highest recorded value reproduced (volitional or evoked) during muscle activation (Minshull et al. 2009). Absolute and relative measures of PF are generally recorded and represent a measure of change in muscle strength (force). Muscle strength in particular, has been considered as a measure of functional disability, predictor of disease progression and development in patients with OA of the knee.
Furthermore, muscle strength has also been reported in the literature for its close relation to patients’ physical performance outcomes such as other aspects of neuromuscular performance (EMD and RFD) being discussed in this section (Mizner, Petterson, Stevens, Vandenborne & Snyder-Mackler 2005, Mizner, Petterson, Stevens, Axe & Snyder-Mackler 2005, Lienhard et al. 2013). Therefore, the importance of measuring changes in PF has historically become more imperative in clinical use as a measure for progression or regression in rehabilitation process. PF can be measured in a number of different ways but the most common and reliable method of measure is in combination with other neuromuscular performance measures such as EMD and RFD that analyse muscular performance outcomes using EMG and dynamometer data (Gleeson et al. 2002, Minshull et al. 2009, Gleeson et al. 2008, Bailey et al. 2014). Inter-day coefficients for PF in the knee extensor musculature using dynamometer readings have been reported to be high, with ICC values above 0.93 ±0.02 and a mean CV% = 8.5% ±3.3 (Mercer et al. 1998, Minshull et al. 2009) proving high reliability of use for PF using a dynamometry. High intra-day coefficients of 0.98 ±0.01, mean CV% = 3.5% ±1.9 and V% = 8.3% – 10.1% have also been reported in the literature (Viitasalo 1980, Minshull et al. 2009) confirming its reproducibility. Moreover, PF was shown to exhibit excellent test-retest reliability in quadriceps strength using seated dynamometry in patients with knee OA (Kean et al. 2010), further confirming the use of PF as measured by dynamometer readings as an effective choice of outcome for measuring another aspect of neuromuscular function. These psychometric properties and consistent ability to detect changes over time in various cohorts of individuals encourages the use of PF for measuring changes in neuromuscular (motor) function along with other indices such as EMD and RFD (Minshull et al. 2007, Gleeson et al. 2008, Hannah et al. 2012, Lienhard et al. 2013, Bailey et al. 2014). Furthermore, literature supports and strongly recommends the use of indices of muscular strength such as PF for use as an outcome measure in patients electing to undergo TKA (Staehli et al. 2010). Literature has reported many other ways of measuring changes in the highest reproducible force (PF) (Riemann et al. 2002, Wilderman et al. 2009, Fu et al. 2013, Baldon et al. 2014, Di Giminiani et al. 2014, Hall et al. 2015, Jenkins et al. 2016), but the psychometric properties exhibited by the measurement of
PF using dynamometry has repeatedly supported its use. Furthermore, the expected changes in PF following the P–SEC intervention are hypothesised to be related due to an increase in neuronal activity in the SC and therefore not morphological changes are expected to occur. Therefore, other direct measurements of muscular strength such as morphological size through the use of ultrasound or biopsy, that also exhibit moderate to large (ICC range 0.62 – 0.88 and CV% = 3.8% – 6.9%) (Folland & Williams 2007) psychometric properties are not suitable for this study.

C. Rate of force development (RFD)

Another commonly used objective outcome for measuring neuromuscular performance is RFD. RFD assesses the intrinsic contractile properties of the muscle during force generation (Aagaard et al. 2002) and is defined as the rate at which force is developed over time (Minshull et al. 2009, Maffiuletti et al. 2010, Smith et al. 2016). The values of RFD are calculated from the slope of the force-time curve at various intervals using data from a dynamometer and EMG and is measured in Newtons per second (N/s) (Minshull et al. 2009, Maffiuletti et al. 2010, Smith et al. 2016). The ability to reproduce force quickly is dependent on neuromuscular activation (Aagaard et al. 2002, Minshull et al. 2009, Maffiuletti et al. 2010, Smith et al. 2016) and is believed to be better at predicting functions which are not necessarily strength based such as tripping, changing direction and sudden stopping (Suetta et al. 2004, Pijnappels et al. 2005). Along with the other neuromuscular performance outcomes mentioned above (EMD and PF), literature has supported the use of RFD in various cohorts of patients including those undergoing and receiving a TKA surgery (Maffiuletti et al. 2010, Angelozzi et al. 2012, Smith et al. 2016, Bailey et al. 2014, Peer 2017). Furthermore, the reliability and reproducibility of RFD has been consistently reported as moderate to high (Minshull et al. 2009) with ICC values of 0.80 ±0.10 and 0.70 ±0.10 and CV% = 20.6% ±7.0 and CV% = 27.0% ±9.2 for healthy individuals. Specific values for reliability and reproducibility in patients undergoing TKA surgery has not been reported yet in the literature but recent studies investigating a similar cohort of patients to the current study support its use for measuring changes in RFD outcomes over time (Peer 2017, Moutzouri 2018). Values amongst individuals vary and are primarily dependent on other factors of neuromuscu-
lar activity (PF and initiation of electrical activity within the muscle). These aspects of RFD makes it a favourable outcome measure for use in the measurement of neuromuscular performance. A study by Angelozzi et al. (2012) using RFD as an outcome measure for physical performance, reported that, measurements of RFD were successful in detecting changes in neuromuscular function up to 12 months following TKA surgery (Maffiuletti et al. 2010, Angelozzi et al. 2012), further confirming its usefulness as an adjunct to the selected outcome measures of neuromuscular performance.

D. Sensorimotor performance - Force error (FE)

Alongside the commonly deployed neuromuscular outcomes of EMD, PF and RFD, that would capture the nature of the time-limited changes in neuromuscular performance capacities challenged in the P–SEC intervention over time (Cavanagh & Komi 1979, Enoka 1988, Minshull et al. 2009), is the measurement of the participants’ capability of sensorimotor acuity as measured by sensorimotor performance. Literature has reported many outcome measures and respective methodologies for measuring aspects of sensorimotor performance, but the ‘gold standard’ is considered to be the centre of pressure (COP)\(^3\) measured using force platforms (McKeon & Hertel 2008, Bell et al. 2011, Donnath et al. 2012). COP related outcomes (including velocity and displacement areas) using force plate apparatus are the most common tools for measuring sensorimotor performance during standing. However, a measurement of sensorimotor performance such as when participants efficiently perceive and regulate levels of force associated with joint stabilisation or movement may be assessed using outcomes such as force error (FE). This outcome relies principally on the performance capabilities of musculoskeletal sensory receptors (Brockett et al. 1997, Gleeson et al. 2013, Bailey et al. 2014, Peer 2017) and has shown effective clinimetric qualities in patient populations electing knee surgeries (Hannah et al. 2012, Bailey et al. 2014, Peer 2017). FE is a dynamic index of sensorimotor performance that measures the error between the target force (e.g. 50% of maximum voluntary contraction (MVC)) and the replicated blinded force

\(^3\)COP was one of the sensorimotor outcomes selected for this thesis study but due to uncontrollable fault in the data capture system of the force plate apparatus, the data acquired during the study was not usable and unreliable for analysis. For this reason, the main sensorimotor outcome of choice has been selected as force sense (FE) and analysis for sensorimotor function will be reported based on analysis of force sense data capture. Its methods of collection has been described in Chapter 4.
(Baltzopoulos & Gleeson 2001, Gleeson et al. 2013, Bailey et al. 2014) from data obtained from a dynamometer (Baltzopoulos & Gleeson 2001, Gleeson et al. 2013). Force values are compared and the difference in score is calculated and used for data analysis. FE has been successfully used as a measure of sensorimotor performance following knee surgery (Bailey et al. 2014, Peer 2017, Peer MA Under review, Moutzouri 2018) and exercise (Brockett et al. 1997, Gleeson et al. 2013). FE values of between 6.3% – 10% have been found in individuals when compared to controls in healthy and individuals undergoing knee surgery (Brockett et al. 1997, Gleeson et al. 2013, Bailey et al. 2014). The psychometric properties for reliability and reproducibility for FE are not very often reported and the only study that has investigated these psychometric properties has reported moderate-to-high intersession reliability (ICC = 0.70) scores (Deshpande et al. 2003) supporting its use for measuring sensorimotor performance. As a result of its methodological properties and characteristic in the ability to identify changes in sensorimotor acuity of the individual, FE fits in well with the remaining outcome measures of neuromuscular function (EMD, RFD, and PF) for measuring effects of a ‘novel’ P–SEC intervention.

The P–SEC intervention being investigated in this thesis study has been developed based on motor-conditioning parameters due to the lack of information regarding SMT that is addressed in Chapter 3. Whilst specific changes in the neuromuscular outcomes of EMD, RFD and PF are expected due to the nature of the intervention favouring ‘motor’ aspects of performance, some carry over of effects in the sensorimotor outcome (FE) might be exhibited due to the close nature of the mechanisms governing the sensorimotor system that encapsulates both neuromuscular and sensorimotor function. For this reason, the primary (EMD) and secondary outcome measures (RFD, PF and FE) in this study have been selected due to their role in measuring aspects of muscular performance that are being targeted by the P–SEC intervention. The use of EMG and dynamometry are considered to be sophisticated measurements of neuromuscular (motor) and sensorimotor performance and often used as the ‘gold standard’ in clinical research (Gleeson 1996, Baltzopoulos & Gleeson 2001, Martin et al. 2006, Stark et al. 2011). Furthermore, the methodological processes adopted for collecting the respective
Objective measurements of neuromuscular and sensorimotor function are important in research because it allows us to measure and quantify objectively whether an intervention has had a significant effect on patients’ physical performance. On the other hand, these outcomes do not provide information with regard to the perceptions of the patients’ physical performance. Outcome measures such as patient-reported outcomes (PROs) provide information about the performance of an intervention as they reflect the patients’ sentiment about their perceived performance at that point in time (Copay et al. 2007). Therefore, PROs have been included in this thesis within the selection of outcome measures in order to identify whether any objectively measured changes that might result from the P–SEC intervention would also translate in a similar manner to patients’ perceived physical performance. Therefore, the following section will include an in-depth critical evaluation of the PROs that have been selected for this study.

2.6 Patient perceived measurements of pain, function and performance capabilities

Patients’ perceptions of their current status in relation to pain, function and health related quality of life (QoL) are often recorded both in research and clinical practice over the years. The reason behind this has been in part due to the endorsement of government registries using patient reported outcomes (PROs)4 as an integration of the patients’ perspective on evaluation of quality and effectiveness of care (Black 2013, Rolfson et al. 2016, Prodinger & Taylor 2018). Measurement of patients’ perceptions are often recorded using scores from selectively chosen questionnaires also referred to

4Other nomenclature referring to PROs include: patient reported outcome measures (PROMS), patient reported measures and patient perceived performance.
as PROs. PROs are questionnaires that are collected to measure patients’ perception on their current symptoms, functional status and health-related QoL (Black 2013, Prodinger & Taylor 2018). PROs have been initially developed for research purposes as a measure of a treatment’s effectiveness from the patient’s perception. Since 2002 PROs have been adopted by registries and government entities from all over Europe including the NHS PROMS programme in the UK (Black 2013, Rolfson et al. 2016, Prodinger & Taylor 2018). In line with patient-centred care, the use of PROs have progressively become more common. Probably as a consequence, a number of questionnaires relating to knee function have been developed in the last two decades. More recently, several studies and reviews have been published comparing psychometric properties of the most commonly used PROs following hip and knee arthroplasty (Dunbar et al. 2001, Harris et al. 2016). Therefore, the scope of this section of the literature review is to describe the rationale for the selected PROs for this thesis and their relative psychometric properties in relation to patients undergoing TKA. Choosing the most suitable PRO to evaluate the efficacy of the intervention or treatment is vital due to its ability to influence decision-making models that have the potential to effect patients’ treatment outcome (Rolfson et al. 2016). The selected PROs should ideally exhibit clinically acceptable psychometric properties of validity, reproducibility and responsiveness to variations in the patient’s condition (Jaeschke et al. 1989, Dunbar et al. 2001, Black 2013). The most commonly reported PROs in relation to knee joint replacement are: the knee society score (KSS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Oxford knee score (OKS), closely followed by: the visual analogue scale (VAS) for pain, short-form (SF) -12 and -36 and the knee injury and osteoarthritis outcome score (KOOS) (Lovelock et al. 2018). The OKS, KOOS and SF-36v2™ have been selected for the purpose of this thesis for inclusion of both knee specific pain, function and QoL as well as general health. In addition to these PROs, the pain self efficacy questionnaire (PSEQ), performance profile (PP) and the long form international physical activity questionnaire (IPAQ) have been added to the list of PROs. The rationale of the selected questionnaires is discussed below.

5Such as the NJR (UK), SKAR and SHAR (Sweden)
PROs are generally split into two main categories: those that measure general health such as SF-36v2\textsuperscript{TM} and others that are more disease specific such as (e.g. OKS, KOOS) (Dunbar et al. 2001, Black 2013). In addition to these PROs are questionnaires that measure specific aspects of habitual physical activity (IPAQ), QoL (e.g. OKS, KOOS), pain self-efficacy (e.g. PSEQ) and self-perceived performance (e.g. PP). A combination of PROs are often preferred to give a clearer overall picture of the patient’s current state. Scores collected from the questionnaires are used to help define specific progress points, e.g. in rehabilitation or for listing patients for elective surgery (Black 2013), but also as a measure of public accountability and performance, e.g. the use of scores for the NHS annual outcomes framework adopted since 2009 (National Joint Registry Annual Report 14th Edition 2018). Pain, function and QoL in elective joint surgery, are the main concerns that generally account for the operation’s success from both the patient and the surgeon’s perspective. Therefore, the selected PROs for this thesis aim to reflect the various aspects of pain and its self-efficacy, levels of habitual physical activity (PA), function and QoL in relation to TKA surgery and the P–SEC intervention. Whilst some of these outcomes such as PA and function can be measured using non-personalised performance-based instruments, measurements of patients self-efficacy, beliefs and QoL require tools such as PROs to be able to measure the patients’ personal perception at that particular time reporting their current experience and state of mind. Answers from the questionnaires could guide the team on the patient’s perceived state, informing their clinical practice and in some cases suggest possible changes for an improved recovery and success following the surgery (Prodinger & Taylor 2018).

A. Disease specific: OKS and KOOS

Along with the WOMAC questionnaire, the OKS and KOOS are the two the most commonly employed disease specific questionnaires for patients undergoing a TKA. Generally favoured over the KOOS, the OKS has consistently reported an excellent interclass correlation coefficient (ICC) of 0.90, with a good construct validity and internal consistency (Dunbar et al. 2001, Jenny & Diesinger 2012, Harris et al. 2016). In fact along with the OHS, it has been endorsed and used as a measurement tool of
clinical performance outcomes by the NHS following the national audit of 2009. The advantages of the OKS include having only 12 questions to answer and an easy scoring system for adaptation in clinical practice (Davies 2002, Jenny & Diesinger 2012) as opposed to the KOOS having a total of 42 questions. Despite this, the OKS and the WOMAC have both been previously criticised for the lack of detailed information about function, pain and QoL. The KOOS was originally developed as an extension to the WOMAC for a younger or more active patient group with knee related injuries incorporating further details about general symptoms including pain and stiffness, function (daily, recreational and sports related) and QoL (Roos et al. 1998, Roos & Lohmander 2003). The KOOS is not the selected PRO of choice in NHS practices across the UK, but it has been favoured in research over the OKS and the WOMAC for several reasons. Firstly, the KOOS questionnaire is considered to have the widest coverage of bodily function (Alviar et al. 2011) and includes more detailed information regarding symptoms, stiffness, pain, function and QoL that both the OKS and the WOMAC address but in brief. Secondly, the subscale ‘sports and recreation’ addresses specific aspects of the patients’ QoL in their level of activities that the OKS and WOMAC both do not address. Furthermore, KOOS subscales of ‘sport and recreation function’ and ‘QoL’ have been reported to be more sensitive and discriminative than the WOMAC constructs of pain, stiffness and function for patients experiencing OA (Roos et al. 1999). Lastly, the whilst the WOMAC and the OKS have a composite scores of the different constructs within the respective questionnaires (for pain, stiffness, function and QoL), the scores of the KOOS are calculated for each subscale separately allowing for comparisons of individual aspects rather than a whole (Roos & Lohmander 2003, Rolfsen et al. 2016).

A recent SR has shown that despite not being the selected outcome-instrument of choice for national health care practices, the KOOS exhibits a high level of internal consistency, reliability and validity with values above Cronbach’s $\alpha$ of 0.70 and an ICC $\geq 0.80$, for all the sub-scales in patients suffering from knee OA (Collins et al. 2016). When evaluated in patients undergoing TKA surgery, the KOOS exhibited a lower overall level of reliability (ICC of $\geq 0.70$) with a moderate to high level of
Chapter 2. Literature Review

Responsiveness (ES and standard response mean [SRM] > 0.80) except for the sport and recreational sub-scale (Peer & Lane 2013). Therefore, for the purpose of this study, the KOOS exhibits clinically acceptable psychometric properties for use with patients suffering from OA and undergoing TKA surgery (Peer & Lane 2013, Collins et al. 2016). In addition, the use of KOOS along with HOOS is supported through the inclusion as outcome measures for hip and knee osteoarthritis in the standards set out by the International Consortium for Health Outcomes Measurement (ICHOM) (http://www.ichom.org/medical-conditions/hip-knee-osteoarthritis/).

B. Generic: SF-36v2

The SF-36 is a 36-item questionnaire developed as a generic questionnaire for gathering and assessing general health information with recommendation of use in various cohorts of patients including those undergoing TKA (Dunbar et al. 2001, Harris et al. 2016). As one of the most common health generic questionnaires, it has received scrutiny for extensive psychometric testing across several countries and in different languages. Its robustness lies in the consistent ability of possessing very good psychometric qualities across different populations including patients suffering from long standing illness such as OA (Kosinski et al. 1999, Bachmeier et al. 2001). The SF-36 is made up of eight areas covering two main aspects: physical and mental health (Instrument Ware Jr & Sherbourne 1992, Jenkinson et al. 1999). Both aspects of the questionnaires have reported moderate to high reliability (>0.70) with physical function having the highest score of 0.90 (Ware Jr 2000). Generally speaking, SF-36 has consistently scored higher than the recommended standard of 0.7 for measures of reliability with some studies also reporting higher than 0.80 (median = 0.84) (Kosinski et al. 1999, Ware Jr 2000). The SF-36v2 is a revised version of the SF-36 developed in 1996 following widespread criticism concerning the layout and wording of some of the questions in the original SF-36 questionnaire (Jenkinson et al. 1999). This updated version of SF-36 has subsequently shown high internal consistency and internal reliability (Cronbach’s α scores exceeding < 0.80 for all domains) and appropriate construct validity in detecting changes in an individual’s health, especially those with longstanding illness such as OA and waiting for TKA surgery when compared to the original version of the SF-36 (Jenkinson et al.
1999, Bachmeier et al. 2001). Jenkinson et al. (1999) also reported a relatively good response rate of 64% (n = 8889) for the SF-36v2\textsuperscript{TM} version. Both components (physical (PC) and mental (MC)) have previously reported high correlations (ICC ⩾ 0.85) for measuring general health status and bodily pain (Ware Jr 2000). These psychometric properties confirm its use for measuring general health status in the cohort of patients selected for this study. Furthermore, the SF-36v2\textsuperscript{TM} has also scored an excellent ICC (0.80) and good content validity (skew 0.11) when used in patients undergoing TKA surgery (Dunbar et al. 2001) further affirming the scope of this questionnaire for use within this thesis.

C. Pain self-efficacy (PSEQ), habitual PA (IPAQ) and perceived physical performance (PP)

The PSEQ is a 10-item pain-related self-efficacy questionnaire that has been developed in the 1980s by (Nicholas 1989) to examine the confidence in performing activities in the presence of pain in patients suffering from long standing pain conditions such as OA (Asghari & Nicholas 2001, Nicholas 2007). Self-efficacy was originally described by Bandura (1977) as the influence of “one’s beliefs in one’s ability to succeed in specific tasks or situations”. In his theory, Bandura (1977) explains how one’s beliefs in self-abilities can play a crucial role in how a person approaches and deals with respective situations they are in. In context, the PSEQ uses this same theory by placing an emphasis on the element of pain (Nicholas 2007), and as such, each question highlights the phrase “despite the pain” (refer to Appendix K). The PSEQ questionnaire has been shown to be clinically useful in obtaining information regarding one’s beliefs in their own capabilities during the presence of pain in patients with chronic conditions (Arnstein et al. 1999, Nicholas et al. 2008). It is a free, quick and easy questionnaire with good response rates and clinical applicability (Nicholas 2007, Nicholas et al. 2008). The PSEQ exhibits good psychometric properties for use in chronic pain patients such as OA including excellent internal consistency (Cronbach’s α 0.90), a high test-retest reliability (0.70; \( p < 0.001 \)) and good construct validity (Asghari & Nicholas 2001, Nicholas 2007). Overall, the PSEQ’s evidence suggests a high degree of reliability and sensitiv-
ity (across a minimum of a 3-month period) for detecting changes in pain or disability (Nicholas 2007). The lack of “gold standard” for self-efficacy makes it hard to compare the PSEQ in its efficacy but evidence suggests strong relationships to measures of physical activity and other pain outcome modalities/instruments. PSEQ scores are useful in identifying patients whose success of treatment will have an underlying perception of pain and their self-belief in relation to function. Low self-efficacy scores are found in patients who are more likely to being at risk of long-term disability (Arnstein et al. 1999), while higher self-efficacy scores showed improved coping strategies and higher pain thresholds and tolerance to experimentally induced pain in patients with chronic OA (Keefe et al. 1997).

Physical activity (PA) has been defined as “…bodily movements produced by the skeletal muscle contraction that increase energy expenditure above basal level. Physical activity manifests itself in work or education, transport, domestic chores and recreation and its key characteristics are frequency, intensity, duration and continuation” (Nosikov & Gudex 2003). This statement was the basis from which the IPAQ was developed with the aim of standardising PA internationally. The questionnaire focuses on gathering information about the total amount of PA done over the past seven days and includes activities carried out during work, house chores, commuting and recreational activities (Craig et al. 2003, Nosikov & Gudex 2003). The reader is referred to Section 4 for further details about the scoring and methodology of the questionnaire. Two versions of the IPAQ exist, both thoroughly examined for their psychometric properties individually, against each other and other OMs. Generally speaking, the IPAQ exhibits moderate test-re-test reliability (ICC > 0.70) and validity (criterion (ICC 0.58) and concurrent (ICC 0.70)) for the UK when tested against other countries, that generally scored much lower (Nosikov & Gudex 2003). Moderate to high values were exhibited with higher response rates (80% – 100%) in questions regarding moderate to vigorous PA (Nosikov & Gudex 2003). Craig et al. (2003) found acceptable reliability (r = 0.70 – 0.90) and moderate validity (r = 0.02 – 0.50) when its use was compared to an accelerometer in a generalised population. Fair to moderate test-re-test reliability (long (ICC 0.70) and short (ICC 0.50)) and relatively weak concurrent validity (long
(r = 0.40) and short (r = 0.30) form) resulted when assessing PA in patients following THA and TKA (Blikman et al. 2013) when compared to physical activity monitors. The latter study also pointed out the rather large (> 1000) MDC for both forms that was reported in this cohort of patients. For this reason and because of the fair to moderate psychometric properties, the IPAQ is generally advised for measuring PA for group-level comparisons over time and not for individual progress. This has been the scope of selecting the IPAQ to the battery of PROs for the study carried out within this thesis. In addition, the long-form has been preferred over the short-form due to its higher scoring rate and more stable test-re-test reliability for use with a similar cohort of patients (Blikman et al. 2013).

The PP questionnaire is a way of measuring psychophysiological fitness performance in a more personalised visual representation (Doyle & Parfitt 1996, 1997, Gleeson et al. 2005, 2008). The questionnaire was originally proposed as a means to understand an athlete’s perception of their own physical performance abilities (Doyle & Parfitt 1996) and has since been developed to understand further correlations of objective and subjective physical performance over time (Doyle & Parfitt 1996, 1997, Gleeson et al. 2005, 2008). It is an outcome instrument more commonly used with the athletic population (Doyle & Parfitt 1996, 1997, Gleeson et al. 2005) and more recently with people undergoing anterior cruciate ligament (ACL) surgery (Gleeson et al. 2008, Bailey et al. 2014, Yates 2016) and TKA surgery (Peer 2017). The PP questionnaire is built by using minimal verbal cues and prompts to allow the patient to express what they believe are characteristics of performance they would like to achieve (refer to Section 4 for in depth information about PP’s methodological use). In comparison to the other generic questionnaires used within this thesis, the PP adds a more personalised outcome instrument to the battery of PROs to measure performance in patients waiting for TKA. The use of a more personalised outcome performance instrument supports the direction towards patient-centred and directed care by making their goals and achievements increasingly more important for successful rehabilitation. Validity (construct and predictive) and reliability of the profile was studied using the profile in the athletic population (Doyle & Parfitt 1996, 1997, Gleeson et al. 2005). Overall a total of 119 ath-
letes were individually given a PP that recorded between 10 – 15 qualities they believed were important for their sport performance. In all three studies, the PP was measured over three (Doyle & Parfitt 1996, Gleeson et al. 2005) and five (Doyle & Parfitt 1997) assessment trials. Results showed a significant difference in profiles between the trials (Gleeson et al. 2005) supporting construct validity through the reduction in profiles’ areas of perceived need ($p < 0.05$) with improved performance ($p < 0.05$) (Doyle & Parfitt 1996, 1997). Reliability of the profile was obtained from the study by Gleeson et al. (2005) who found no significant inter-day differences in scoring the questionnaire with an intra-individual coefficient of variation of ±4.7% to ±6.8% (68% confidence limits) and ±9.2% to ±13.3% (95% confidence limits) for 10 profile constructs. Despite this, concerns about the ability of the profile to detect minimal changes in a population’s performance was expressed across all three studies (Doyle & Parfitt 1996, 1997, Gleeson et al. 2005) with recommendations for better use with a cohort of patients whose changes between constructs would be larger, for example, following an injury or surgery. Therefore, the addition of the PP questionnaire to the battery of outcome instruments used for this study is believed to be a useful tool to detect changes in perceived performance for the cohort of patients that were being investigated.

The internal consistency have only been calculated for the KOOS and the SF-36v2™ questionnaires due to their ability within their scoring methodology of extracting individuals scores of the sub-scales. The constructs that evaluate pain SF-36v2™ (2-item bodily pain subsection) has been autonomously analysed and found to have a high internal consistency (Cronbach’s $\alpha$ of 0.80) and a high test-re-test reliability of 0.80 (Hawker et al. 2011) in patients experiencing knee OA. Individual scores for the KOOS’ sub-scales that individually address all three main areas of pain, physical function and QoL also exhibit high internal consistency and reliability for patients with knee OA (Cronbach’s $\alpha$ ranging from 0.70 – 0.90 and ICC ranging from 0.80 – 0.90) (Collins et al. 2016). Along with the detailed critical evaluation in the previous sections, these findings further confirm that the PROs selected within this study are suitable to measure appropriate changes in patients waiting for a TKA surgery receiving an intervention whose main purpose is to alter the patients’ perceptions of their pain, habitual
physical activity, function and QoL.

The ‘novel’ intervention under investigation within this thesis (P–SEC) aims to improve physical aspects of performance that have the potential to also alter patients’ perceptions of their own physical capabilities. Since patients electing to undergo TKA experience a complex array of difficulties including pain, physical function and decreased QoL, these are important aspects which should be recorded by the PROs selected for the study. The sections above have included an in-depth analysis of the psychometric properties these questionnaires exhibit in relation to patients electing for a TKA surgery and undergoing an exercise intervention. Therefore, the selected PROs (OKS, KOOS and SF-36v2TM, PP, IPAQ, PSEQ) for this study have been chosen to help express patients’ perceptions of their experience of physical performance capabilities by including a vast array of constructs within the questionnaires that address different aspects of pain–self efficacy, habitual level of physical activity, function and their QoL that represent the patient’s beliefs in their abilities to perform tasks despite the presence of e.g. pain (Hamilton et al. 2017).

Patients’ perceived pain performance in relation to activities of daily living will be recorded through the generic health questionnaire SF-36v2TM (physical component - PC; bodily pain subscale), OKS (pain constructs) and KOOS Painsubscale. More personalised patient’s perception of pain is collected from the PSEQ and PP questionnaire. Most of the PROs ask the participant to rate their pain, function or QoL experienced over the previous seven days with the exception of the PSEQ and the PP (when the pain construct is included). Whilst most of the other questionnaires relate to ‘how much’ or whether or not they have experienced pain over the past 7-day period, the PSEQ and the PP explore the relationship between the patient’s belief in their own capabilities of performing a task at that moment in time despite the presence of pain, or whether or not pain is an important factor that will play an important role in their rehabilitation’s success.

As opposed to the KOOS and OKS which are knee specific PROs, the SF-36v2TM
and the IPAQ provide a more generic representation of the QoL and the habitual physical activity levels respectively. The IPAQ focuses on collecting specific parameters of PA across the previous 7-day period at the time the questionnaire is taken using metabolic equivalent task (MET) scores that are not collected by any of the other questionnaires. Whilst the SF-36v2™ questionnaire gathers information about the patient’s current general health, level of physical and mental function as compared to last year. The SF-36v2™ is the only questionnaire included in this thesis that provided a measure of the participants’ mental-state that none of the other questionnaires measure whilst the KOOS questionnaires includes specific subscales of sports and recreation function that the other knee specific questionnaire (OKS) did not include and therefore will be able to analyse this aspect in a little bit more detail.

For ease of reference and comparison, Tables 2.1 and 2.2 below list the PROs generally used to measure different outcomes in patients with longstanding OA and electing to undergo TKA surgery for appropriate measures of pain, habitual levels of physical activity, function and QoL. The questionnaires listed in Tables 2.1 and 2.2 are the ones recommended for use by e.g. national joint registries, due to their respective psychometric properties in patients with knee OA and waiting for TKA surgery.
Table 2.1: The table below is a comparison of psychometric properties of the most commonly used questionnaires for patients with OA and TKA (Asghari & Nicholas 2001, Salaffi et al. 2003, Roos & Lohmander 2003, Escobar et al. 2007, Dinjens et al. 2014, Hawker et al. 2011, Blikman et al. 2013, Peer & Lane 2013). The list is based on information from these latter studies and from the national joint registry (NJR) both in the NHS and in other European countries. **The ones highlighted in bold are the selected outcome measures for this thesis.** *Key:* knee society score (KSS); Western Ontario and McMaster University osteoarthritis index (WOMAC); Oxford knee score (OKS); visual analogue scale (VAS); short form health questionnaire (SF-12 and SF-36v2™); Knee injury and osteoarthritis outcome score (KOOS); international physical activity questionnaire (IPAQ); performance profile questionnaire (PP); pain self efficacy questionnaire (PSEQ) and coefficient of variation (CV).

<table>
<thead>
<tr>
<th>PROM</th>
<th>Reliability (ICC)</th>
<th>Validity</th>
<th>Internal consistency (Cronbach’s α)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KSS</td>
<td>≥ 0.79</td>
<td>Excellent</td>
<td>≥ 0.76</td>
</tr>
<tr>
<td>WOMAC</td>
<td>0.58 – 0.92</td>
<td>Excellent</td>
<td>&gt; 0.83</td>
</tr>
<tr>
<td>OKS</td>
<td>0.94</td>
<td>0.73 (skew)</td>
<td>Good</td>
</tr>
<tr>
<td>VAS</td>
<td>0.71 – 0.94</td>
<td>0.62 – 0.91</td>
<td>–</td>
</tr>
<tr>
<td>SF-36</td>
<td>&gt; 0.70</td>
<td>Good</td>
<td>&lt; 0.80</td>
</tr>
<tr>
<td>KOOS</td>
<td>&gt; 0.83/ ≥ 0.70</td>
<td>Excellent</td>
<td>0.74</td>
</tr>
<tr>
<td>IPAQ</td>
<td>&gt; 0.66</td>
<td>0.58 – 0.74</td>
<td>–</td>
</tr>
<tr>
<td>PP</td>
<td>CV = ±4.7% – ±13.3%</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>PSEQ</td>
<td>0.73</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>
Table 2.2: The table below includes values for reliability and validity of the most commonly used questionnaires for TKA as reported in a systematic review by Dunbar et al. (2001). The scores reported are the mean scores for all the subscales combined. The questionnaires highlighted in bold are the ones selected for this thesis. Key: Nottingham health profile (NHP); sickness impact profile (SIP); short form health questionnaire (SF-12 and SF36); Oxford knee score (OKS) and Western Ontario and McMaster university osteoarthritis index (WOMAC).

<table>
<thead>
<tr>
<th>PROM</th>
<th>Reliability (ICC)</th>
<th>Validity (skew)</th>
<th>Internal consistency (Cronbach’s α)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHP</td>
<td>0.91</td>
<td>1.35</td>
<td>0.74</td>
</tr>
<tr>
<td>SF-12</td>
<td>0.02</td>
<td>N/A</td>
<td>0.88</td>
</tr>
<tr>
<td>SIP</td>
<td>0.79</td>
<td>2.91</td>
<td>0.80</td>
</tr>
<tr>
<td>SF-36</td>
<td>0.75</td>
<td>0.11</td>
<td>0.85</td>
</tr>
<tr>
<td>Lequense</td>
<td>0.85</td>
<td>0.42</td>
<td>0.77</td>
</tr>
<tr>
<td>OKS</td>
<td>0.94</td>
<td>0.73</td>
<td>0.93</td>
</tr>
<tr>
<td>WOMAC</td>
<td>0.92</td>
<td>0.53</td>
<td>0.93</td>
</tr>
</tbody>
</table>
2.7 Effects of cross-education (CE) in rehabilitation

Patients with a long history of knee related pathologies such as OA often experience difficulty in physical function (reported as deterioration in muscular performance) that is exhibited in both legs. This bilateral weakness has been confirmed many times within the literature (Hurley et al. 1994, Berth et al. 2002, Maffiuletti et al. 2010, Zeni Jr & Snyder-Mackler 2010) and has also been negatively linked to post-operative function (Zeni Jr & Snyder-Mackler 2010). This weakness in the contralateral (other) limb is believed to occur due to the shared neuronal circuitry at the spinal cord level (Carroll et al. 2006, Oliveira et al. 2013, El-Gohary et al. 2016, Schlenstedt et al. 2017, Harput et al. 2018, Frazer et al. 2018). Therefore, any afferent inhibitory signals that are directed at the physical function of the diseased limb, will also effect the contralateral limb (Carroll et al. 2006, Oliveira et al. 2013, El-Gohary et al. 2016, Schlenstedt et al. 2017, Harput et al. 2018, Frazer et al. 2018) resulting into a deterioration in physical function although to a lesser extent than that observed in the diseased limb. Similarly, when training benefits that are achieved in the trained limb where inhibited neural activation patterns are overcome, improvements in the contralateral limb have been reported similar to the training limb but to a lesser extent and is known as cross-education (CE) (Scripture et al. 1894, Enoka 1988, Zhou 2000, Munn et al. 2004, Carroll et al. 2006, Manca et al. 2017).

CE (Zhou 2000) is a research area that has been studied for over a 100 years (Scripture et al. 1894) and investigates the changes in the outcomes occurring in the non-trained (contralateral) limb (Enoka 1988, Zhou 2000, Munn et al. 2004, Carroll et al. 2006, Manca et al. 2017). Early studies (Enoka 1988, Weir et al. 1995) did not observe any significant CE effects despite the intriguing concept and this was mainly attributed to poor experimental design and methodological quality of these early studies. However, research interest in this field increased over the years and subsequent studies confirmed the presence of CE (8%) in the untrained limb following a period of unilateral conditioning (Munn et al. 2004, Carroll et al. 2006). Pooled results from 13 studies included within these reviews revealed a 3.8% (95% CI -2.2 – 9.8%; \( p = 0.02 \))
and a 10.4% (95% CI 3.5 – 17.3%; p < 0.01) increase in strength in the contralateral upper and lower limb respectively following a period of unilateral limb strengthening (Munn et al. 2004, Carroll et al. 2006). A more robust and recent review updated these figures and reported that a meta-analysis of 31 RCTs revealed an 11.9% (95% CI 9.1% – 14.8%; p < 0.00001) increase in strength in the contralateral limb following a period of unilateral limb strengthening (Manca et al. 2017). These results showed that unilateral limb training causes a moderate to large effect size (SMD = 0.7 95% CI 0.5 – 0.9) increase in strength to the contralateral (untrained) limb (Manca et al. 2017). The studies included in this review (Manca et al. 2017) were all RCTs looking specifically at strength training for CE. Although having RCTs and very strict inclusion criteria increases the robustness of the review, it should be noted that the methodological quality of the included studies was generally poor. Several methodological criteria associated with the internal validity of the studies were not fulfilled, therefore the risk of bias reported was high. Methodological quality, lack of controls and small sample sizes were also issues encountered within the earlier studies (Weir et al. 1995, Munn et al. 2004, Carroll et al. 2006). A more recent RCT (Harput et al. 2018) reported even higher strength gains ranging from 28% – 31% in the untrained limb following a period of strength training (concentric and eccentric) in patients recovering from an anterior cruciate ligament reconstruction (ACLr).

Strength training programmes are often the conditioning programmes of choice for investigating CE-related effects in the untrained limb. The CE effects reported when conditioning focused on eccentric muscular contractions have been larger (17.7% and 31%) than those observed following concentric muscular contractions (28% and 11.3%) (Manca et al. 2017, Harput et al. 2018) respectively. Therefore, identifying that CE effects are observed in higher amounts when conditioning programmes focus on eccentric muscular contractions. The large differences in the effects reported between these two studies is largely attributed to the difference in the selected cohort of patients where one study based their effects on healthy subjects as opposed those that underwent an ACLr knee surgery where underlying complex physiological interactions my incur in the increase in CE. When CE effects were investigated following the application of a sen-
sorimotor based intervention, a statistically significant \((p < 0.05)\) improvement (43%) in neuromuscular and sensorimotor function was reported (Schlenstedt et al. 2017). Other studies that also reported similar improvements in sensorimotor function of the untrained limb also reported significant effects of CE (Oliveira et al. 2013, El-Gohary et al. 2016).

Whilst the exact mechanisms behind CE-related effects are still unknown (Frazer et al. 2018), alterations in the shared neural activity patterns of both limbs are believed to be the primary cause (Scripture et al. 1894, Enoka 1988, Zhou 2000, Munn et al. 2004, Carroll et al. 2006, Frazer et al. 2018). Recent studies substantiating these claims are slowly increasing (Latella et al. 2012, Kidgell et al. 2015, Hortobágyi et al. 2011), with some studies even showing a direct linkage between central and peripheral neural activity in the untrained limb, measured as CE (Hortobágyi et al. 2011, Lepley & Palmieri-Smith 2014, Kidgell et al. 2015). These studies have shown that an increase in neural activity at the SC level influenced by supraspinal and corticospinal inputs, influences the efferent motor neuron (MN) output through the shared spinal connection (Carroll et al. 2006, Hortobágyi et al. 2011, Oliveira et al. 2013, Lepley & Palmieri-Smith 2014, Kidgell et al. 2015, El-Gohary et al. 2016, Schlenstedt et al. 2017, Harput et al. 2018, Frazer et al. 2018), resulting in increased physical performance outcomes such as muscular strength (e.g. peak force (PF), rate of force development (RFD) or electromechanical delay (EMD)) or improved SM function (e.g. improved centre of pressure (COP), proprioception acuity and force (FE)/angle reproduction). Patients with ongoing injury or disease (e.g. OA, ACLr, TKA) present with long term pain, swelling and neuromuscular inhibition (AMI) (Hurley et al. 1994, Palmieri et al. 2004, Rice & McNair 2010, Rice et al. 2014). Primarily effecting muscular strength, AMI is a phenomenon that alters physical performance (muscular activation) through an increased neurally derived inhibitory process (Hurley et al. 1994, Palmieri et al. 2004, Rice & McNair 2010, Rice et al. 2014). These physiological features often manifest in decreased muscular strength (Berth et al. 2002) and sensorimotor/neuromuscular function (e.g. decreased joint stability and balance) (Hurley et al. 1997, Hurley & Scott 1998) that is often manifested in both limbs. The results obtained from studies that have inves-
tigated healthy subjects (Munn et al. 2004, Manca et al. 2017) have reported smaller CE (8% – 12%) effects when compared to others whose cohort of subjects including patients following knee surgery (28% – 31%) (Harput et al. 2018) or a neurological condition such as a stroke or multiple sclerosis (24% – 46%) after a similar pattern of conditioning (Manca et al. 2016, Ehrensberger et al. 2016). These studies and the underlying physiological mechanisms suggest that the potential for change within these selected patients would be higher than those obtained in healthier individuals whose neural control within their joint is not affected by disease or surgery, but there is currently not enough literature to support this notion.

Unsurprisingly, the training effects achieved in the trained limb has always been reported to be much higher than those observed through CE (48% vs. 7%) (Munn et al. 2005, Oliveira et al. 2013). However, the clinical benefits of CE can be observed in situations when conditioning the desired limb is not possible or even detrimental to the patients’ rehabilitation status such as during periods of immobilisation after a fracture or severe acute pain following surgery (Munn et al. 2005, Manca et al. 2017). Immobilisation requires the patient to decrease mobility of the respective limb in order to allow proper healing. This period of immobilisation although beneficial, more often results in muscle atrophy and loss of function due to prolonged misuse of that limb (Veldhuizen et al. 1993, Magnus et al. 2010). Utilising the concepts of CE through exercise-conditioning has aided patients in attenuating loss of function and muscle atrophy (Magnus et al. 2010), restoring bilateral symmetry following a stroke (Ehrensberger et al. 2016) and managing severely weakened limbs due to multiple sclerosis (Manca et al. 2016, 2017). A recent study investigated the effects of CE vs. immobilisation (no training to the non-injured limb) and showed that, training the contralateral limb decreased muscle atrophy of the injured (immobilised) limb when compared to control subjects (immobilisation only - no intervention) (Magnus et al. 2010), therefore highlighting the fact that CE-related improvements outweigh no training conditions playing a crucial role in rehabilitation. Furthermore, CE-related effects can be used to maximise effectiveness of rehabilitation by minimising strength loss and potential complications due to misuse whilst enhancing patients’ recovery (Farthing et al. 2009),
by enabling patients to maintain a higher level of function in the injured limb prior to remobilisation, allowing for immediate benefits that potentially facilitates the rehabilitation process such as in patients undergoing TKA surgery.

In the current study, effects of CE were investigated in order to evaluate the observed effects in neuromuscular and sensorimotor performance outcomes of the untrained limb following a ‘novel’, short (1 week; 9 sessions as opposed to 6–12 weeks; 18 sessions) period of exercise-conditioning in patients waiting for TKA. Effects of CE will be measured in both limbs regardless of which limb is undergoing surgery (this is explained in further details in the subsequent Chapter 4). The utilisation of the contralateral (non-surgical) limb within the P–SEC programme would offer an alternative to training the leg undergoing surgery during these periods of time where patients are less mobile and experience acute episodes of severe pain. On the other hand, the CE effects observed in the non-surgical leg will help identify any carry over of the training effects delivered from the ‘novel’ P–SEC intervention.

2.8 Chapter summary

In summary (Figure 8.1), the evidence presented above concludes that:

- The integrity and function of the SMS of patients with ongoing OA of the knee is compromised causing a decrease in neuromuscular (motor) and sensorimotor function of the knee joint system that is exhibited in both knees;

- These decreased performance capabilities have been found to persist even up to a year following surgery despite the surgery’s success and have been linked with leading to tripping and falling;

- Pre-surgical exercise-conditioning programmes have been trying to address these issues but the generic conditioning parameters used in contemporary practices have led to short term effects that are not clinically significant;

- EB-SMT is the preferred type of conditioning for eliciting changes within these
neurally derived decreased performance capabilities but the literature does not provide enough information regarding the clinical efficacy for replication of use;

- Motor-based conditioning parameters are more well established and therefore, development of the ‘novel’ pre-surgery exercise-conditioning programme (P–SEC) has been based on motor-conditioning parameters that have been consistently supported within the literature for improving aspects of neuromuscular and sensorimotor control;

- The neuromuscular (EMD, RFD and PF) and sensorimotor (FE) outcome measures selected for this study exhibit good clinimetric and psychometric properties for capturing the nature of the time-limited changes in neuromuscular and sensorimotor performance capacities over time that would be affected by the nature of the P–SEC intervention programme;

- Along with the objective measures of physical capabilities, the combination of PROs selected (OKS, KOOS, PSEQ, IPAQ, SF-36v2™ and PP) to measure changes in patients’ perception of physical performance related capabilities during the pre-surgery P–SEC intervention and post-surgery care pathway, have been well documented for their excellent psychometric properties of reliability and reproducibility, especially amongst similar cohorts of patients with chronic knee OA and electing for TKA surgery;

- There is supporting evidence with regard to the effects and the corresponding benefits of CE for improving bilateral symmetry, accentuating and facilitating rehabilitation when training the limb undergoing surgery is not possible.
Figure 2.6: The figure above is a visual representation of the thesis outline. The dashed lines represent the relationships that are currently unknown or not clearly defined in the literature. The research questions are defined in blue whilst the yellow boxes are the chapters where these questions are addressed.
2.9 Research objectives

The primary objective of this research was to undertake a randomised controlled trial in order to investigate the effects of ‘novel’ formulation of pre-surgery exercise-conditioning (P–SEC) programme for motor performance on both objectively measured and patient-perceived performance capabilities in patients waiting to undergo TKA surgery. A secondary objective is to investigate and quantify any cross-education effects observed in objectively measured performance capabilities of the untrained limb in patients waiting to undergo TKA surgery.

2.10 Research questions

Following a review of the current literature, three major questions were sought to be answered through the employment of this research study. These questions are the following:

1. What is the efficacy of a ‘novel’ pre-surgery exercise-conditioning (P–SEC) programme on objectively measured physical performance capabilities (neuromuscular and sensorimotor) during the pre- and post-surgery phases of care pathway of patients electing to undergo TKA surgery? The effectiveness of the P–SEC conditioning will be gauged against local contemporary practice (no conditioning/control).

2. What is the effect of the ‘novel’ P–SEC intervention on patients’ perception of physical performance related capabilities during the pre- and post-surgery phases of care pathway of patients electing to undergo TKA surgery?

3. What is the efficacy of a P–SEC intervention on objectively measured physical performance capabilities (neuromuscular and sensorimotor) in the untrained limb as a result of CE during the pre- and post-surgery phases of the care pathway of patients electing to undergo TKA surgery?
2.11 Research hypotheses

A thorough review of the existing literature led to the development of the following hypotheses: Hypothesis 1 and 2 are aimed at answering what the effects of a ‘novel’ P–SEC conditioning programme on objectively-measured and patient perceived performance capabilities and its efficacy in patients waiting for a TKA surgery. Whilst hypothesis 3 is related to identifying the effects of the P–SEC conditioning programme on objectively-measured and patient perceived performance capabilities as measured in the non-trained limb in patients waiting for TKA surgery, that result from CE effects.

**Hypothesis 1: Chapter 5**

**H_0**: There are no significant differences in the selected neuromuscular (EMD, RFD and PF) and sensorimotor (FE) performance outcome measures following the application of a ‘novel’ motor-conditioning programme (P–SEC) in patients waiting for TKA surgery.

**H_1**: There are significant differences in the selected neuromuscular (EMD, RFD and PF) and sensorimotor (FE) performance outcome measures following the application of a ‘novel’ motor-conditioning programme (P–SEC) in patients waiting for TKA surgery.

**Hypothesis 2: Chapter 6**

**H_0**: There are no significant differences in the selected patient reported outcomes (for pain, habitual physical activity, function and QoL: OKS, KOOS, PSEQ, IPAQ, SF-36v2™ and PP) following the application of a ‘novel’ motor-conditioning programme (P–SEC) in patients electing TKA surgery during the pre- or post-surgery phase.

**H_1**: There are significant differences in the selected patient reported outcomes (for pain, habitual physical activity, function and QoL: OKS, KOOS, PSEQ, IPAQ, SF-36v2™ and PP) following the application of a ‘novel’ motor-conditioning programme (P–SEC) in patients electing TKA surgery during the pre- or post-surgery phase.
Hypothesis 3: Chapter 7

\( H_0 \): There are no significant differences in the selected neuromuscular (EMD, RFD and PF) and sensorimotor (FE) performance outcomes as measured in the untrained limb (CE) following the application of a ‘novel’ motor-conditioning programme (P-SEC) in patients waiting for TKA surgery.

\( H_1 \): There are significant differences in the selected neuromuscular (EMD, RFD and PF) and sensorimotor (FE) performance outcomes as measured in the untrained limb (CE) following the application of a ‘novel’ motor-conditioning programme (P-SEC) in patients waiting for TKA surgery.
Chapter 3

Efficacy of clinical sensorimotor training: A systematic review with meta-analysis

Abstract

Background: Exercise-based sensorimotor training (EB–SMT) has become increasingly popular due to its minimal use of equipment and ease of application in clinical and rehabilitative settings. However, inconsistent results exist regarding its efficacy and this may be due to heterogeneity amongst the studies’ parameters characteristics of physiological stress applied during the EB–SMT and experimental designs. Purpose: The primary aim of this systematic review was to critically investigate the efficacy of EB–SMT in adults while the second aim was to characterise the dosage of EB–SMT delivering favourable improvements in SM performance. Data sources: Five bibliographic databases: Medline, SPORTDiscus, Cochrane Library, CINAHL and SCOPUS were searched between January 2011 until February 2018. The SR was performed using guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The quality of the eligible studies was reviewed using the CONSORT checklist. Data extraction and synthesis: Twenty-four studies were included in the review. Meta-analysis of two studies indicated significant SM training effects (3 times a week over 4 weeks) on dynamic balance (z = 4.38 p < 0.001; standard
CHAPTER 3. EFFICACY OF CLINICAL SENSORIMOTOR TRAINING: A SYSTEMATIC REVIEW WITH META-ANALYSIS

mean difference of 1.14 (95 %CI [0.630, 1.653])). Systematic analysis of dose-effect responses to EB–SMT was not possible amongst the remaining studies which lacked descriptions of physiological intensity or effort. **Limitations:** Precision of estimating treatment effects of EB–SMT was limited by small samples in the contemporary literature. **Conclusion:** The results from the meta-analysis confirmed the efficacy of EB–SMT. Evidence from the 24 studies was not sufficiently robust and detailed to identify the most efficacious parameters for EB–SMT. Further research is required with appropriate reporting of physiological stress and its progression amongst EB–SMT protocols.

**Keywords:** sensorimotor, neuromuscular, balance, proprioceptive, plyometric, training, systematic review

**A. Introduction**

Sensorimotor training (SMT) is a concept developed to establish improvements in the sensorimotor (SM) system’s capacity and functional capability following musculoskeletal injuries (Liao et al. 2013, Cruz-Diaz et al. 2015, Bonacci et al. 2011) and other medical conditions such as Parkinson’s disease and cerebral palsy (van de Port et al. 2012, Adsuar et al. 2012, Tarakci et al. 2013, Schlenstedt et al. 2015). Although historically, SMT has been endorsed by research for its benefits to SM performance and injury prevention (McKeon et al. 2008, Zech et al. 2009, 2010, Hübscher et al. 2010), evidence regarding how to achieve maximum clinical efficacy remains elusive. In fact, the only consensus statement for the delivery of SMT (American College of Sports Medicine (ACSM)), lacks specificity about requisite conditioning stresses (frequency, intensity, duration and mode) for guiding its effective delivery in clinical practice (Garber et al. 2011). Heterogeneity within the methods used to deliver SMT (for example, exercise-based (EB) conditioning, visual imagery (Schwenk et al. 2014), whole body vibration (Adsuar et al. 2012) and exergaming (Fung et al. 2012, Tarakci et al. 2013)), within research designs (RCT\(^1\) vs. cohort) and within the reporting of physiological conditioning stresses, has led to ambiguity regarding the most advantageous facets of SMT. A specific type of SMT, exercise-based SMT (EB–SMT) is popular amongst clinicians

\(^1\)randomised controlled trial
due to its minimal requirement for equipment and ease of application in clinical and rehabilitative settings. Generally, EB–SMT has been shown to improve functional and physiological performance (McKeon et al. 2008, Avelar et al. 2016, Benis et al. 2016), reduce the incidence of ligamentous knee injuries (Sugimoto et al. 2014) and decrease fear of falling (Gusi et al. 2012) by means of a favourable integration of physiological responses to both sensory and motor stimuli (Clark & Lephart 2015). EB–SMT has also been used effectively as a focal intervention during peri–surgical care for patients undergoing total knee arthroplasty (Moutzouri et al. 2017, Peer 2017). Nevertheless, conflicting findings associated with EB–SMT for the general population continue to be reported (Bonacci et al. 2011, De Ridder et al. 2015, Hall et al. 2015, Dilek et al. 2016), and may be partially driven by diversity in the delivery–modes for EB–SMT. For example, exercises in a standing position have been delivered either in stationary or dynamic modes. Stationary standing exercises make use of weight–bearing and different surfaces such as foam–rubber pads (Hirase et al. 2015, Bennell et al. 2014), balance boards (Karakaya et al. 2015) and balance systems (Gusi et al. 2012, Linens et al. 2016, Pohl et al. 2015, Liao et al. 2013) to offer combined sensory and motor interaction for conditioning stimuli for preparation towards the subsequent effective initiation of movements. By contrast, dynamic weight-bearing exercises condition the participant to successfully maintain balance whilst in motion during movements characterised by agility and explosiveness, such as jumping (Huang et al. 2014, McKeon et al. 2008). The length of exercise programme for efficacious EB–SMT has also remained ill-defined, with heterogeneity of findings reported amongst studies. Improved SM changes have been elicited by both short (≤ 4 weeks (McKeon et al. 2008, Kumar et al. 2013)) and longer (6 – 12 weeks (Bennell et al. 2014, Hirase et al. 2015, Avelar et al. 2016)) durations of EB–SMT. Equivalence of SM efficacy for short- and longer-duration EB–SMT should favour the former approach as a more efficient use of clinical time. Improvements to the SM system’s performance may also be moderated by the selection of progression methods adopted during the EB–SMT. For example, conceptual theories describe how SM improvements are acquired through repetitive practice of a sensory guided motor behaviour (Wolpert et al. 2011), a process commonly referred to as SM learning (Schmidt & Lee 2013). Improvements in SM performance have been
more frequently elicited by means of repetition-based progression (Sekir & Gur 2005, Kumar et al. 2013, Bonacci et al. 2011, Bennell et al. 2014, Benis et al. 2016, Cuğ & Wikstrom 2016), where participants are required to repeat a given task for as many times as is necessary to achieve a criterion level of performance (Wolpert et al. 2011).

Previous systematic reviews (Zech et al. 2009, 2010, Hübscher et al. 2010, Steib et al. 2017) have not attempted to identify the most efficacious characteristics for the delivery of EB-SMT for use in clinical practice, but have focused instead on its efficacy for injury prevention, leaving a potentially important gap in the literature. Therefore, the purpose of this systematic review was firstly to critically investigate the efficacy of EB–SMT and secondly, to characterise the dosage of EB–SMT delivering favourable improvements in SM performance capacity.

B. Methodology

Data sources and searches
A comprehensive review of the existing literature was undertaken following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(Moher et al. 2009). Five bibliographic databases were interrogated for studies published prior to February 2018. The search included the following databases: Medline (via EBSCOhost Research database), SPORTDiscus (via EBSCOhost Research database), Cochrane Library, CINAHL (via EBSCOhost Research database) and SCOPUS (via Athens Library). For each database, individual and comprehensive search strategies were constructed using subject-headed mapping (refer to appendix A.1). Each database was interrogated using the following search terms: sensorimotor training, neuromuscular training, neuromotor training, balance training, plyometric training, proprioceptive training, outcome measures. All terms were searched as keywords [MeSH] and/or text words. In order to identify randomised controlled trials (RCTs), the following search terms were used: randomised controlled trials, clinical trials, placebo, control* and random*. Relevant titles and abstracts identified by the systematic literature search were screened by the reviewer (AMR). Predetermined selection criteria were used to evaluate potentially relevant studies. Where there was insufficient
information to determine its eligibility, the full article was interrogated. Consensus on inclusion was reached after independent review and subsequent discussion between the two reviewers (AMR and NG). In addition to the databases, the reference sections of the included articles were searched for eligible articles. Authors were contacted regarding missing or contradictory data, with up to two reminders, over a standardised period of two months.

Study selection
Publications were selected for inclusion if: (1) the research involved the delivery of an EB-SMT intervention; (2) participants were adult (> 18 years) and electing orthopaedic surgery (including unilateral or bilateral total joint arthroplasty), recovering from occupational or sports-related injury, or were asymptomatic; (3) the study provided description of its physiological stress during conditioning (including: exercise mode, frequency, intensity and duration) associated with the SMT intervention; (4) physical function and/or SM performance were evaluated (self-reported and/or performance-based); (5) the study had a controlled experimental design comparing an EB-SMT intervention with a placebo-type intervention, a standard treatment or no-intervention. The EB-SMT programme was defined as an intervention that involved participants completing a specific activity with their limbs for more than one session and involved activities such as balance-, plyometric-, neuromuscular- and proprioceptive-type conditioning; (6) the study was reported in English; (7) the study was published between January 2011 to February 2018 to reflect post-consensus statement findings (ACSM) (Garber et al. 2011). A study was excluded if: (1) its findings reflected the effect of an education programme or of complementary therapies (such as acupuncture, osteopathy, reflexology, etc); (2) the SMT was delivered to participants suffering from a neurological condition, a mental health condition or undergoing amputation surgery; (3) there was no longitudinal evaluation of the SMT’s effect.

Data extraction and quality assessment
Data extraction from the selected studies was performed by the first author (AMR). Customised data extraction forms were used to systematically collect information re-
Figure 3.1: PRISMA flow diagram demonstrating the patterns of inclusion of journal papers through the systematic process of the review. Key: *Three articles (Liao et al. 2015, Jagdhane et al. 2016, Bennell et al. 2015) were excluded due to various reasons mentioned in the results section; **Final search includes three articles that were obtained after the search strategy for further analyses of articles already included from the search strategy (McKeon et al. 2008, Sekir & Gur 2005, Bennell et al. 2014).
regarding the type of EB-SMT used (balance, plyometric, proprioceptive etc.), parameters (frequency, volume, duration and intensity), outcome measures, progression styles and compliance to programmes. Participants’ characteristics were also extracted. The methodological quality of the studies was assessed using a 33-item list developed from the CONSORT checklist for observational longitudinal studies (Tooth et al. 2005). The higher the score, the more robust the study is and the higher the quality of the results.

Data synthesis and analysis
A meta-analysis was performed amongst studies with similar outcomes of SM performance or physical function, involving EB-SMT with comparable dosages of conditioning and in participants with homogeneous characteristics. A random effects analysis was undertaken for each study using the method of DerSimonian & Laird (1986) to assess the pooled effect of a SM intervention. The meta-analysis was conducted using the ‘metan’ procedure in Stata (Stata Statistical Software 2013, College Station, TX: StataCorp LP). Where outcome measures were congruent, raw mean post-SMT intervention between-group differences were calculated. Statistical significance was accepted at p < 0.05. Where possible, effect size estimates were calculated for within-group comparisons using Cohen’s \( d \) (using mean and pooled standard deviation and adjusting for sample size) (Thalheimer & Cook 2002). An effect size value of 0.20 represents a small magnitude of change, 0.50 a moderate change, and values > 0.80 represent large changes (Thalheimer & Cook 2002). A qualitative review of studies was performed when evidence could not be pooled.

C. Results

Literature search
The literature search yielded 1188 references, with 55 unique trials identified as being potentially eligible for inclusion (refer to Figure 3.1). Twenty-four studies satisfied inclusion criteria for this systematic review. Three studies satisfied inclusion criteria and had offered sufficient homogeneity amongst outcome measures to justify data synthesis using a meta-analysis: Linens et al. (2016) (n = 34), McKeon et al. (2008) (n = 31) and Cuğ & Wikstrom (2016) (n = 28). The latter study lacked baseline control measures
and was excluded from the meta-analysis. Exclusions were due to inaccessibility of the full text review (Jagdhane et al. 2016, Scarneo et al. 2017, Pfie et al. 2016), redundancy of data already within included studies\(^2\) (Liao et al. 2015, Bennell et al. 2015) or insufficient information about the EB–SMT intervention parameters for the remainder of the excluded studies. In addition, three further studies (McKeon et al. 2008, Sekir & Gur 2005, Bennell et al. 2014) were identified and included by means of manual interrogation of the reference lists of the included studies, securing a total number of 24 studies for this review. The excluded 31 candidate studies did not contain sufficient information on the exercise’ parameters for the delivery of SMT to permit its replication of use.

**Methodological quality and risk of bias within the studies**

Ten out of the 24 studies (Avelar et al. 2016, Bennell et al. 2014, Bitterli et al. 2011, Cruz-Diaz et al. 2015, Gusi et al. 2012, Hall et al. 2015, Hirase et al. 2015, Liao et al. 2013, Bonato et al. 2017, Shih et al. 2018) scored higher than 20 out of a possible score of 33 on the CONSORT checklist, which is designed to reveal the extent of weaknesses of reporting of longitudinal research (Tooth et al. 2005). Sample and target population were reported in all of the studies but justification of how sample size was calculated was only reported in seven (Bennell et al. 2014, Bitterli et al. 2011, Cruz-Diaz et al. 2015, Hall et al. 2015, Hirase et al. 2015, Bonato et al. 2017, Shih et al. 2018). The majority (19) of the included studies (24) reported participants’ eligibility, consent and attrition rates at each stage of data collection, whereas the others were more sporadic in their descriptions (Bonacci et al. 2011, Jacobson et al. 2011, Gusi et al. 2012, Huang et al. 2014, Cuğ & Wikstrom 2016). Reasons for patient attrition rates and reasons for ‘loss to follow-up’ was reported in the majority of the studies (Avelar et al. 2016, Bennell et al. 2014, Benis et al. 2016, Bitterli et al. 2011, Bonato et al. 2017, Cruz-Diaz et al. 2015, De Ridder et al. 2015, Dilek et al. 2016, Hall et al. 2015, Hirase et al. 2015, Jacobson et al. 2011, Liao et al. 2013, Shih et al. 2018). Methodological execution (type of study, objectives, hypothesis) was reported in all of the studies. The impact of bias during the studies’ delivery and analysis of data was poorly reported. Only seven out of the 24 studies included a qualitative measure of bias (Bitterli et al. 2011, Cuğ &

\(^2\)The original studies which reported the data and effects of the EB–EMT intervention were included.
Participants’ characteristics

Average age across the 24 included studies was 43.8 years (±22.6; range: 18 – 82). Nine studies focused attention on participants aged over 60 years, while 15 studies reported on participants aged between 20 and 59 years. Female participants comprised 65 % of the studies’ populations, including contributions from three single-sex studies (Avelar et al. 2016, Benis et al. 2016, Bonato et al. 2017). Fifteen studies (refer to Table 3.1) investigated EB-SMT responses in participants with conditions such as knee osteoarthritis (OA) (Bennell et al. 2014, Kumar et al. 2013, Sekir & Gur 2005), chronic ankle instability (CAI) (Cruz-Diaz et al. 2015, De Ridder et al. 2015, Mettler et al. 2015, McKeon et al. 2008, Linens et al. 2016, Shih et al. 2018)) and who had elected to undergo surgery such as total hip replacement (THR) (Pohl et al. 2015, Bitterli et al. 2011). Eight studies focused on healthy (asymptomatic) participants (Bonacci et al. 2011, Jacobson et al. 2011, Hirase et al. 2015, Karakaya et al. 2015, Avelar et al. 2016, Benis et al. 2016, Cuğ & Wikstrom 2016, Bonato et al. 2017). Participants’ levels of habitual physical activity ranged from those associated with institutionalised but physically active older adults (Jacobson et al. 2011, Gusi et al. 2012, Hirase et al. 2015, Avelar et al. 2016) to those of professional/elite athletes (Benis et al. 2016, Bonacci et al. 2011, Cruz-Diaz et al. 2015, Huang et al. 2014, Bonato et al. 2017).
Table 3.1: Includes all 24 studies selected for this review with their respective population number (n), sample and respective CONSORT scores for methodological quality. Abbreviations: OA = Osteoarthritis; THR = Total hip replacement; CAI = Chronic ankle instability; SIS = Subacromial impingement syndrome; FAI = Functional ankle instability.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Total n =</th>
<th>Population/condition</th>
<th>CONSORT score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelar et al. (2016)</td>
<td>23</td>
<td>Active, Older women</td>
<td>21</td>
</tr>
<tr>
<td>Bennell et al. (2014)</td>
<td>100</td>
<td>Older adults, Knee OA</td>
<td>23</td>
</tr>
<tr>
<td>Benis et al. (2016)</td>
<td>29</td>
<td>Athletes, Healthy</td>
<td>19</td>
</tr>
<tr>
<td>Bitterli et al. (2011)</td>
<td>80</td>
<td>Older adults, THR</td>
<td>22</td>
</tr>
<tr>
<td>Bonacci et al. (2011)</td>
<td>8</td>
<td>Triathletes, Healthy</td>
<td>15</td>
</tr>
<tr>
<td>Bonato et al. (2017)</td>
<td>160</td>
<td>Athletes, Healthy</td>
<td>24</td>
</tr>
<tr>
<td>Cuğ &amp; Wikstrom (2016)</td>
<td>28</td>
<td>Young adults, Healthy</td>
<td>13</td>
</tr>
<tr>
<td>Cruz-Diaz et al. (2015)</td>
<td>70</td>
<td>Athletes, CAI</td>
<td>20</td>
</tr>
<tr>
<td>De Ridder et al. (2015)</td>
<td>64</td>
<td>Healthy, CAI</td>
<td>14</td>
</tr>
<tr>
<td>Dilek et al. (2016)</td>
<td>61</td>
<td>Middle age, SIS</td>
<td>18</td>
</tr>
<tr>
<td>Gusi et al. (2012)</td>
<td>40</td>
<td>Older adults, Fallers</td>
<td>20</td>
</tr>
<tr>
<td>Hall et al. (2015)</td>
<td>62</td>
<td>Adults, Post-knee surgery</td>
<td>23</td>
</tr>
<tr>
<td>Hirase et al. (2015)</td>
<td>93</td>
<td>Active, Older adults</td>
<td>20</td>
</tr>
<tr>
<td>Huang et al. (2014)</td>
<td>30</td>
<td>Athletes, FAI</td>
<td>12</td>
</tr>
<tr>
<td>Jacobson et al. (2011)</td>
<td>25</td>
<td>Active, Older adults</td>
<td>18</td>
</tr>
<tr>
<td>Karakaya et al. (2015)</td>
<td>59</td>
<td>Young adults, Healthy</td>
<td>13</td>
</tr>
<tr>
<td>Kumar et al. (2013)</td>
<td>44</td>
<td>Middle age, Knee OA</td>
<td>14</td>
</tr>
<tr>
<td>Mettler et al. (2015)</td>
<td>31</td>
<td>Young adults, CAI</td>
<td>15</td>
</tr>
<tr>
<td>McKeon et al. (2008)</td>
<td>31</td>
<td>Young adults, CAI</td>
<td>14</td>
</tr>
<tr>
<td>Liao et al. (2013)</td>
<td>113</td>
<td>Older adults, Post-knee surgery</td>
<td>20</td>
</tr>
<tr>
<td>Linens et al. (2016)</td>
<td>34</td>
<td>Young adults, CAI</td>
<td>16</td>
</tr>
<tr>
<td>Pohl et al. (2015)</td>
<td>58</td>
<td>Lower limb post-surgery</td>
<td>17</td>
</tr>
<tr>
<td>Sekir &amp; Gur (2005)</td>
<td>22</td>
<td>Middle age, Knee OA</td>
<td>14</td>
</tr>
<tr>
<td>Shih et al. (2018)</td>
<td>45</td>
<td>Middle age, FAI</td>
<td>23</td>
</tr>
</tbody>
</table>
CHAPTER 3: EFFICACY OF CLINICAL SENSORIMOTOR TRAINING: A SYSTEMATIC REVIEW WITH META-ANALYSIS

Table 3.2: Table for outcome measures (OM) and effect sizes in relation to the respective sensory, motor or combined sensorimotor OM found in the 24 studies included within this review. Abbreviations: S – sensory; M – motor; SM – sensorimotor; RPE – rate of perceived exertion; RFD – rate of force development; MVIC – maximum voluntary isometric contraction; PT – peak torque; PF – peak force; AFP – ankle force production; CMC – coefficient of multiple correlation; RMSE – root mean square error; SEBT – star excursion balance test; SLS – single leg stance; SCT – stair climb test; COP – centre of pressure; COPvel – centre of pressure velocity; AP – antero-posterior; ML – medio-lateral; PM – postero-medial; PL – postero-lateral; PSI/SI – postural stability index; BIS – balance index score; TUGT – timed up and go test; CST/CRT – chair stand/raise test; OLR – one leg raise; TST – tandem stance test; JPS – joint position sense; TTB/TTS – time to balance/stabilise test; FRT – functional reach test; FR – foam rubber surface; SS – stability surface; SLDL – single leg drop landing.

| Author, year | SMT intervention type | SMT type | Sensory Motor (S) | Motor (M) | Sensorimotor (SM) | Frequency (no. of sessions/week) | Intensity | Duration (weeks) | Volume (total no. of sessions) | Exercises (number and reps) | Time duration per session (minutes) | Relevant OM to SM intervention (S) | Effect Size (Cohens’ d) | Relevant OM to SM intervention (M) | Effect Size (Cohens’ d) | Relevant OM to SM intervention (Combined SM) | Effect Size (Cohens’ d) |
|--------------|----------------------|----------|------------------|-----------|-------------------|-------------------------------|----------|-----------------|-------------------|-------------------------------|-------------------------------|-------------------------------|---------------------------|--------------------------------|---------------------------|--------------------------------|---------------------------|--------------------------------|---------------------------|
| Avelar et al. 2016 | Circuit based WB balance training (both) | ✓ | 2 | - | 12 | 24 | 13 | 50 | SM | - | - | RFD; PT | 0.5 | 0.7 | COP (AP/ML) | 6-min walk test, 1.0/0.4 | CST, TUGT |
| Bennell et al. 2014 | WB static standing exercises with equipment (stationary) | ✓ | 2 (2 weeks) and 1 (10 weeks) | Level of effort self rated. 5 – 10 on modified Borg rating scale of RPE (CR-10) | 12 | 14 | 6/3 | 30 – 40 | SM + function | - | - | MVIC | - | SLS, SCT, CST, Step test | 0.5 |
| Benis et al. 2016 | Circuit based WB dynamic exercises with equipment (dynamic) | ✓ | 2 | - | 8 | 16 | 10/10 – 20 | 30 – 40 | M | - | - | - | - | Y-Balance test (PM/PL right and left) | 0.9 – 1.1 |

Continued on next page. Key: ✓ = present; - = absent; X = values not present for calculation, ? = unknown.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>SMT intervention type (stationary or dynamic)</th>
<th>Sensory Motor (S)</th>
<th>Motor (M)</th>
<th>Frequency (no. of sessions /week)</th>
<th>Intensity</th>
<th>Duration (weeks)</th>
<th>Volume (total no. of sessions)</th>
<th>Exercises (number and reps)</th>
<th>Time duration per session (minutes)</th>
<th>OM type</th>
<th>Relevant OM to SM intervention (S)</th>
<th>Effect Size (Cohens' d)</th>
<th>Relevant OM to SM intervention (M)</th>
<th>Effect Size (Cohens' d)</th>
<th>Relevant OM to SM intervention (Combined SM)</th>
<th>Effect Size (Cohens' d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitterli et al. 2011</td>
<td>Mixed (WB/NWB) sensorimotor exercise programme. No equipment (stationary)</td>
<td>✓</td>
<td></td>
<td>2</td>
<td>Pain guided. Participants encouraged to stop when pain sets in</td>
<td>2 – 6 varied</td>
<td>6/10</td>
<td>-</td>
<td>S M + function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Biodex</td>
<td>X</td>
</tr>
<tr>
<td>Bonacci et al. 2011</td>
<td>Plyometric training: explosive exercises and different surfaces (dynamic)</td>
<td>✓</td>
<td></td>
<td>3</td>
<td></td>
<td>8</td>
<td>24</td>
<td>11/6 – 20</td>
<td>30</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.8/1.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bonato et al. 2017</td>
<td>WB Standing exercises (dynamic)</td>
<td>✓</td>
<td></td>
<td>4</td>
<td></td>
<td>7</td>
<td>98</td>
<td>23/varied</td>
<td>30</td>
<td>SM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y-balance test; Counter movement jump (CMJ)</td>
</tr>
<tr>
<td>Cug et al. 2016</td>
<td>WB balance exercises with equipment (dynamic)</td>
<td>✓</td>
<td></td>
<td>3</td>
<td></td>
<td>4</td>
<td>12</td>
<td>4/42</td>
<td>30</td>
<td>SM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>AFP</td>
</tr>
</tbody>
</table>

Continued on next page. Key: ✓ = present; - = absent; X = values not present for calculation; ? = unknown.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>SMT intervention type (stationary or dynamic)</th>
<th>Sensory Motor (S)</th>
<th>Sensorimotor (SM)</th>
<th>Frequency (no. of sessions /week)</th>
<th>Intensity</th>
<th>Duration (weeks)</th>
<th>Volume (total no. of sessions)</th>
<th>Exercises (number and reps per session)</th>
<th>Time duration per session (minutes)</th>
<th>OM type</th>
<th>Relevant OM to SM intervention (S)</th>
<th>Effect Size (Cohens' d)</th>
<th>Relevant OM to SM intervention (M)</th>
<th>Effect Size (Cohens' d)</th>
<th>Relevant OM to SM intervention (Combined SM)</th>
<th>Effect Size (Cohens' d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruz-diaz et al. 2015</td>
<td>Circuit based WB dynamic exercises with equipment (dynamic)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>6</td>
<td>18</td>
<td>7/2</td>
<td>(45s work / 30s rest)</td>
<td>45 - 50</td>
<td>M + function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>PSI</td>
<td>X</td>
</tr>
<tr>
<td>DeRidder et al. 2015</td>
<td>WB balance exercises with equipment as HEP (dynamic)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>8</td>
<td>24</td>
<td>4-8/3x20s or 2/3 sets of 10</td>
<td>-</td>
<td>SM + function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilek et al. 2016</td>
<td>WB and non WB exercises (both)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>6</td>
<td>18</td>
<td>7/10</td>
<td>-</td>
<td>SM + function</td>
<td>Kinesthesia</td>
<td>X</td>
<td>MVIC</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Gusi et al. 2012</td>
<td>WB balance exercises on Biodex balance system (stationary)</td>
<td>✓</td>
<td>2</td>
<td>-</td>
<td>12</td>
<td>24</td>
<td>15</td>
<td>SM</td>
<td>-</td>
<td>-</td>
<td>Knee extensor and flexor force</td>
<td>0.2-0.4</td>
<td>Biodex: Static balance (FRT)</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hall et al. 2015</td>
<td>WB neuromuscular exercises with equipment (stationary)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>12</td>
<td>8</td>
<td>6/varied</td>
<td>-</td>
<td>M + function</td>
<td>-</td>
<td>-</td>
<td>PF</td>
<td>X</td>
<td>OLR 30s</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Continued on next page. Key: ✓ = present; - = absent; X = values not present for calculation; ? = unknown.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>SMT intervention type (stationary or dynamic)</th>
<th>Sensory Motor (S)</th>
<th>Motor (M)</th>
<th>Sensory-motor (SM)</th>
<th>Frequency (no. of sessions /week)</th>
<th>Intensity</th>
<th>Duration (weeks)</th>
<th>Volume (total no. of sessions)</th>
<th>Exercises (number and reps)</th>
<th>Time duration per session (minutes)</th>
<th>OM type</th>
<th>Relevant OM to SM intervention (S)</th>
<th>Relevant OM to SM intervention (M)</th>
<th>Effect Size (Cohens’ d)</th>
<th>Relevant OM to SM intervention (Combined SM)</th>
<th>Effect Size (Cohens’ d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirase et al. 2015</td>
<td>Group WB balance exercises with equipment (stationary)</td>
<td>✓</td>
<td>1</td>
<td>-</td>
<td>16</td>
<td>16</td>
<td>10/?</td>
<td>60</td>
<td>SM + function</td>
<td>- - - -</td>
<td>TST; OLST; (FR/SS); TUGT; CST</td>
<td>0.6 – 1.2</td>
<td>0.2 – 0.6; 0.1 – 0.4</td>
<td>0.5 – 0.8/ 0.2 – 0.4/ 0.2 – 1.0/ 0.1 – 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang et al. 2014</td>
<td>WB balance exercises and plyometric exercises with equipment (dynamic)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>6</td>
<td>18</td>
<td>6 – 8/ varied (10 reps x 2/3 sets)</td>
<td>SM</td>
<td>-</td>
<td>SLDL X</td>
<td>COP; OLST; TTS</td>
<td>2.7; 1.5</td>
<td>0.9; 0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobson et al. 2011</td>
<td>WB balance and strengthening exercises with equipment (stationary)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>12</td>
<td>36</td>
<td>7/30-60s hold</td>
<td>SM</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued on next page. Key: ✓ = present; - = absent; X = values not present for calculation, ? = unknown.
### Table 3.2 – Continued from previous page

| Author, year | SMT intervention type (stationary or dynamic) | Sensory Motor (S) | Sensorimotor (SM) | Frequency (no. of sessions /week) | Intensity | Duration (weeks) | Volume (total no. of sessions) | Exercises (number and reps) | Time duration per session (minutes) | OM type | Relevant OM to SM intervention (S) | Effect Size (Cohens’ d) | Relevant OM to SM intervention (M) | Effect Size (Cohens’ d) | Relevant OM to SM intervention (Combined SM) | Effect Size (Cohens’ d) |
|--------------|---------------------------------------------|------------------|------------------|----------------------------------|----------|----------------|---------------------------|-------------------------|-------------------------------|---------|--------------------------------|----------------|--------------------------------|----------------|--------------------------------|----------------|--------------------------------|----------------|
| Karakaya et al. 2015 | WB balance, stretching and strengthening exercises with equipment (stationary) | ✓ | 5 | - | 2 | 10 | 10 – 12/10 | - | SM | - | - | - | - | BIS | 1.2; 1.4; 1.3 |
| Kumar et al. 2013** | WB balance exercises using different surfaces with additional contemporary practice. (stationary) | ✓ | 3 | - | 4 | 12 | 10/7 | - | S + function + pain | JPS error | 1.3 | - | - | - | - | - |
| Liao et al. 2013 | WB balance exercises with equipment (stationary) | ✓ | 3 | - | 8 | 54 | 9/varied | 60 | SM + function | - | - | - | - | - | - | - | - | - |

*Continued on next page. Key: ✓ = present; - = absent; X = values not present for calculation; ? = unknown.*
<table>
<thead>
<tr>
<th>Author, year</th>
<th>SMT intervention type (stationary or dynamic)</th>
<th>Sensory Motor (S)</th>
<th>Sensorimotor (SM)</th>
<th>Frequency (no. of sessions/week)</th>
<th>Intensity</th>
<th>Duration (weeks)</th>
<th>Volume (total no. of sessions)</th>
<th>Exercises (number and reps)</th>
<th>Time duration per session (minutes)</th>
<th>OM type</th>
<th>Relevant OM to SM intervention (S)</th>
<th>Effect Size (Cohens’ d)</th>
<th>Relevant OM to SM intervention (M)</th>
<th>Effect Size (Cohens’ d)</th>
<th>Relevant OM to SM intervention (Combined SM)</th>
<th>Effect Size (Cohens’ d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linens et al. 2016</td>
<td>WB balance exercises with equipment (stationary)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>4</td>
<td>12</td>
<td>5/40s hold</td>
<td>8-10</td>
<td>SM + function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>TTB; Foot lift; test; SEBT; figure of 8 hop test</td>
<td>0.9; 0.8; 0.9 – 1.4; 0.9</td>
<td></td>
</tr>
<tr>
<td>Mckeen et al. 2008*</td>
<td>WB balance exercises using equipment and including explosive exercises (dynamic)</td>
<td>✓</td>
<td>3</td>
<td>-</td>
<td>4</td>
<td>12</td>
<td>5/10 or 30 – 90s hold</td>
<td>20</td>
<td>SM + function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>COPvel; TTB; SEBT</td>
<td>0.1/0.5; 0.5; 0.7</td>
<td></td>
</tr>
<tr>
<td>Mettler et al. 2015*</td>
<td>WB balance exercises using equipment and including explosive exercises (dynamic)</td>
<td>✓</td>
<td>3</td>
<td>?</td>
<td>4</td>
<td>12</td>
<td>5/10 or 30 – 90s hold</td>
<td>20</td>
<td>SM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>COP</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pohl et al. 2015</td>
<td>WB balance exercises with equipment (stationary)</td>
<td>✓</td>
<td>6/4/2</td>
<td>-</td>
<td>3</td>
<td>6-18</td>
<td>3/30s x6</td>
<td>18</td>
<td>SM + function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>JPS; SI; Gait</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Continued on next page. Key: ✓ = present; - = absent; X = values not present for calculation; ? = unknown.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>SMT intervention type</th>
<th>Sensory Motor (S)</th>
<th>Sensorimotor (SM)</th>
<th>Frequency (no. of sessions /week)</th>
<th>Intensity</th>
<th>Duration (weeks)</th>
<th>Volume (total no. of sessions)</th>
<th>Exercises (number and reps)</th>
<th>Time duration per session (minutes)</th>
<th>OM type</th>
<th>OM to SM intervention (S)</th>
<th>Effect Size (Cohens' d)</th>
<th>OM to SM intervention (M)</th>
<th>Effect Size (Cohens' d)</th>
<th>OM to SM intervention (Combined SM)</th>
<th>Effect Size (Cohens' d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sekir et al. 2005**</td>
<td>Multi station WB balance exercises (stationary)</td>
<td>✓</td>
<td>2</td>
<td>-</td>
<td>6</td>
<td>12</td>
<td>11/1-3</td>
<td>-</td>
<td>S + M + function</td>
<td>JPS error, kinaesthesia</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>OLST; TST; TUGT; 15-m walk; CRT;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shih et al. 2018</td>
<td>WB dynamic and static exercises (both)</td>
<td>✓</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>8</td>
<td>15-20</td>
<td>4/2 sets x 5 reps x 5 cycles</td>
<td>SM + function</td>
<td>-</td>
<td>-</td>
<td>MVIC (Peroneus Longus) (-0.6) - Y-Balance test (A/PL/PM) 0.5/0.1/0.7</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>-</td>
</tr>
</tbody>
</table>
Synthesis of results: meta-analysis (n = 2)

Only two studies (McKeon et al. 2008, Linens et al. 2016) matched for parameters’ characteristics and outcome measure and were included in the meta-analysis. Pooled results for the two studies showed an overall significant gain in dynamic balance (SEBT), compared to control, for SMT involving dynamic standing and weight-bearing exercises ($z = 4.38 \, p < 0.001$), with a standard mean difference of $1.14$ (95% CI [0.630, 1.653]) and homogeneity ($I^2 = 0.0 \%$) between studies ($\chi^2 (d.f. = 1) = 0.04 \, p > 0.05$ (refer to Table 3.3)). Estimates of between-study variance ($\tau^2 \approx 0$) and weighted mean difference (WMD) were also calculated and shown in Table 3.3 and Figure 3.2.

![Star Excursion Balance Test (SEBT)](image)

Figure 3.2: Meta-analysis results showing standardised mean differences for the included studies by McKeon et al. (2008) and Linens et al. (2016).

Qualitative synthesis of results for all included studies (n = 24)

Delivery for EB–SMT varied extensively amongst the 24 studies. In general, the characteristics of EB–SMT delivery that have elicited significant performance enhancements in the OMs has been: 3 times per week (Cuğ & Wikstrom 2016, McKeon et al. 2008, Cruz-Diaz et al. 2015, McKeon et al. 2008, Kumar et al. 2013), over a period of 4 –
Table 3.3: Pooled effect sizes (ES) (95% CI), Pooled weighted mean difference (WMD) (95% CI) values and respective weight percentages (%) for STATA analysis of McKeon et al. (2008) and Linens et al. (2016) studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>ES [95% CI]</th>
<th>% Weight</th>
<th>WMD [95% CI]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKeon et al. (2008)</td>
<td>1.087 [0.323 – 1.793]</td>
<td>48.45</td>
<td>0.110 [0.039 – 0.181]</td>
<td>47.83</td>
</tr>
<tr>
<td>Linens et al. (2016)</td>
<td>1.194 [0.453 – 1.878]</td>
<td>51.55</td>
<td>0.120 [0.052 – 0.188]</td>
<td>52.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pooled ES and WMD</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>D + L pooled ES</td>
<td>1.142 [0.630 – 1.653]</td>
<td>100.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>I – V pooled WMD</td>
<td>–</td>
<td>–</td>
<td>0.115 [0.066 – 0.164]</td>
<td>100.00</td>
</tr>
</tbody>
</table>

12 weeks (Cuğ & Wikstrom 2016, Mettler et al. 2015, McKeon et al. 2008), involving at least 12 sessions (McKeon et al. 2008, Cuğ & Wikstrom 2016, Linens et al. 2016, Sekir & Gur 2005) and lasting an average of 32 minutes per session. This formulation of EB–SMT resulted in moderate to large within-group effect sizes (ES) (refer to Table 3.2) for sensory measures (centre of pressure/velocity (COP/COPvel); time to balance (TTB) test; joint position sense (JPS)) and motor (star excursion balance test (SEBT); figure of 8 hop test; ankle force production (AFP)) outcome measures. The majority of the studies included in the review, did not report a qualitative or quantitative intensity of effort or work’ intensity associated with the exercises (such as the percentage of the participant’s daily maximal voluntary contraction (MVC) of a particular muscle or participant’s perceived level of exertion). One study (Bennell et al. 2014) used rate of perceived exertion (RPE) as a quantifiable measure of the level of work’ intensity at which participants were expected to work. Another study used pain’ measurements to guide prescribed levels of effort (Bitterli et al. 2011).

**Mode of EB–SMT:**

The mode of EB–SMT exercises commonly varied between two modes in the weight-bearing position: (1) stationary (exercises that require the participant to maintain balance in one position whilst counteracting minimal external perturbations associated with sensory input such as eyes closed and balance on a foam surface) or (2) dynamic
exercises that require forces associated with the weight of the participant to be managed in a standing position whilst counteracting large external perturbations such as those experienced during jumping and changing direction) exercises. Both styles of EB-SMT have shown the ability to elicit significant post-training effects (refer to Table 3.2) with moderate to high ESs found for both sensory and motor outcome measures. Amongst the studies included in the review, five (Pohl et al. 2015, Hall et al. 2015, Cuğ & Wikstrom 2016, Dilek et al. 2016, Shih et al. 2018) failed to report efficacy using either of the described modes of EB–SMT.

**Progression of stimuli associated with SMT intervention:**
Eight out of the 24 studies did not document whether or not progression was applied within the intervention process, whilst the remaining 16 studies had progression documented extensively. Amongst the latter 16 studies, four had based progression on the extent of change in participants’ exercise capacity as perceived by a specialist in exercise conditioning (Hall et al. 2015, Cruz-Diaz et al. 2015, Avelar et al. 2016, Linens et al. 2016). The progression of intensity of SM stimuli during the intervention was not individualised within 10 studies (Sekir & Gur 2005, Bitterli et al. 2011, Bonacci et al. 2011, Jacobson et al. 2011, Liao et al. 2013, Kumar et al. 2013, De Ridder et al. 2015, Dilek et al. 2016, Huang et al. 2014, Karakaya et al. 2015), whilst two other studies (Benis et al. 2016, Cuğ & Wikstrom 2016) had a pre-defined set of targets that the participants were required to progress through sequentially. Progression was implemented heterogeneously amongst studies. Some studies used progression based on “error”, where the participant progressed according to the reduction in number of errors exhibited during the exercises, whilst others progressed according to a predetermined number of repetitions per week or per session. The results from studies with similar progression methods could not easily be collated because of concomitant heterogeneity amongst other important parameters of experimental design. Nevertheless, when comparisons of contrasting methods to manage progression during EB–SMT (improving error-rates vs. predetermined increasing numbers of repetitions) was evaluated, this yielded no significant differences to the extent of improvements in dynamic balance (SEBT) (Cuğ & Wikstrom 2016).
**D. Discussion**

This systematic review revealed 24 trials that investigated the effects of EB–SMT in adults. Two out of the 24 studies (McKeon et al. 2008, Linens et al. 2016) were closely-matched on the characteristics of study parameters such as frequency, duration and outcome measures, and included for meta-analysis. The results of the meta-analysis showed statistically significant ($p < 0.05$) improvements in SM performance for dynamic balance (SEBT), confirming the efficacy of EB–SMT. Nevertheless, the limited nature of information based on only two studies and 64 participants in total, (McKeon et al. 2008, Linens et al. 2016) preclude quantification of the characteristics of EB–SMT that might deliver optimal gains for clinical use.

**Parameters characteristics and sensorimotor learning**

The meta-analysis results showed tentatively that EB-SMT with a duration of 12 sessions, delivered across four weeks, and lasting approximately 20 minutes each session, resulted in significant improvements of SM performance in dynamic balance (SEBT). The effect sizes (Cohen’s $d = \geq 1.0$) exhibited in these two studies (McKeon et al. 2008, Linens et al. 2016) were also comparable in magnitude ($d = 0.6 – 1.1$) to another study (Cuğ & Wikstrom 2016) within this review that involved a training programme of a similar duration. Although the results of the meta-analysis are encouraging, they should be interpreted with caution being based on only two studies with a relatively high risk of bias (CONSORT score 14 and 16, respectively). In addition, the lack of detail within these studies about physiological intensity used in the delivery of EB–SMT does not allow for appropriate quantification of parameters associated with efficacious delivery.

With regard to the duration of the EB–SMT, studies with both shorter (2 weeks) (Karakaya et al. 2015) and longer (6 – 24 weeks) (Cruz-Diaz et al. 2015, Benis et al. 2016, Bonato et al. 2017) EB–SMT durations have also revealed large ESs ($d = 1.2 – 1.4$ (BI) (Karakaya et al. 2015); $d = 0.7 – 1.8$ (SEBT) (Cruz-Diaz et al. 2015); $d = 0.9 – 1.1$ (Y–Balance test) (Benis et al. 2016); $d = 1.1 / 0.6$ Y–Balance test and counter
movement jump respectively (Bonato et al. 2017)) in SM performance. These results may imply that longer duration protocols, where participants’ exposure to EB–SMT is increased (e.g. from 2 to 16 weeks), may be wasteful of clinical time since shorter programmes are eliciting similar magnitude of changes in SM performance. However, at this point in time, the available evidence is limited. Further research is needed to confirm the ideal duration of EB–SMT programmes to optimally balance the need for the greatest improvements in SM performance against the most efficient use of clinical time.

Both modes of EB–SMT delivery (stationary and dynamic exercise) were found to provoke statistically significant improvements in SM performance in all but five studies (Pohl et al. 2015, Hall et al. 2015, Cuğ & Wikstrom 2016, Dilek et al. 2016, Shih et al. 2018). Whilst Pohl et al. (2015) and Hall et al. (2015) made use of a stationary type of EB–SMT, the remaining three used a mixture of both stationary and dynamic EB–SMT (Cuğ & Wikstrom 2016, Dilek et al. 2016, Shih et al. 2018). Overall, both modes of delivery seem to be equally efficacious and capable of eliciting moderate to large effect sizes ($\geq 0.7$) in SM outcomes, even when volume of exposure to conditioning stimuli within the EB–SMT programmes varied (for example 8 sessions vs. 24 sessions of EB-SMT delivery) (Avelar et al. 2016, Shih et al. 2018). It is important to note that parameters such as the number of sessions, frequency and the duration of the EB–SMT do not necessarily reflect the amount of physiological stress to which the participants were exposed to. Therefore, in addition to the latter parameters, precise physiological intensity parameters are required in order to identify and quantify optimal physiological stress associated with the EB–SMT and required to elicit improvements in SM performance outcomes. This review revealed an overall lack of precise reporting of the physiological intensity. As such, the review was unable to draw any formal conclusions about the physiological dosing associated with efficacious responses of participants to EB–SMT.

Finally, an exercise programme’s efficacy for improving SM performance is also influenced by the method used for regulating progression of exercise stress and the amount of practice in sensory guided motor behaviour (Schmidt & Lee 2013). Theoret-
ically, SM learning is believed to occur more effectively through repetition- compared to error-based procedures (Wolpert et al. 2011). However, findings in this review have been conflicting. For example, the magnitude of effect sizes (range $d = 0.5 – 1.3$) achieved in the studies that used repetition-based procedures to replicate progression (Sekir & Gur 2005, Kumar et al. 2013, Bonacci et al. 2011, Bennell et al. 2014, Benis et al. 2016, Cuğ & Wikstrom 2016) was similar in potency of effect (range $d = 0.2 – 1.4$) compared to procedures regulating progression training using time (Gusi et al. 2012, Avelar et al. 2016) or a combination of both repetition and time (McKeon et al. 2008, De Ridder et al. 2015, Hall et al. 2015, Mettler et al. 2015, Linens et al. 2016, Pohl et al. 2015) ($d = 0.2 – 1.0$). In addition only one study (Cuğ & Wikstrom 2016), compared two different styles of progression (repetition- vs. error-based) and reported no significant differences between the two between these two specific styles of regulation for progression in training. Therefore, despite conceptual theories favouring repetition-based regulation of training progression, this review suggests that alternative methods of regulating might be equally effective in provoking improvements in SM performance.

E. Strengths and limitations of the review

This SR benefitted from using PRISMA guidelines and focused attention on evidence derived only from studies involving controlled experimental designs. The SR is novel and has compiled a comprehensive interrogation of evidence investigating the efficacy of EB–SMT. Furthermore, this review includes unique critical evaluations of the characteristics of training programmes, including the consideration of the application of physiological stress (i.e. mode, frequency, intensity (when reported), duration, progression). The review’s limitations include the following: Firstly, only studies written in the English language were included and other existing and relevant studies may not have been included. Secondly, although study selection was based on predetermined inclusion criteria, only the main author assessed full-text articles for eligibility. Two authors might have reduced potential error or bias in study selection. Finally, small sample sizes (e.g. $n = 8$ to $23$ in several of the included studies) may give rise to a greater vulnerability for an experimental design having insufficient statistical power and concomitant intrusions from inflated type II error rates.
F. Conclusion and recommendations

This systematic review confirmed the efficacy of EB–SMT, but heterogeneity the included studies’ parameters prevented quantification of parameters for establishing the most efficacious protocol of EB–SMT for clinical use. Despite evidence from the 24 studies showing efficacious improvements in SM performance, the contemporary literature does not offer sufficiently robust evidence and information to identify the most efficacious parameters for EB–SMT. Further research into this subject area is required with appropriate reporting of physiological stresses and methods used to regulate training progression within EB–SMT for its optimal delivery in clinical applications.

Therefore,

- Meta-Analysis results confirm the efficacy of EB–SMT for improving SM performance in dynamic balance.

- There is currently not enough evidence for the recommendation of the most efficacious parameters for EB–SMT delivery, regardless of the reported improvements in SM performance.

- Further research is required in order to identify the ideal parameters for EB–SMT that would bring about the most efficacious improvements in SM outcome performance measures.

- Future research should report more detailed information regarding the physiological stresses prescribed during EB–SMT, including the effort or intensity associated with the conditioning exercises.
Chapter 4

Methodology

This chapter contains descriptive information about the apparatus and methods for the delivery of the outcome measures used during the delivery of this study. This chapter also describes in detail the practical delivery of the P–SEC protocol and the apparatus used during its delivery. In depth information about the literature behind the use of the specific outcome measures and the scientific background behind the development of the P–SEC protocol can be found in Chapter 2.

4.1 Study design

A single-centre, assessor-blinded, random-allocation, controlled trial was designed and delivered at the Robert Jones and Agnes Hunt Orthopaedic hospital NHS Foundation Trust (RJAH NHS Trust).

4.2 Ethical approval

Ethical approval for this study was granted by the South East Scotland Research Ethics Committee 01 (IRAS 198930; REC reference 17/SS/0005; see Appendix B), research and development department at RJAH NHS Trust, Oswestry (RL1 715; see Appendix C), and Queen Margaret University, Edinburgh (see Appendix D). This study conformed to requirements of the Declaration of Helsinki. The protocol in this study was registered with the www.ClinicalTrials.gov Protocol Registration and Results System (NCT03113032) as well as the International Standard Randomised Controlled Trials
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Number registry (ISRCTN75779521) prior to enrolment of the first participant.

4.3 Study sample

The word patient/s is often being used to refer to those that have not necessarily participated in the study but have been part of the initial screening process. Participant/s are the group of people who have consented and were randomised to take part in the study.

The sample-size and cohort of patients that have been chosen in this study are detailed as follows:

A. Sample size calculation

A sample size was estimated that would offer requisite experimental design sensitivity associated with factorial ANOVA involving condition/group (Experimental P–SEC$_{\text{IPSI}}$ (surgical) vs. Experimental P–SEC$_{\text{CONTRA}}$ (non-surgical) vs. Control (no conditioning); independent measures), time (pre-surgery and pre-P–SEC intervention baseline: $\sim$10-weeks [T1], at 2-weeks [T2], post-P–SEC intervention: at 1-week pre-surgery [T3], day of surgery [T4]$^1$, vs. 6-weeks post-surgery [T5]; repeated measures) and leg (conditioned vs. control (no conditioning); repeated measures) for separate group mean comparisons of primary outcomes, i.e. electromechanical delay (EMD), and secondary outcomes, i.e. objectively-measured neuromuscular (rate of force development (RFD) and peak force (PF)), sensorimotor (force error (FE)) and patient perceived performance capabilities and pain self-efficacy. Approximately 45 – 65 patients (www.sportsci.org; official ACSM website calculator) electing to undergo TKA was calculated for appropriate experimental design sensitivity and statistical power (0.7 – 0.8; commensurate with an exploratory trial) for describing changes in the primary outcome measure (EMD) across the period of the experiment, and involving random allocation of participants to groups (Type II error: 0.20; Type I error: 0.05; relative effect size$^2$:

$^1$Or same week of surgery which normally resulted 1 week after the P–SEC intervention.

$^2$Raw effect size in previous experiments has been between 5 – 8% measured by coefficient of variant, expressed relative to the magnitude of the pooled standard deviations (SD) associated with: (i) the mean inter-group responses at specified points in time for assessment being compared, or (ii) between
moderate to large (0.5 – 0.7)). Estimating an inflated sample-size that would properly take into account the sample’s likely rate of attrition and the rate at which participants will volunteer, suggests that the research team needed to approach approximately 60 patients for participation. Previous PhD studies conducted at the RJAH NHS Trust showed a high compliance rate (>90%). However, the feasibility of achieving the required sample size and the requisite experimental design sensitivity has been considered carefully against known rates of surgery for the candidate patient group (TKA: ~100 patients per annum) and conservative estimates of patient-recruitment (60% volunteering) and drop-out rates (80% retention) during a data acquisition period of 0.92 years (16-week period of evaluation; total study duration: 0.92-years, i.e. 11-months). This size of sample population offered a 0.7 – 0.8 power of proper detection of moderate relative effect size in the remaining secondary outcome measures.

B. Inclusion and exclusion criteria

Potential participants in this study were selected from the patient waiting-list for a TKA of 5 consultants all performing the same TKA procedures on patients who fit the following criteria:

- are over the age of 18 who were diagnosed with severe osteoarthritis (OA) of the knee and awaiting a TKA;
- who had a contralateral knee OA/TKA;
- who had other orthopaedic conditions affecting the contralateral leg.

Patients were excluded from this study if:

- they were undertaking a TKA due to a knee joint disease other than OA;
- they suffered from a rheumatic or neurological disorder;
- they had any other orthopaedic conditions affecting lower body function such as amputations;

responses of the surgical-leg and contra-lateral control-leg at a given assessment occasion, and adjusted for repeated measures (correlation associated with ipsi-lateral inter-assessment and contra-lateral leg comparisons assumed to be at least 0.7).
they exhibited signs of reduced mental capacity affecting their ability to follow exercise programme.

4.4 Participants’ recruitment and randomisation

Following the study’s ethical approval, potential participants were identified from the patient waiting-list. Some patients were invited to participate in the study during the first initial consultation with the surgeon, that typically varied between 10 – 12 weeks\(^3\) prior to the scheduled operation. When this was not possible, potential participants from the patient waiting-list were identified by the surgeon and were alternatively contacted through a phone call by the chief investigator (C.I.) following the approval from the respective surgeon. Patients that satisfied the inclusion criteria, were given (or sent by post/e-mail) a copy of the patient information sheet (see Appendix E) and offered participation in the study by the C.I. together with the surgeon (see Appendix F). Those patients who met the inclusion criteria and volunteered for the study were offered participation by the C.I. and signed informed consent (see Appendix G) was obtained prior to enrolment. Participants’ routine pre- and post-surgery TKA care offered at RJAH NHS Trust (RJAH NHS Trust website: www.rjah.nhs.uk/About-Us/Publications/Patient-Leaflets/Knee-Replacement-Booklet.aspx), was not withheld in any way.

Randomisation of participants into groups was carried out using a block randomisation procedure generated by the local statistician at RJAH NHS Trust hospital. The participants were randomly assigned to one of three groups, corresponding to: Group 1: P–SEC intervention to the surgical leg (P–SEC\(_{IPSi}\)); Group 2: P–SEC intervention to the non-surgical leg (P–SEC\(_{CONTRA}\)); and Group 3: a control “current practice” group (Control) no intervention, in blocks of 3 or 6 patients at any point in time. Additional randomisation in the early stages of participant recruitment was pre-programmed by the statistician in order to further decrease the likelihood of the C.I. (AMR) from figuring out the sequence of randomisation. In order to further minimise bias and increase

\(^3\)Average of 75 days (11-weeks) waiting time to surgery
the blinding of the C.I. to participant allocation to group, the list generated by the statistician was sent to an independent research member (AB) who was not involved in any of the data collection procedures. The C.I. was then informed about the allocated patient to the study through a secured internal email system, and using a patient identification code for the trial (e.g. P–SEC01), indicating whether the new participant was in the current practice group (Control) or whether the intervention was to be delivered on the right leg (e.g. P–SEC01 = R P–SEC) or the left leg (e.g. P–SEC01 = L P–SEC). Participants were asked to avoid mentioning which leg was due for surgery to help keep the C.I. blinded to group allocation throughout the study. To allow for appropriate concealment, the participant allocation-to-group list was kept by the independent research member (AB) throughout the data capture period and was only given to the C.I. following completion of the data capture and input of data for analyses.

4.5 Surgical procedure

Although total knee arthroplasty surgery is a mutual decision taken between the patient and the surgeon, NHS guidelines are in place to help orthopaedic surgeons define the diagnosis. The severity of the knee arthritis is firstly assessed by means of radiographic images and secondly knee score questionnaires such as the Oxford Knee Score (OKS) are also taken into consideration as a measure of the patient’s pain and function. The RJAH NHS Trust institute adopts the OKS questionnaire and those patients scoring less than 26 points are regarded as eligible for surgery. The TKA surgery performed in the patients selected for the study was performed under general or spinal (+/- sedation) anaesthesia with saphenous nerve block. TKA surgical procedure was performed by an experienced orthopaedic surgeon or supervised trainee using a medial parapatellar approach. Damaged articular surfaces were replaced by a Medial Rotation Knee™ (MRK™) prosthesis. The endoprosthesis components were cemented and modular bearing components were also used. During the surgery, a tourniquet (300 mmHg) was used until the implants were cemented in place. The total duration of the operation was 60 minutes without any complications. Post-operative medications included Clexane, for prevention of blood clots (40mg once daily low molecular weight heparin taken
over 2-weeks), tranexamic acid 1g six hours post- surgery and antibiotics (two IV doses of cefuroxime 750 mg) for prevention of infections. Enhanced recovery protocol at the RJAH NHS Trust hospital included an additional 150mL 0.2% ropivcane local anaesthetic infiltration intra-operatively. Post-op rehabilitation included mobilisation first day post-op and daily range of motion exercises. Patients were discharged from hospital at 3-5 days post-operatively following appropriate stair management rehabilitation.

4.6 Study protocol

The design of this study involved taking five repeated measures of assessments of patients electing a TKA surgery, starting from the time when patients were listed for surgery (∼10 – 12 weeks before surgery) up to 6-weeks after surgery (refer to Figure 4.1). The last assessment point (i.e. 6-weeks after surgery), which coincided with a scheduled outpatient clinical review, was used to acquire and quantify any retention of P-SEC’ effects post-TKA surgery. This data was based on patients’ response to tests of neuromuscular and sensorimotor performance capacities. The periodisation of assessments was selected to reflect important logistical and clinical epochs in the patients’ pathway of surgical and rehabilitative care. The assessments quantified and described objective (neuromuscular and sensorimotor) and patient-reported measures of performance capabilities, levels of habitual physical activity and pain self-efficacy prior to and around the time of surgery. Both limbs of the included participants were assessed for the selected outcome measures. Note: the performance outcome of the untrained leg acted as a potential experimental control in the study for contra-lateral limb comparisons and cross-education effects.

The five testing events occurred at the following time points: (i) T1 at ∼10 – 12 weeks pre-surgery\(^4\); (ii) T2 at 2-weeks prior to surgery pre-P–SEC intervention; (iii) T3 at 1-week prior to surgery post-P–SEC intervention; (iv) T4 during the same week of surgery\(^5\) and (v) T5 ~ 6-weeks post surgery. Some of the sessions were performed alongside scheduled pre-admission appointments, physiotherapy visits or meetings with

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\(^4\)Average of 75 days (11-weeks) waiting time to surgery

\(^5\)Average of 3.7 days prior to surgery
their surgeon. When this was not possible, participants were asked to attend at their own convenience. Each assessment session lasted no longer than one and a half hours, whilst the exercise sessions lasted approximately 20-minutes each occasion. Further information about the delivery of the P–SEC protocol can be found below in Section 4.8.

4.7 Data collection

During each assessment session, subjective outcome measures, i.e. patient reported outcomes (PROs), and objective outcome measures, i.e. physical and physiological performance, were recorded. During the first assessment session, the participants were familiarised to the recording procedures and the study protocol. This initial session was
also used to establish and record baseline measurements, which is referred to as testing point \textbf{T1}. Each assessment session began by recording the following information: their assessment of neuromuscular and sensorimotor performance using electromyography (EMG) and dynamometer instruments; Patient-reported outcome measures included: the knee injury and osteoarthritis score (KOOS), the Oxford Knee Score (OKS), the 36-Item Short Form Health Survey version 2 (SF-36v2\textsuperscript{TM}), the Performance Profile (PP), the International Physical Activity Questionnaire (IPAQ) and the Pain Self-Efficacy Questionnaire (PSEQ). The psychometric and clinimetric properties of the outcomes used within this study have been discussed in Chapter 2 to support their usage. The PP questionnaire was generated with participants during their first assessment session and used as a template for subsequent follow-ups. The participants completed all other questionnaires during the dynamometer and the EMG set up, in no particular order. Prior to all testing sessions, participants were accustomed to the assessment procedures, which included a standardised warm-up (walking along a 150 m corridor at a their preferred speed) for approximately five minutes. Figure 4.2 highlights the primary and secondary outcome measures taken during the test occasions.

4.7.1 Objective assessment 1: Neuromuscular and sensorimotor measurements

(i) Participant and dynamometer orientation

During each assessment session, the participant was seated comfortably on a custom-built dynamometer (Gleeson et al. 2008) as shown in Figure 4.3. The leg was secured to the bilateral level arm of the dynamometer with a calf pad strapped comfortably close to the lateral malleolus. In addition, a blue seat strap around the upper thighs and hips was used to minimise pelvis movements and ensured localised action to the involved musculature. The dynamometer was adjusted to the individual on initial assessment. These settings were recorded and repeated at each assessment session. The dynamometer was set with the knee joint and the centre of rotation aligned as closely as possible. A knee flexion position of between \(30 - 45^\circ\) (\(0^\circ\) representing full extension) (Gleeson
et al. 2002) and a hip angle at approximately 110° (Vahtrik et al. 2012) between the backrest and the seat was maintained throughout the testing. The angles were measured using a manual goniometer for each participant individually at every assessment session. Prior to the initiation of the assessment procedures, the dynamometer was calibrated using a hand held 10 kg mass as a 100 N weight reference.

(ii) Electromyography recordings

Electromyographic activity (EMG) was recorded from the quadriceps: Rectus Femoris (RF) and Vastus Lateralis (VL) musculature in order to assess indices of neuromuscular and sensorimotor performance. EMG is a non-invasive tool for recording muscle function (Kollmitzer et al. 1999) and has been successfully used in previous studies along
side the dynamometer to evaluate indices of neuromuscular and sensorimotor performance (Gleeson et al. 2013, Bailey et al. 2014). EMG recordings from the quadriceps musculature (RF and VL) were obtained using bipolar semi-rectangular surface electrodes (self-adhesive Ag/AgCl 20×25 mm, Spes Medica S.r.l, Italy). The electrodes were applied longitudinally over the muscle belly parallel to the orientation of the muscle fibres, at a distance of approximately 15–20 cm from the base of the patella for the RF and slightly laterally for the VL (Mathur et al. 2005, Wong & Ng 2006, Minshull et al. 2007, Bailey et al. 2014). Confirmation of the appropriate location was done by taking a second reference point (the anterior superior iliac spine) and a measure of the distance between the latter and the base of the patella was noted. The electrodes were placed where the two points met (at the muscle belly) on the quadriceps musculature. The quadriceps femoris muscle was selected for physiological assessment, as this muscle is associated with knee OA (Hurley 2003, Mizner, Petterson, Stevens, Vandenborne & Snyder-Mackler 2005), and an important predictor of disability (McAlindon et al. 1993, Fukagawa et al. 1995, Chandler et al. 1998). The inter-electrode distance was set at 30 mm and a reference electrode was placed 30 mm below the recording electrodes (Minshull et al. 2007, Bailey et al. 2014). Standardised skin-preparation techniques using
light skin abrasion followed by cleaning the skin with alcohol was used during every
assessment session (Mercer et al. 1998, Gleeson 2013). This method of skin preparation,
allowed for an inter-electrode impedance of less than 5 kΩ (Bailey et al. 2014, Gleeson
2013). Inter-electrode impedance was measured using a hand held multi-meter (Digital
Multimeter, B&Q MS8233A). Electrode placement was standardised across inter-day
testing by marking and measuring according to anatomical landmarks using a measur-
ing tape and a light marker. Notes were also made during every session to allow for
consistency between sessions. The ‘raw’ unfiltered EMG signals were passed through
a differential amplifier (1902 Mk IV; Cambridge Electronic Design, UK), with input
impedance 10,000 MΩ, CMRR 100 dB gain of 1000 and filtered (Butterworth 2nd-
order; 1 kHz cut-off frequency). “The signals, which incorporated minimal intrusion
from induced currents associated with external electrical and electromagnetic sources
and noise inherent in the remainder of the recording instrumentation, were analogue-to
digitally converted at 2.5 kHz sample rate, ensuring a significant margin of reserve be-
tween the highest frequency expected in the EMG signal and the Nyquist frequency.”
(Minshull et al. 2009).

(iii) Assessment of neuromuscular performance

Indices of neuromuscular performance of the knee extensor and flexor musculature in
both knees were assessed. Once the limb of each participant is secured in position on
the dynamometer, they were asked to perform a specific muscle warm-up that included
progressively stronger isometric contractions: $2 \times 25\%, 50\%, 75\%$ and $100\%$ of subjec-
tively judged maximum voluntary contraction (Minshull et al. 2007, 2009). During the
warm up, each contraction was retained for 2 – 3 seconds and subsequent 10-second
rest prior to the next contraction was allowed for appropriate neuromuscular recovery
(Moore & Kukulka 1991). Following a 5-minute rest, the participants received a verbal
signal from the researcher, given randomly within 1 – 4 seconds asking them to attempt
to activate their quadriceps muscle as rapidly and forcefully as possible by extending the
knee joint against the apparatus. A force meter (300 kg compression, tension load cell,
Tedea-Huntleigh, Cardiff, UK) attached to the level arm recorded the force output in
Newtons (N). Another verbal signal informed the participant to relax the muscle after
a 2–3 second contraction period. The maximal contraction was repeated three times in a row with a 10-second rest/recovery period. Participants received verbal encouragement during all three trials. The consistency of testing procedures was maintained by employing the same observer with standardised commands.

(iv) Indices of neuromuscular performance

Indices of neuromuscular performance, which consisted of electromechanical delay (EMD), peak force (PF) and rate of force development (RFD) were recorded three times in every assessment session and the mean responses were subsequently derived for final statistical analysis. The PF was measured as the highest force response during each trial and was recorded in Newtons (N). The EMD was defined as the time delay between the onset of EMG and the onset of force during the trials recorded in milliseconds (ms) as can be seen in Figure 4.4. The RFD was defined as the time difference between the onset of EMG and the onset of force as well as the rate/rapidity by which the force increased following its onset recorded in Newtons per second (N/s). The onset of electrical activity as well as the muscle force were defined as the first point in time where the recorded signals consistently exceeded the 95% confidence limits of the background electrical noise amplitude (Minshull et al. 2007, 2009, 2011).

(v) Assessment of sensorimotor performance - Force matching task

Sensorimotor performance was defined as the error in matching a ‘blind’ target force. During each testing assessment, the participants were given a familiarisation trial whereby each participant familiarised themselves with 50% of their daily peak force (blinded), for their quadriceps musculature (Pincivero et al. 2000, Gleeson et al. 2013, Bailey et al. 2014). During the familiarisation trial, the participant was given verbal feedback by the researcher (e.g. “a little bit higher/lower”) to facilitate further improvements in performance precision. Following this period of familiarisation, the ‘force matching task’ test was performed by the participant where they were asked to reproduce 50% of their daily peak force, for three consecutive times with 10 seconds of recovery between each test. During the recording period, no verbal feedback regarding the force was given. The mean response of three trials was used for analysis using the
Figure 4.4: Raw EMG data representing the measurement of electromechanical delay (EMD) (Peer 2017).

The calculated force error (FE) values describe a constant error or bias around a target force where lower FE values reflect better sensorimotor performance (Gleeson et al. 2013).

4.7.2 Objective assessment 2: Anthropometric measurements

Height, mass and BMI

Anthropometric data such as height (cm), body mass (kg), BMI (kg·m$^{-2}$), recorded comorbidities and medications were collected through the review of the participants’ medical files after enrolment onto the orthopaedic waiting list. This data was normally recorded and measured by a qualified nurse during the pre-admission clinic, which took
place approximately three/four weeks prior to surgery. No patient identifiable data was collected or recorded for the trial purposes throughout the duration of the trial. The latter was to conform with the rules and regulations of the RJAH NHS Trust hospital as well as those imposed by the REC.

4.7.3 Patient reported outcome measures (PRO)

A total of six patient reported questionnaires were collected on each of the five data assessment sessions. The questionnaires gathered information regarding perceived performance capacities of physical function and pain during the time of surgery, before and after the P–SEC intervention. All six questionnaires were completed while measurements of neuromuscular and sensorimotor performance were being set up or saved to a password-protected hardware, in order to allow efficient use of time for neuromuscular recovery when maximal forces were being recorded. The selected questionnaires have been previously used in quantifying pain, function and quality of life especially in patients with TKA (Bade et al. 2010, Calatayud et al. 2017, Desmeules et al. 2013, Huber et al. 2015). In fact, the OKS, KOOS and SF-36v2 are amongst the questionnaires also used as outcome measures at RJAH NHS Trust and by the National Joint Registry for TKA (www.njrcentre.org.uk).

(i) Knee injury and Osteoarthritis Score (KOOS)

The KOOS (see Appendix H) is a 42-item self-report questionnaire that determines patient-relevant changes by capturing a broader evaluation of physical function than is needed for daily activities. The KOOS consists of five subscales: pain (9 items), other symptoms (7 items), function in daily living (ADLs) (17 items), function in sport and recreation (Sport/Rec) (5 items), and knee related quality of life (QoL) (4 items) (KOOS User’s Guide 2012; www.koos.nu). The KOOS score exhibits clinically acceptable psychometric properties with high level of responsiveness (effect sizes and standard response means > 0.80), and reliability (ICC ≥ 0.70) (Peer & Lane 2013). During the assessments, the participants were asked to read the instructions carefully found in the first page of the questionnaire prior to completing the questionnaire by indicating each item with a cross or a tick. The rating system of the KOOS questionnaire uses
a 5-point Likert scale, scoring items from 0 (no problems) to 4 (extreme problems). The completed KOOS questionnaires were entered into a pre-prepared scoring spreadsheet downloaded from the KOOS website (www.koos.nu). Manual calculations for each subscale were performed using the formula:

\[
\text{score} = 100 - \left( \frac{\text{mean of the items within the subscale}}{4} \right) \times 100. \tag{4.2}
\]

An aggregate score is not calculated from the KOOS. Instead the KOOS authors recommend that each dimension is analysed and interpreted separately (Roos et al. 1998). If the completed questionnaire included ‘missing data’, a value was substituted with the average value for that subscale. If there were more than 50% of the subscale items absent then the response was considered invalid and no subscale score was calculated (KOOS User’s Guide 2012; www.koos.nu). If a mark was placed outside the box, the closest answer was chosen. If two answers were marked for the same question, the box indicating the most severe problem was recorded as the participant’s response.

(ii) Oxford Knee Score (OKS)

The OKS (see Appendix I) is a 12-item knee-specific, self-administered questionnaire, which evaluates pain and function (Dawson et al. 1998). The OKS questionnaire is a valid and reliable instrument (Davies 2002, Murray et al. 2007, Jenny & Diesinger 2012) and is sensitive to clinically important changes over time (Davies 2002). In fact, the OKS is the patient-reported outcome measure of choice to evaluate TKA in England, Wales and North Ireland (National Joint Registry Annual Report 14th Edition 2018). Participants were asked to answer the 12-item questionnaire by marking the answers by a tick or a cross. Any queries regarding specific terminology or wording were addressed and explained to the participant but no advice on how to answer the questions was given.

Different scoring systems are available for the OKS. This study followed the scoring system adopted by Murray et al. (2007). This type of scoring system is also consistent with the RJAH NHS Trust practice whereby each question is scored on a four-point
Likert scale with 4 being the best outcome. Individual scores are summarised with overall scores running from 0 – 48. The scores represent no adverse symptoms and excellent joint function when scoring 48, whilst very poor joint function when scoring 0. If a question was left unanswered, it was considered as a ‘missing data’, and was substituted with the average value of all other responses. If more than two questions were omitted, the overall score was not calculated. In the case that more than one answer was given for the same question, the worst response was adopted for scoring purposes.

(iii) The 36-Item Short Form Health Survey (SF-36v2™)

The SF-36v2 (see Appendix J) is a general health-related quality of life instrument (Instrument Ware Jr & Sherbourne 1992), which reflects eight multi-items of health dimensions: physical functioning (10 items); social functioning (2 items); role limitations due to physical problems (4 items); role limitations due to emotional problems (3 items); mental health (5 items); energy/vitality (4 items); pain (2 items) and general health perception (5 items). The SF-36 has been widely used in clinical and research settings and has the sensitivity to highlight changes in patients undergoing TKA surgery (Kiebzak et al. 2002). The SF-36v2™ was constructed to correct deficiencies identified in the SF-36 and show improvement mainly in terms of wording and format reducing floor and ceiling effects to responses (Jenkinson et al. 1999). The participants answering the SF-36v2™ were also asked to fill in the 36 multiple choice questionnaire by ticking or circling the most appropriate answer. Any questions referring to terminology used in the questionnaire were explained to the participant when enquired. For each dimension, the score of the items was coded and transformed to a scale from 0 (worst possible health state measured) to 100 (best possible health state measured). Data inputting was done manually and scores then transformed using an excel scoring sheet with UK based population weight scores. Items that were left blank (i.e. ‘missing data’), were inputted as the mean values of the remaining items for the subscales, according to the SF-36 guidelines (Instrument Ware Jr & Sherbourne 1992).
(iv) Pain Self Efficacy Questionnaire (PSEQ)

The PSEQ (see Appendix K) is a frequently used subjective questionnaire measuring patient’s perception to activity in the presence of pain (Nicholas 2007, Nicholas et al. 2008). This self-reported measurement of perceived performance can be compared to objective measurements of activity as a way to compare patients perceptions versus objectively measured levels of activity in the presence of pain. The participants were asked to rate how confidently they believe they can perform the activities described despite the presence of pain by circling their answer on a 7-point Likert scale. Each item on the scale rated the scores from 0 (not at all confident) to 6 (completely confident). The scores of the individual questions were then added and the total score was calculated, ranging from 0 – 60. The higher the score, the stronger self-efficacy beliefs were.

(v) Performance profile activity questionnaire (PP)

The performance profile (see Appendix L) technique (Butler & Hardy 1992, Butler et al. 1993) is an individualised assessment instrument that allows people to construct a visual display of themselves with respect to their performance targets. This outcome instrument has been frequently used in athletes (Gleeson et al. 2005, Weston 2008) and in clinical settings (Gleeson et al. 2008, Bailey et al. 2014, Peer 2017). The performance profile exhibits good psychometric properties such as validity (Gleeson et al. 2008, Doyle & Parfitt 1996, 1997) and reliability (Gleeson et al. 2005).

The PP was explained to each participant during the first assessment and repeated again at the beginning of each follow-up assessment session. Doyle & Parfitt (1997) found that this repetition provided participants with more practice time, which yielded more accurate results of their profile. Therefore, on the first assessment session, extra time was allotted by the researcher for a detailed explanation. To guarantee consistency, the same researcher provided the same instructions for the PP to each individual participant. Participants were asked to provide responses to the following question: “In your opinion, what qualities/characteristics would you use to describe the knee that
Participants were encouraged to think about what physical qualities they would like improved, and were advised that the profile is based on personal preference, therefore there are no right or wrong answers. If participants were unable to ‘construct’ the questionnaire, the researcher used questions to help cue the participants to generate words that were suitable to them. Previous literature has identified that prompts from the assessor were helpful in the process of bringing personal ‘constructs’ into consciousness (Butler & Hardy 1992). In the majority of cases only limited assistance was required; only a few participants required examples of completed PPs. Common examples of ‘constructs’ that participants reported were: ‘pain’, ‘stiffness’, ‘giving way’ and ‘unreliable’. Participants were encouraged to define at least five constructs, as this number is considered appropriate for clinical practice (Yates 2016), but this was more often not possible as participants found it hard to come up with several constructs. Figure 4.5 shows a completed PP representing participants’ self-perceived physical needs to obtain optimal functioning. Following the generation of constructs, the participants were asked “How would you rate the operating knee in comparison to the opposite knee at the present time on each of the qualities/characteristics you have listed?”. Participants were asked to shade in the chart, from no shading (0) indicating “completely different/not at all like this”, to all rows being shaded (10) indicating “very similar/very much like this”. To represent the knees’ function, an average score was calculated by adding the scores (maximum score 10) of the five most important constructs together, and subsequently, dividing the sum by the number of constructs (i.e. 5).

(vi) International Physical Activity Questionnaire (IPAQ)

The participants’ physical activity was monitored using the long-form IPAQ questionnaire (see Appendix M). This long-form version of IPAQ assesses in detail the frequency and duration of participation in vigorous, moderate, and walking activity, and the time spent sitting during the last seven days, whether or not this was representative of their usual routine (for example, if they were abroad or unwell). The IPAQ is considered valid (Craig et al. 2003), reliable (Blikman et al. 2013) and commonly used in scientific
CHAPTER 4. METHODOLOGY

Figure 4.5: An example of a completed PP chart representing participants self-perceived physical needs in order to obtain functioning. Areas indicated in grey represent perceived current state on the scale of 0 (not at all like this/very different from opposite knee) to 10 (very much like this/very similar to opposite knee).

studies (Rütten et al. 2003, Tehard et al. 2005, Schmitt et al. 2008). Data cleaning process was done based on the IPAQ scoring protocol (IPAQ research committee, 2005; https://sites.google.com/site/theipaq/scoring-protocol). In brief, this protocol consisted of participant’s recording their duration time (in hours) of active and sitting behaviour, which was then converted into minutes during data processing. If participants indicated “don’t know” or missed to fill in the information for ‘time’ or ‘days’ then that case was not considered for analysis. Behavioural outliers were defined for participants with implausible activity data. For example, days with activity data exceeding a total sum of 960 minutes (16 hours) of walking, moderate and vigorous time variables were excluded from this study’s analysis. Time values on activities with less than 10 minutes were re-coded to ‘zero’ based on 100 minutes evidence indicating that at least a minimum of 10 minutes of activity is required to achieve health benefits (IPAQ Research Committee 2005 (Committee n.d.); World Health Organisation 2017 (Organisation 2018)). In addition, all walking, moderate and vigorous time variables exceeding three hours or 180 minutes per day were truncated and re-coded to 180 minutes. This re-coding permits a maximum of 21 hours of activity per week for each category (three hours
multiplied by seven days). Data collected with the IPAQ questionnaire can be re-
ported as a continuous measure or as a median metabolic equivalent (MET)-minute. 
Metabolic equivalents are multiples of the resting metabolic rate and a MET-minute 
is computed by multiplying the MET score of an activity by the number of minutes 
the activity was performed (IPAQ Research Committee 2005). Mean values for walk-
ing, moderate-intensity activities and vigorous-intensity activities within each domain 
were calculated using the formulas below. Total scores may also be calculated for each 
domain (work, transport, domestic and garden, and leisure) and for an overall grand 
total. The following equations are a few of the formulas used during the calculation of 
the IPAQ long form questionnaire scores:

**Work domain:**

\[
\text{Walking MET} - \text{minutes/week at work} = 3.3 \times \text{walking minutes} \\
\times \text{walking days at work}
\]  \hspace{0.5cm} (4.3)

**Active transportation domain:**

\[
\text{Walking MET} - \text{minutes/week for transport} = 3.3 \times \text{walking minutes} \\
\times \text{walking days for transportation}
\]  \hspace{0.5cm} (4.4)

**Domestic and garden/yard work domain:**

\[
\text{Vigorous MET} - \text{minutes/week yard chores} = 5.5 \times \text{vigorous-intensity activity minutes} \\
\times \text{vigorous-intensity days}
\]  \hspace{0.5cm} (4.5)

**Leisure time domain:**

\[
\text{Walking MET} - \text{minutes/week leisure} = 3.3 \times \text{walking minutes} \\
\times \text{walking days for leisure}
\]  \hspace{0.5cm} (4.6)
Total scored for all walking, moderate and vigorous physical activity:

Total walking MET – minutes/week = Walking MET

– minutes/week (work + for transport + for leisure)

(4.7)

Total physical activity scores:

Total physical activity MET – minutes/week

= sum of Total (Walking + Moderate + Vigorous) MET – minutes/week scores

(4.8)

4.8 Delivery of P–SEC protocol

The P–SEC protocol was designed and delivered over three alternate days, approximately two weeks before scheduled TKA surgery. The first day of delivery was usually at the beginning of the week (e.g. Monday). This day also marked assessment point T2 which was taken before the first P–SEC session was delivered (see Figure 4.1). Prior to the delivery of the P–SEC exercise protocol, no specific warm up was done as the walk to the rehabilitation area (approximately 150 m long) was considered sufficient warm up. The delivery of the P–SEC protocol was held in the rehabilitation area of the Physiotherapy Department at the RJAH NHS trust hospital. The equipment used for the delivery of the protocol was the knee extensor machine (Life fitness, model number FZLE-500023; www.lifefitness.com) pictured in Figure 4.6. To ensure consistency, the knee extensor machine model used for the delivery of the P–SEC protocol was the same one used for every participant on each exercise occasion. Calibration of the machine was done regularly by the Physiotherapy Department at the RJAH NHS Trust hospital (RJAH machine reference number RJH00195) with the most recent calibration being January 2018.
4.8.1 Equipment set up

When the participant was comfortably seated, the machine settings were adjusted to have the knee starting position set at $90^\circ$ and the padded leg rest lying just above the ankle joint (representing a similar lever point to the dynamometer cuff used during assessment of neuromuscular function). The back rest (see Figures 4.6 and 4.7), and the knee and padded leg rest positions were recorded during the first session and kept consistent throughout the delivery of the programme over the other two days for each participant.

Figure 4.6: Knee extensor machine used to deliver P-SEC protocol: (a) side view (b) front view.

4.8.2 Randomisation of participants to groups

As mentioned in Section 4.4, participants were randomly allocated to groups through a computerised programme. The C.I. (AMR) was blinded to the randomisation process and was only told which participants will be receiving the exercise protocol and on which leg. The participants were told on the first exercise session whether the exercise protocol will be delivered on the ‘right’ or ‘left’ leg. The C.I. who also delivered the exercise protocol, encouraged the participants not to inform them as to whether that leg was the surgical leg or not to further increase the blinding process.
4.8.3 Delivery of P–SEC protocol

Once the participant was in a comfortable set position, the one repetition maximum (1RM) of the experimental leg was determined (Jamurtas et al. 2000). The latter was identified individually on every P–SEC delivery day. The 1RM was identified by asking the participant to lift the bar with the experimental leg for a number of times with increasing weight, until their maximum weight lifted was achieved and noted. The 1RM was determined and identified as the maximum weight the participant could lift with the experimental leg. Once the 1RM was identified, the participant was given 4 minutes of rest and recovery prior to the commencement of the exercise delivery (Hultman et al. 1967). During this period of recovery, the researcher calculated the a physiologically based percentage effort (between 60% - 100% of their 1RM) selected for the three sessions that will be delivered during that day (see Table 4.1). This was done by choosing a weight that was calculated as a percentage of the 1RM of the day. In the case where the percentage calculation resulted in a weight that was not precisely available on the machine, the closest weight was selected. Using this type of method to select the loads on the extensor machine resulted in delivering different loads to the knee during the sessions. This method of delivery aims to reproduce a patterning of
the intensity of exercise and progression for increasing physiological stimuli for adaptation (ranging between 60% and 100% of participant’s capacity, with cyclical delivery patterns (known as ‘micro-cycling’)) \(^6\). Such intensities are hypothesised to be capable of eliciting clinically important effects in participants awaiting TKA and to be a counteraction to attenuated post-surgical neuromuscular capacities (Rice & McNair 2010). The percentage loads were adapted in a manner delivering the highest weight in the middle session so as to allow the first session as an introductory lower weight.

Table 4.1: The table below represents an example of the progressive loading adopted for the P–SEC protocol that was delivered to the two experimental groups: P–SEC(surgical) and P–SEC(non-surgical). The loading progression highlights the nine sessions (S1-S9) delivered over a 1-week period (e.g. Monday to Monday), with rest days interspersed amongst conditioning days and prior to data capture point T3.

<table>
<thead>
<tr>
<th>Session (S)</th>
<th>Monday (% MVC)</th>
<th>Tuesday</th>
<th>Wednesday (% MVC)</th>
<th>Thursday</th>
<th>Friday (% MVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>65%</td>
<td>REST</td>
<td>S4</td>
<td>70%</td>
<td>60%</td>
</tr>
<tr>
<td>S2</td>
<td>100%</td>
<td>DAY</td>
<td>S5</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>S3</td>
<td>85%</td>
<td></td>
<td>S6</td>
<td>80%</td>
<td>70%</td>
</tr>
</tbody>
</table>

During the exercise sessions (refer to Figure 4.8), the participants were asked to raise the machine’s weight-loaded lever arm against gravity, using knee extension manoeuvres and concentric muscle actions from both legs. Following a momentary pause in the movement at full knee extension (Fig. 4.8(b)), the participant was asked to gently lower the pre-defined experimental leg whilst still momentarily holding the weight with the opposite leg (Fig. 4.8(c)). Following this very brief period, the participant was required then to let go of the weight and attempt to arrest and counteract the downward trajectory of the weight very briefly (< 1.5 seconds, avoiding nociceptor responses (Fein 2012)) in mid-range (approximately 45° angle) (Fig. 4.8(d),(e)), using an eccentric muscle action of the extensor muscles of only the leg prescribed by the experimental design. The exercise was completed by further relaxation of the patient’s involved knee extensor musculature and a safe dropping of the load under gravity to its resting starting

\(^6\)Percentage progressions were developed starting with a high loading period titrating to a lower loading period (to allow for restoration and recovery following appropriate loading)
Figure 4.8: P-SEC exercise delivery. Figures (a) (initial position) – (f) (finishing position) represent the action sequence executed during the delivery of the P-SEC programme. This sequence would be repeated quickly for 4 times in one session using a percentage weight as discussed in text.

position within the machine’s enclosure (Fig. 4.8(f)). This movement was practised twice (without load) prior to the delivery of the protocol until the participants learnt the movement of halting the weight and letting it go quickly with the desired experimental leg. When the participant was familiar and confident with the exercise, the protocol was initiated. The above movement was repeated four times at one set weight percentage with 15 – 20 seconds of rest between repetitions to allow for neuromuscular recovery (Moore & Kukulka 1991) and 1 minute of rest in between sessions. A total of 12 exercises were delivered over approximately 15 minutes with an additional 5 minutes for finding the 1RM and recovery period given prior to initiation of exercises. In view of this, the total time required to deliver the protocol of 3 sessions in one day was done over a period of 20 minutes including setting up and the delivery of 12 exercises.
4.8.4 Recordings during each session

During each exercise session, the participants were asked their subjective pain level of the day and recorded as VAS to record any pain experienced from the previous session. Each participant was asked whether or not any further symptoms developed during or following the last session. During the delivery of the exercise, each participant was asked whether he/she was experiencing any pain or other symptoms in order to subjectively monitor adverse reactions to the exercise protocol.

4.8.5 Health and safety procedures

Health and safety procedures were taken according to the RJAH NHS Trust hospital policies. Participants were always brought during the department’s opening hours with the presence of a senior member of staff present on the premises. In line with the health and safety procedures of the hospital, the equipment was cleaned with alcohol wipes following use to avoid contamination between patients.

4.9 Statistical Analysis

The effects of reconstruction surgery and novel pre-surgery (P–SEC) protocol was analysed using group means ±SD for each outcome measures unless otherwise stated. Comparative statistical analysis using quantitative data was performed using IBM Statistical Package for the Social Science (IBM SPSS, Illinois, USA) version 23.0 for Windows software. The Shapiro-Wilk test was used to assess normality of data. If normality of the data was not confirmed, appropriate transformations (Log$_{10}$) were adopted. The effects of the P–SEC programme was analysed separately for each outcome measure using factorial (3-way) ANOVA (group [P–SEC$_{PSI}$; P–SEC$_{CONTRA}$; Control] x leg [Surgical; Non-surgical] x time [T1 – T5]), with repeated measures on the latter two factors. Assumptions underpinning the use of ANOVA for repeated measures were checked. Greenhouse-Geisser ($\eta$) was used to counter any violations. A priori Reverse Helmert orthogonal difference testing was used in conjunction with ANOVA. The statistical alpha level was set at $p < 0.05$. Missing or ‘outlier’ data were taken into account on an ‘case-by-case’ basis separately for each outcome measure, and the rea-
sons for absence or abnormality of a datum point were recorded. Missing data were imputed using a multiple imputations approach (Bennett 2001) and a *per protocol* analyses was performed on the resultant data set for all outcome measures, unless otherwise stated. In the event that a participant decided to withdraw from the study, their data were subsequently excluded from the final statistical analyses, but was included within subsequent ‘intention-to-treat’ analyses to check for the intrusion of bias. Descriptive statistics used to characterise groups mean ±SD responses amongst the outcome measures are also used with in the relative chapters. Outcome responsiveness (indices of effect size (ES) and percentage changes to baseline) were also calculated and reported. Calculated effect sizes was calculated using *Cohen’s d* using the Equation 5.1 in Chapter 5.

### 4.10 Chapters 5 – 7 – Results chapters

The following results Chapters (5, 6, 7) will describe and critically evaluate the results obtained following the P–SEC intervention in relation to neuromuscular and sensorimotor outcomes, patients reported physical performance, habitual physical activity and pain self-efficacy (PROs) and finally the effects of CE observed in the untrained limb following the application of the P–SEC intervention. The results will be discussed in relation to the effects in the pre-surgery phase for changes in the selected outcomes following the P–SEC intervention (T3) and any retention of effects observed two weeks after prior to surgery (T4). Furthermore, a discussion of the effects observed at six weeks after surgery will be discussed in relation to the complex interactions exhibited around that time.

### 4.11 Chapter 8 – General discussion

The final Chapter 8 will include an overall summary of the observed effects for each chapter in relation to the main research questions mentioned at the end of Chapter 2. The general discussion will summarise, integrate and critically evaluate the main findings observed following the application of a ‘novel’ pre-surgery exercise-conditioning programme (P–SEC) in patients electing TKA surgery. An in-depth discussion on
the potential underlying mechanisms and correlations amongst the findings will be reported. In addition, a further consideration of the limitations of the study and potential improvements towards future research along with possible recommendations of use will be discussed.
Chapter 5

Results 1: Changes in muscular performance following a pre-surgical intervention (P–SEC)

The effects of pre-surgery exercise-conditioning (P–SEC) on neuromuscular and sensorimotor performance in patients electing total knee arthroplasty (TKA).

5.1 Introduction

Patients suffering from end-stage knee osteoarthritis (OA) and concomitant disease-related changes to joint structure and function, commonly elect to undergo TKA (Arthritis research UK 2018, National Joint Registry Annual Report 14th Edition 2018, Scottish Arthroplasty Project 2018). Chronic physiological adaptations such as persistent pain, swelling and arthrogenic muscular inhibition (AMI) involving both sensory and motor knee joint receptors (Hurley et al. 1997, Hurley & Scott 1998, Torry et al. 2000) are frequent sequelae of structural changes to a joint (Rice & McNair 2010, Pietrosimone et al. 2011, Calatayud et al. 2017) and hinder its stability and functional
capacity (Suchomel et al. 2018). Mechanisms associated with AMI dampen motor unit (MU) excitability and limit full voluntary muscle activation by means of decreased α motoneuron (MN) activity and ultimately, the potential for effective dynamic joint stability (Palmieri et al. 2004, 2005, Héroux & Tremblay 2006, Rice et al. 2014). A complex interaction amongst the effects of OA, elective surgery and rehabilitative conditioning has resulted in concomitant deficits in quadriceps strength (27 % (OA limb) vs. 41% (contralateral)) (Petterson et al. 2008), balance capabilities and movement control (Piva et al. 2010, Rätsepsoo et al. 2011) that persist for up to a year following TKA surgery (Silva et al. 2003). It is notable that 20% – 30% of patients undergoing TKA continue to be dissatisfied with the outcome (Hurley et al. 2010). As such, countering shortfalls in function and performance continues to be a priority to alleviate the potential risks associated with further knee joint instability and injury (Lephart et al. 1997).

Common types of conditioning used for eliciting neuromuscular (motor) and sensorimotor changes (Risso et al. 2018 under review; refer to Chapter 3) include those focusing on the physiological specificity of strengthening exercises to elicit increased morphological size and others with more varied conditioning stimuli for improving neuromuscular performance with emphases on speed-of-movement (time-limited movement) such as during ballistic, plyometric and related challenges to motor performance (Suchomel et al. 2018). In order to quantify the effects of complex interventions and heterogeneous conditioning stimuli on neuromuscular and sensorimotor performance characteristics in patients awaiting TKA, a correspondingly sophisticated array of outcomes would be required (Peer et al. 2017). Alongside the commonly deployed outcome of peak force (PF), electromechanical delay (EMD), measuring the speed with which muscle force can be initiated, and rate of force development (RFD), reflecting the rapidity with which meaningful levels of force are achieved, would capture the nature of time-limited changes in neuromuscular performance capacities over time (Enoka 1988, Cavanagh & Komi 1979, Minshull et al. 2007) and provide proxy markers to the limits for dynamic stabilisation during mechanical loading of joint systems (Gleeson et al. 1998, Mercer et al. 1998, Minshull et al. 2007, 2009, Hannah et al. 2012, Costa et al. 2010).
CHAPTER 5. RESULTS 1: CHANGES IN MUSCULAR PERFORMANCE FOLLOWING A PRE-SURGICAL INTERVENTION (P–SEC)

2013). Similarly, the capability of patients to have sensorimotor acuity and to efficiently perceive and regulate levels of force associated with joint stabilisation or movement may be assessed using outcomes such as force error (FE). This outcome relies principally on the performance capabilities of musculoskeletal sensory receptors (Brockett et al. 1997, Gleeson et al. 2013, Bailey et al. 2014, Peer 2017) and has shown effective clinimetric qualities in patient populations electing knee surgeries (Hannah et al. 2012, Bailey et al. 2014, Peer 2017).

Moderate evidence exists on the effectiveness of exercise in OA management (Jessep et al. 2009, Fransen et al. 2015). Recent reviews and studies indicate that many rehabilitative conditioning programmes for OA treatment (Moutzouri et al. 2016, 2017, Peer et al. 2017) or for pre-habilitation prior to TKA (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015) and (Risso et al. 2018 under review refer to Chapter 3) lack robust physiological training principles and fail to accommodate muscle adaptation from exercise. Where the delivery of contemporary rehabilitative conditioning has been modified to incorporate physiological principles, RCTs have shown pronounced gains in functional and neuromuscular performance capabilities (Bailey et al. 2014, Moutzouri 2018), but not necessarily under other conditions (Wang et al. 2016, Chesham & Shanmugam 2017), despite established conceptual underpinnings (Gür et al. 2002, Vikne et al. 2006, Moran & Wallace 2007).

Similarly, a recent prospective cohort study has demonstrated that better range of motion, greater quadriceps force, faster sit-to-stand test and a longer walking distance are correlated with better activities of daily living (ADL) and higher patient satisfaction levels post-TKA (Van Onsem et al. 2016), emphasising that the correctly-designed programme can offer a clear benefit. Optimal dosages of stimuli for enhancing sensorimotor acuity remains elusive (Risso et al. 2018 under review refer to Chapter 3) but contemporary pre-habilitative interventions focus on more than 18 sessions of conditioning over 6 - 8 weeks, (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015, Calatayud et al. 2017) with commensurate logistical burdens. Importantly, investigating the feasibility of an innovative pre-surgery, condensed and
physiologically-principled delivery (9 sessions (1-week); high-intensity (60% to 100% of daily 1RM); AMI-related nociceptor-averse (exercises lasting < 1.5s) using approximately 50% of the dosage of conditioning sessions and even less time for exposure to conditioning stimuli (≈ 17%)) of focal sensorimotor and neuromuscular rehabilitative conditioning, may have clear TKA-related benefits. Generally, patients' avoidance of exercise is often due to pain or the fear of pain. Therefore, the innovative exercise intervention would need to have successfully ameliorated limitations to patients' training responses caused by increasing levels of pain-related and deconditioning-related AMI and other nociceptor stimulation. However, while this novel approach to exercise conditioning has not yet been verified within hospital-based care pathways, pilot work has shown its potential for efficacy (Peer & Gleeson 2018). The P–SEC could offer increased cost-effectiveness due to its brevity and versatility, potential application to other related surgical procedures and temporal needs for conditioning, and the capacity for preparing patients physically for surgery.

Therefore, the primary aim of this study was to investigate the effects of a novel pre-surgery exercise-conditioning (P–SEC) on neuromuscular and sensorimotor performance in patients electing total knee arthroplasty (TKA). While a principal focus of the research are the conditioning-related responses of the leg undergoing TKA, an important additional consideration are the responses of the non-trained contralateral leg to a phenomenon called cross-education (CE) (Scripture et al. 1894, Enoka 1988), which despite consistent evidence of gains in asymptomatic populations (Munn et al. 2004, Carroll et al. 2006, Manca et al. 2017), has been under-researched in patients electing knee surgeries including TKA (Swank et al. 2011, Peer 2017, Harput et al. 2018), and so far ignored within TKA pre-habilitative applications. Further details of the rationale for the investigation of the effects of CE associated with P–SEC in patients electing TKA, experimental methodologies and findings can be found in Chapter 7. Secondly, although the primary aim of the P–SEC intervention is to improve physical aspects of performance capabilities, the transference of effects to be reflected in patients’ perceived capabilities is also an important aspect. Objective measurements of physical performance capabilities are not designed to allow for appropriate quantification of patients’
perceived performance. PROs on the other hand, have been consistently endorsed in clinical and research practices for their ability to identify the effects of an intervention on patients’ perceived physical function and QoL. Further details of the rationale for the investigation of the effects of P–SEC on physical function, habitual PA and QoL in patients electing TKA, experimental methodologies and findings can be found in Chapter 6. Lastly, the effects of the ‘novel’ intervention will also be quantified for changes over time (pre- and post-surgery) and for any carry-over of effects (Chapters 6 and 7).

5.1.1 Summary

Chronic physiological adaptations such as persistent pain, swelling and AMI accompany end-stage OA and are frequent sequelae of structural changes to a joint, hindering its stability and functional capacity. A complex interaction amongst the effects of OA, elective TKA surgery and rehabilitative conditioning has resulted in concomitant deficits in neuromuscular performance, balance capabilities and sensorimotor performance that persist for up to a year following surgery. Only moderate evidence exists on the effectiveness of exercise in OA management and the contemporary literature highlights that many rehabilitative conditioning programmes for OA treatment lack robust physiological training principles and fail to accommodate muscle adaptation from exercise. By contrast, and although optimal dosages of stimuli for enhancing sensorimotor acuity remain elusive, exercise conditioning programmes that have been modified to incorporate physiological principles and whose delivery of stimuli dosage has been condensed to offer increased versatility, have shown substantive efficacy. Importantly, it is hoped that assessing the feasibility of an innovative pre-surgery, condensed and physiologically-principled delivery of focal sensorimotor and neuromuscular rehabilitative conditioning, which mitigates against limitations to patients’ training responses caused by increasing levels of pain-related and deconditioning-related AMI, may have clear TKA-related benefits, especially in preparing patients physically for surgery.
CHAPTER 5. RESULTS 1: CHANGES IN MUSCULAR PERFORMANCE FOLLOWING A PRE-SURGICAL INTERVENTION (P–SEC)

5.2 Methods

A. Study design, ethical approval and participants

A single-centre (UK based NHS Trust), assessor-blinded, randomised controlled trial design was used for this study. The trial was registered on the clinicaltrial.gov register (NCT03113032) and the international standard randomised controlled trial number register (ISRCTN75779521) prior to the enrolment of the first participant. Ethical approval for this study was granted by the South East Scotland Research Ethics Committee 01 (IRAS 198930; REC reference 17/SS/0005; refer to Appendix B), research and development department at RJAH NHS Trust (RL1 715; refer to Appendix C) and Queen Margaret University (refer to Appendix D), Edinburgh. Since this study was performed using the same cohort of participants recruited for the main study, the reader is referred to Chapter 4 Section 4.4 for a full description of participant characteristics and randomisation procedures. Briefly, 46 participants diagnosed with severe knee OA and waiting for TKA were selected from a ‘patient waiting-list’ and randomised into one of three groups: Group 1: where P–SEC intervention was delivered to the surgical leg (P–SECIPSI); Group 2: where the P–SEC intervention was delivered to the non-surgical leg (P–SECCONTRA); and Group 3: a control “current practice” group (Control), where no intervention was delivered. Patients were recruited over an 11-month period (May 2017 to April 2018) from a waiting-list of five orthopaedic consultants all performing the same TKA procedure (MRK™).

B. Participant enrolment and general characteristics

The following section briefly lists some of the general characteristics that are shared amongst all three results Chapters (Chapter 5, Chapter 6 and Chapter 7) including participant enrolment, general characteristics, drop-outs and reported adverse reactions and changes baseline physical activity and in one repetition maximum (1RM). A total of 255 patients were approached from the ‘patient waiting list for a TKA’ from a UK based National Health Service (NHS) Foundation Trust hospital (RJAH) Oswestry, between May 2017 to February 2018 with completion of data collection in April 2018 (11-month period). The number was subsequently reduced to a total of 46
CHAPTER 5. RESULTS 1: CHANGES IN MUSCULAR PERFORMANCE FOLLOWING A PRE-SURGICAL INTERVENTION (P–SEC)

Figure 5.1: P–SEC flow-chart: flow of participants throughout the study based on the CONSORT guidelines for longitudinal studies. **Key: * = reasons for exclusion include: non-fulfilment of inclusion criteria (n = 10), inability to commute for the required number of sessions (n = 55), non-responders following initial contact (n = 90) and inability to commit due to work or personal issues (n = 54). ** = reasons for drop-outs following initial assessment included: unable to attend further due to personal issues (n = 3), did not wish to continue (n = 2), operation date was postponed (n = 4) or moved up with no time to deliver any further sessions (n = 5).
who signed the informed consent and were randomised into groups. The reasons for which participants were not enrolled in the study included: commuting issues (n = 55), non-responders following initial contact (n = 90), non-fulfilment of inclusion criteria (n = 10) and work and personal commitments (n = 54). The flow of participants across the study is highlighted in the CONSORT-based flow-chart Figure 5.1. Reasons for participant loss-to-follow-up at each phase of data collection is also included with reasons given within the caption of the figure. Participant characteristics for age, BMI and surgery waiting time are included for reference in Table 5.1.

Table 5.1: Participant characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.0 ±9.3</td>
<td>71 ±10.0</td>
<td>70.5 ±8.6</td>
</tr>
<tr>
<td>BMI (kg·m$^{-2}$)</td>
<td>28.2 ±14.6</td>
<td>27.3 ±18.1</td>
<td>28.9 ±10.3</td>
</tr>
<tr>
<td>Surgery waiting time (days)</td>
<td>75.0 ±52.4</td>
<td>75.1 ±50.9</td>
<td>68.8 ±35.9</td>
</tr>
<tr>
<td>Right knee operated (number)</td>
<td>26</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Previous arthroplasty (number)</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>MRK™ (number)</td>
<td>46</td>
<td>22</td>
<td>24</td>
</tr>
</tbody>
</table>

Drop-outs and reported adverse reactions

No participants dropped out of the study during the delivery of the exercise-conditioning (P–SEC) programme and no serious adverse reactions were reported. One participant was required to terminate her participation in the trial during assessment sessions due to an unrelated development of thrombophlebitis a few days before the surgical procedure. With respect to pain, only one participant reported ‘mild pain’ during the delivery of the P–SEC intervention whilst no pain was reported in the remaining 18 participants who were exposed to the P–SEC intervention. Two other participants reported mild muscle soreness during the rest days and another two participants reported a decreased sensation of stiffness and pain on mobility following the end of their exercise programme.

1RM changes during the P–SEC intervention

Fourteen out of 19 participants experienced an increase (4.3 ±3.3 kg) in their 1RM by the ninth conditioning session (end of the week). Only two participants experienced a
decline in 1RM towards the last session and three participants did not experience any changes in their 1RM following completion of the P–SEC intervention sessions.

Table 5.2: Changes in 1RM during the P–SEC intervention for those participants receiving the intervention only (n = 19). Key: * = decline in 1RM as reported in two of the participants. ** = no changes in 1RM were found at the end of the 9 sessions.

<table>
<thead>
<tr>
<th>Participant</th>
<th>1RM day 1 (kg)</th>
<th>1RM day 2 (kg)</th>
<th>1RM day 3 (kg)</th>
<th>1RM changes between Day 1 – Day 3 (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>5.0</td>
<td>7.5</td>
<td>10.0</td>
<td>5.0</td>
</tr>
<tr>
<td>02</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>0.0**</td>
</tr>
<tr>
<td>03</td>
<td>55.0</td>
<td>55.0</td>
<td>57.5</td>
<td>2.5</td>
</tr>
<tr>
<td>04</td>
<td>20.0</td>
<td>20.0</td>
<td>25.0</td>
<td>5.0</td>
</tr>
<tr>
<td>05</td>
<td>35.0</td>
<td>37.5</td>
<td>37.5</td>
<td>2.5</td>
</tr>
<tr>
<td>06</td>
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<td>30.0</td>
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<td>2.5</td>
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<td>07</td>
<td>17.5</td>
<td>17.5</td>
<td>20.0</td>
<td>2.5</td>
</tr>
<tr>
<td>08</td>
<td>10.0</td>
<td>15.0</td>
<td>15.0</td>
<td>5.0</td>
</tr>
<tr>
<td>09</td>
<td>20.0</td>
<td>25.0</td>
<td>27.5</td>
<td>7.5</td>
</tr>
<tr>
<td>10</td>
<td>32.5</td>
<td>40.0</td>
<td>45.0</td>
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<td>25.0</td>
<td>5.0</td>
</tr>
<tr>
<td>12</td>
<td>50.0</td>
<td>40.0</td>
<td>42.5</td>
<td>-7.5*</td>
</tr>
<tr>
<td>13</td>
<td>35.0</td>
<td>40.0</td>
<td>40.0</td>
<td>5.0</td>
</tr>
<tr>
<td>14</td>
<td>12.5</td>
<td>15.0</td>
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<td>2.5</td>
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<td>15</td>
<td>50.0</td>
<td>47.5</td>
<td>50.0</td>
<td>0.0**</td>
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<tr>
<td>16</td>
<td>30.0</td>
<td>20.0</td>
<td>25.0</td>
<td>-5.0*</td>
</tr>
<tr>
<td>17</td>
<td>57.5</td>
<td>57.5</td>
<td>62.5</td>
<td>5.0</td>
</tr>
<tr>
<td>18</td>
<td>20.0</td>
<td>25.0</td>
<td>30.0</td>
<td>10.0</td>
</tr>
<tr>
<td>19</td>
<td>25.0</td>
<td>25.0</td>
<td>25.0</td>
<td>0.0**</td>
</tr>
</tbody>
</table>

Level of physical activity (PA) at baseline

Detailed levels of PA for each participant were collected through the IPAQ questionnaire at each assessment point (T1 – T5). Baseline PA analysis confirmed that the participants randomised into groups had similar levels of physical activity ($p > 0.05$). Further analysis of the IPAQ questionnaire can subsequently be found in the results section of Chapter 6 Section 6.3.4.

C. Assessment procedure and data capture

This section outlines briefly the methods and assessment procedures employed. The reader is referred to Chapter 4 Section 4.7.1 for an in depth description of the assess-
The study was designed as a randomised controlled trial, with repeated measures, and conducted over a period of \( \approx 17 - 18 \) weeks (119 days), where the initial assessment was taken \( \approx 11 - 12 \) weeks\(^{1}\) prior to surgery. Patients electing for TKA were randomised into groups and assessed on five subsequent occasions. During each of the five assessment sessions (T1 – T5), outcomes of neuromuscular (EMD, RFD, PF) and sensorimotor (FE) performance were recorded. These performance outcomes were measured using data gathered from surface EMG electrodes placed on the knee extensor (vastus lateralis [VL] and rectus femoris [RF]) musculature of both the leg that received the P–SEC conditioning and the untrained leg. This procedure was the same for both experimental groups and controls. Assessment procedures lasted \( \approx 90 \) minutes during each testing occasion. The participants randomised into the intervention groups (P–SEC\textsubscript{IPSI} (Surgical) and P–SEC\textsubscript{CONTRA} (Non–Surgical)) were exposed to nine sessions (across 1 week) of exercise-based conditioning between time point T2 (2 weeks prior to surgery) and T3 (1 week prior to surgery). Patients in the control group received contemporary practice (i.e. no exercise). The reader is referred to Figure 4.1 (Chapter 4 Section 4.6) for a visual representation of the study’s timeline and delivery of the P–SEC protocol. The timing of assessments was selected to reflect important logistical and clinical epochs in the patients’ surgical pathway and rehabilitative care. The information gathered during the assessment procedures quantified and described objective measures of neuromuscular and sensorimotor performance prior to and around the time of surgery. Information gathered around the delivery of the intervention (T2 – T4) quantified the changes in neuromuscular and sensorimotor performance resulting from the P–SEC intervention. Information gathered from the post-surgery assessment point (T5) will envisage as an end-point comparison for identifying any possible gains (although these were not anticipated due to the brevity of P–SEC) or hindrance to the post-surgery recovery of patients in the intervention groups as a result of the P–SEC conditioning.

\(^{1}\)Average of 75 days (11 weeks) waiting time to surgery
D. Exercise-conditioning intervention (P–SEC) delivery

The first session of conditioning was delivered on the same day as assessment session T2 (pre-intervention) (refer to Chapter 4 Section 4.6), with exercises following the assessment session. No designated warm-up was delivered prior to the exercises as the walk to the rehabilitation area from the hospital’s reception (approximately 150 m long) was considered sufficient to act as both a general and a specific warm-up, without unduly risking the potential for local muscular fatigue. For the delivery of the exercise programme, a regularly calibrated knee extensor machine (Life fitness, model number FZLE-500023; www.lifefitness.com) (Figure 4.6) was used. The reader is referred to Chapter 4 for in-depth details of the P–SEC protocol delivery.

E. Statistical analyses

Comparative statistical analysis using quantitative data was performed using IBM Statistical Package for the Social Science (IBM SPSS, Illinois, USA) version 23.0 for Windows software. Results were presented as mean ±SD, unless otherwise specified. The Shapiro-Wilk test was used to assess normality of data. If normality of the data was not confirmed, appropriate transformations (Log10) were adopted. The effects of the P–SEC programme was analysed separately for each outcome measure using factorial (3-way) ANOVA (group [P–SECIPSI; P–SECCONTRA; Control] x leg [Surgical; Non-surgical] x time [T1 – T5]), with repeated measures on the latter two factors. Assumptions underpinning the use of ANOVA for repeated measures were checked. Greenhouse-Geisser (GG) was used to counter any violations. A priori Reverse Helmert orthogonal difference testing was used in conjunction with ANOVA. The statistical alpha level was set at $p < 0.05$. Missing or ‘outlier’ data were taken into account on an ‘case-by-case’ basis separately for each outcome measure, and the reasons for absence or abnormality of a datum point were recorded. Missing data were imputed using a multiple imputations approach (Bennett 2001) and a per protocol analyses was performed on the resultant data set for all outcome measures, unless otherwise stated. Descriptive statistics used to characterise group means ±SD amongst the outcome measures have also been used.
CHAPTER 5. RESULTS 1: CHANGES IN MUSCULAR PERFORMANCE FOLLOWING A PRE-SURGICAL INTERVENTION (P–SEC)

Relative ES associated with the influence of P–SEC, was computed using Cohen’s $d$ (refer to Equation 5.1) for parametric tests (Cohen 1988). For each outcome, comparison was made to baseline assessment (which was taken as mean score of T1 and T2) performance as the reference, unless otherwise stated

$$d = \frac{M_1 - M_2}{\text{pooled SD}} \quad (5.1)$$

In Equation 5.1, $M_1$ refers to the group mean score at a point of reference (e.g. baseline), $M_2$ refers to the group mean score at the comparison point of interest, and $\text{SD}_{\text{pooled}}$ references the associated population heterogeneity (SD) corresponding to $M_1$ and $M_2$. The calculated effect sizes ($d$) will be classified as small ($\leq 0.2$), medium ($\leq 0.5$) or large ($\leq 0.8$) (Cohen 1988).

5.3 Results

Per protocol analysis was reported for each outcome measure unless otherwise stated. Accounting for loss-to-follow-up and appropriate imputation of missing data, complete data sets from a total number of 29 participants were available for analysis (Control $n = 12$; P–SEC$_{IPSI}$ (Surgical leg) $n = 9$; and P–SEC$_{CONTRA}$ (Non-Surgical leg) $n = 8$). Assessment of the potential for bias associated with loss-to-follow up was undertaken using baseline data. The results indicated no statistical significance ($p < 0.05$) for comparisons of data from participants that were loss-to-follow-up and those that completed the study. Furthermore, analysis for learning effects of baseline assessments (T1 – T2) was undertaken and the results revealed a non-significant ($p < 0.05$) effect for all three groups, indicating that there was no learning effects due to the exposure to experimental procedures during the initial stages. Shapiro-Wilk test for normality in-

\footnote{For clarity within the following sections, the nomenclature used as P–SEC$_{IPSI}$ is referring to the leg undergoing surgery (i.e. Surgical leg), whilst P–SEC$_{CONTRA}$ refers to the contra-lateral leg (i.e Non-Surgical leg). Due to the nature of the methodological design, where the P–SEC intervention is delivered to the both the Surgical (P–SEC$_{IPSI}$) and Non-Surgical (P–SEC$_{CONTRA}$) leg in two separate groups and the contralateral leg is measured as control, the results below are discussed with reference to both groups and both legs.}
dicated an overall non-significant result \((p > 0.05)\) for all neuromuscular (EMD, RFD, PF) and sensorimotor performance outcomes for each assessment point, for the data in the allocated groups and overall, therefore confirming that the data was normally distributed (Refer to Table Q.1 in Appendix Q).

5.3.1 Changes in electromechanical delay (EMD)

A. EMD changes in Rectus Femoris (RF) musculature

Factorial ANOVA showed a significant group x time x leg interaction for EMD\(_{RF}\) \((F(6,79) = 9.6; p < 0.005)\) indicating that while performance in the legs of the Control group remained relatively constant during the experimental period (T1 - T4), the performance of the P–SEC trained leg of patients undergoing surgery on the same leg (group: P–SEC\(_{IPSI}\)) or the contralateral leg (group: P–SEC\(_{CONTRA}\)) improved (shorter EMD scores) to a greater extent (peak ES = 1.8; Table 5.5) than the corresponding performance of the leg that does not receive conditioning (peak ES = 0.4) (Figure 5.2) rejecting the null hypothesis (Section 2.11 Hypothesis 1).

A priori difference contrasts suggest that the extent of interaction between baseline (mean of EMD\(_{RF}\) performance at T1 and T2) and immediately post-P–SEC (T3) \((F(1,26) = 26.0; p < 0.01)\), between T3 (mean of T1 - T3) and 1-week post-P–SEC (T4) \((F(1,26) = 3.6; p < 0.04)\), and between pre-surgery (mean of T1 - T4) and 6-weeks post surgery (T5) \((F(1,26) = 6.1; p < 0.01)\) contributed most to the overall significant 3-factor ANOVA interaction. Please note that full consideration of the important CE-related findings for EMD\(_{RF}\) performance of the leg that does not receive P–SEC directly, is dealt with in Chapter 7 pages 163 – 167.

Prior to surgery, P–SEC elicits substantive improvements in the EMD\(_{RF}\) performance that are sustained until at least 1-week after the cessation of the conditioning. However, it is likely that the complex interaction of major surgery and the effects of the immediate post-TKA care-pathway including rehabilitative conditioning, contrived to reduce the rapidity with which the knee extensor muscles could be activated at 6-weeks following surgery to a level of performance that had matched that of Controls, but which had been below baseline performance.
B. EMD changes in Vastus Lateralis (VL) musculature

The effects of P–SEC on EMD_{VL} were similar to those of EMD_{RF} with factorial ANOVA having shown a significant group x time x leg interaction ($F_{(6,77)} = 10.3; p < 0.001$) indicating that while performance in the knee extensors of patients in the Control group remained relatively constant during the experimental period (T1 - T4), the performance of the P–SEC trained leg of patients undergoing surgery on the same leg (group: P–SEC_{IPSI}) or the contralateral leg (group: P–SEC_{CONTRA}) improved (shorter EMD scores) to a greater extent (peak ES = 1.7; Table 5.5) than the corresponding performance of the leg that does not receive conditioning (peak ES = 0.4) (Figure 5.2) rejecting the null hypothesis (Section 2.11 Hypothesis 1). A priori difference contrasts suggest that significant interactions between baseline (mean of EMD_{VL} performance at T1 and T2) and immediately post-P–SEC (T3) ($F_{(1,26)} = 29.6; p < 0.01$), and between pre-surgery (mean of T1 - T4) and 6-weeks post surgery (T5) ($F_{(1,26)} = 6.6; p < 0.01$) contributed most to the overall significant 3-factor ANOVA interaction, but in contrast to the findings for EMD_{RF}, other comparisons were not influential. CE-related findings for EMD_{VL} performance of the leg that does not receive P–SEC directly, is dealt with in Chapter 7 pages 163 – 167.

It had been biologically plausible to have anticipated similar patterns of responses to conditioning of functionally synergistic muscles (VL and RF). As such, both EMD_{RF} and EMD_{VL} showed similarly substantive P–SEC-related gains in performance prior to surgery, but ultimately, a level of performance at 6 weeks following surgery that had matched that of Controls.

5.3.2 Changes in rate of force development (RFD)

Factorial ANOVA showed a significant group x time x leg interaction for RFD ($F_{(6,75)} = 2.2; p < 0.04$) indicating that when compared to the relatively constant performance of legs of Control patients during the experimental period (T1 - T4), the performance of the P–SEC trained leg of patients undergoing surgery on the same leg (group: P–SEC_{IPSI}) or the contralateral leg (group: P–SEC_{CONTRA}) improved to a greater extent.
Figure 5.2: Group means and ±SD from the 3-way ANOVA interaction for Electromechanical delay (EMD) for both muscles (rectus femoris (EMD$_{RF}$; ms) and vastus lateralis (EMD$_{VL}$; ms)). The values are across all five assessment points (T1 – T5) where T1 is the first initial assessment at time = 0 relative to surgery (≈ 11 – 12 weeks pre-surgery). The graphs on the left hand side represent the values obtained for all three groups when the P–SEC intervention was delivered to the Surgical leg (P–SEC$_{IPSI}$) whilst the graphs on the Right represent the values obtained when the intervention was delivered to the Non-Surgical leg (P–SEC$_{CONTRA}$). The * above and under assessment T3 indicates that a priori difference contrasts suggest the extent of interaction between baseline (mean of EMD performance at T1 and T2) and immediately post-P–SEC (T3) contributed most to the overall significant 3-factor ANOVA interaction. Similarly, the * over T4 (for EMD$_{RF}$ and T5 for both EMD, indicates that overall interaction being also contributed by mean scores at T1 – T3 vs. T4, and T1 – T4 vs. T5. Key: P–SEC$_{CONTRA}$ (P–SEC delivered to the non-surgical leg); P–SEC$_{IPSI}$ (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (≈ 11 – 12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery), T4 as time 12 weeks (week of surgery) and T5 as time 18 weeks (6 weeks post-surgery).
CHAPTER 5. RESULTS 1: CHANGES IN MUSCULAR PERFORMANCE FOLLOWING A PRE-SURGICAL INTERVENTION (P–SEC)

(peak ES = 0.6; Table 5.5) than the corresponding performance of the leg that does not receive conditioning (peak ES = 0.3) (Figure 5.3[a and b]) rejecting the null hypothesis (Section 2.11 Hypothesis 1). A priori difference contrasts suggest that the extent of interaction between baseline (mean of RFD performance at T1 and T2) and immediately post-P–SEC (T3) \( (F_{(1,26)} = 5.5; p < 0.05) \) contributed most to the overall significant 3-factor ANOVA interaction. Please note that full consideration of the important CE-related findings for RFD performance of the leg that does not receive P–SEC directly, is dealt with in Chapter 7 pages 163 – 167.

The P–SEC intervention elicits substantive improvements in the RFD performance of the knee extensor musculature compared to control that was most prominent at the end of the 1-week period of conditioning. However, as had been noted previously for EMD, it is likely that the complex interaction of major surgery and the effects of the immediate post-TKA care-pathway including rehabilitative conditioning, contrived to reduce the rate at which the knee extensor muscles could develop force at 6-weeks following surgery to a level of performance that had matched that of Control patients, but which had been below baseline performance.

5.3.3 Changes in peak force (PF)

Factorial ANOVA showed a significant group x time x leg interaction for PF \( (F_{(5,66)} = 3.6; p < 0.005) \) indicating that while performance in the legs of the Control group remained relatively constant during the experimental period (T1 – T4), the performance of the P–SEC trained leg of patients undergoing surgery on the same leg (group: P–SEC\_IPSI) or the contralateral leg (group: P–SEC\_CONTRA) improved to a greater extent (peak ES = 0.5; Table 5.5) than the corresponding performance of the leg that does not receive conditioning (peak ES = 0.2) (Figure 5.3) rejecting the null hypothesis (Section 2.11 Hypothesis 1). A priori difference contrasts suggest that the extent of interaction between baseline (mean of PF performance at T1 and T2) and immediately post-P–SEC (T3) \( (F_{(1,26)} = 5.9; p < 0.01) \), between T3 (mean of T1 - T3) and 1-week post-P–SEC (T4) \( (F_{(1,26)} = 3.4; p < 0.05) \), and between pre-surgery (mean of T1 – T4) and 6-weeks post surgery (T5) \( (F_{(1,26)} = 3.2 ; p < 0.05) \) contributed most to the
Figure 5.3: Group means and ±SD from the 3-way ANOVA interaction for rate of force development (RFD; N/s) and peak force (PF; N). The values are across all five assessment points (T1 – T5) where T1 is the first initial assessment at time = 0 relative to surgery (≈ 11 – 12 weeks pre-surgery). The graphs on the left hand side represent the values obtained for all three groups when the P–SEC intervention was delivered to the Surgical leg (P–SEC_IPSI) whilst the graphs on the Right represent the values obtained when the intervention was delivered to the Non-Surgical leg (P–SEC_CONTRA). The * above and under assessment T3, T4 or T5 indicates that a priori difference contrasts suggest that the extent of interaction between baseline (mean of RFD performance at T1 and T2) and immediately post-P–SEC (T3) contributed most to the overall significant 3-factor ANOVA interaction. Similarly, for PF with the addition of the overall interaction being also contributed by mean scores at T1 – T3 vs. T4, and T1 – T4 vs. T5. Key: P–SEC_CONTRA (P–SEC delivered to the non-surgical leg); P–SEC_IPSI (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (≈ 11 – 12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery), T4 as time 12 weeks (week of surgery) and T5 as time 18 weeks (6 weeks post-surgery).
overall significant 3-factor ANOVA interaction. Please note that full consideration of
the important CE-related findings for PF performance of the leg that does not receive
P–SEC directly, is dealt with in Chapter 7 pages 163 – 167.

Prior to surgery, P–SEC elicits substantive improvements in the PF performance
that are sustained until at least one week after the cessation of the conditioning. How-
ever, it is likely that the complex interaction of major surgery and the effects of the
immediate post-TKA care-pathway including rehabilitative conditioning, contrived to
reduce the strength of the knee extensor muscles at six weeks following surgery to a
level of performance that had matched that of control patients, but which had been
below baseline performance.

5.3.4 Changes in sensorimotor function - force error (FE)

Sensorimotor performance as measured by FE showed a significant group x time x leg
interaction \( F(8,104) = 2.1; p < 0.05 \) indicating that while performance in the legs of the
Control group remained relatively constant during the experimental period (T1 – T4),
the performance of the P–SEC trained leg of patients undergoing surgery on the same
leg (group: P–SEC\(_{IPS1}\)) or the contralateral leg (group: P–SEC\(_{CONTRA}\)) improved to
a greater extent (peak ES = 0.9; Table 5.5) than the corresponding performance of
the leg that does not receive conditioning (peak ES = 0.1) (Figure 5.4) confirming the
initial hypothesis (Section 2.11 Hypothesis 1). A priori difference contrasts suggest
that the extent of interaction between baseline (mean of FE performance at T1 and
T2) and immediately post-P–SEC (T3) \( F(1,26) = 6.4; p < 0.01 \) contributed most to
the overall significant 3-factor ANOVA interaction but in contrast to the findings for
EMD\(_{RF}\) and PF, other comparisons were not influential. Please note that full consid-
eration of the important CE-related findings for FE performance of the leg that does
not receive P–SEC directly, is dealt with in Chapter 7 pages 163 – 167.

Prior to TKA surgery, it is interesting to note that despite its emphasis on 'motor'
conditioning, P–SEC elicited an immediate and substantive improvement in FE per-
formance (less error) that was prominent at the end of P–SEC conditioning but not
necessarily sustained thereafter. As has been noted for other indices of neuromuscular performance (EMD, RFD and PF), it is likely that at six weeks following surgery (T5), sensorimotor acuity was reduced (more error) to a level that is below that at baseline due to a complex interaction of major surgery and the effects of the immediate post-TKA care-pathway including rehabilitative conditioning.

Figure 5.4: Group means and ±SD from the 3-way ANOVA interaction for force error (FE; %). The values are across all five assessment points (T1 – T5) where T1 is the first initial assessment at time = 0 relative to surgery (≈ 11 – 12 weeks pre-surgery). The graphs on the left hand side represent the values obtained for all three groups when the P–SEC intervention was delivered to the Surgical leg (P–SECIPSI) whilst the graphs on the Right represent the values obtained when the intervention was delivered to the Non-Surgical leg (P–SECCONTRA). The * under and above assessment T3 indicates that a priori difference contrasts suggest that the extent of interaction between baseline (mean of FE performance at T1 and T2) and immediately post-P–SEC (T3) contributed most to the overall significant 3-factor ANOVA interaction. Key: P–SECCONTRA (P–SEC delivered to the non-surgical leg); P–SECIPSI (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (≈ 11 – 12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery), T4 as time 12 weeks (week of surgery) and T5 as time 18 weeks (6 weeks post-surgery).
Table 5.3: **Trained Leg**: Means and ±SD for assessments T2 – T5 of both intervention groups (P–SECIPSI and P–SECCONTRA) on the trained leg. Calculated effect sizes and percentage changes are relative to baseline T2 pre-P–SEC intervention. **Key**: * = within-subjects contrast significance (p < 0.05). EMD - electromechanical delay (ms); RF - rectus femoris muscle; VL - vastus lateralis muscle; RFD - rate of force development (N/s); PF - peak force (N); FE - force error (%).

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<th>Outcome variable</th>
<th>T2 Mean ±SD</th>
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<th>T4 Mean ±SD</th>
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<th>ES T2 - T3</th>
<th>ES T2 - T4</th>
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<tr>
<td>EMDRF (ms) P–SECIPSI</td>
<td>45.33 ±7.21</td>
<td>33.56 ±6.00</td>
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<td>55.11 ±8.08</td>
<td>-1.78</td>
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<td>-35.10*</td>
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<td>11.83*</td>
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<td>EMDVL (ms) P–SECIPSI</td>
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<td>33.89 ±6.43</td>
<td>38.89 ±8.27</td>
<td>56.33 ±9.43</td>
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<td>637.22 ±145.72</td>
<td>451.78 ±82.90</td>
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<td>0.43</td>
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<td>974.88 ±220.65</td>
<td>917.13 ±189.17</td>
<td>0.52</td>
<td>0.36</td>
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<td>PF (N) P–SECCONTRA</td>
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### Table 5.3 – Continued from previous page

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<th>T4 Mean ± SD</th>
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<th>ES T2 - T4</th>
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<th>% change T2 - T4</th>
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<tr>
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<td>-23.51*</td>
<td>-8.07</td>
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Table 5.4: **Untrained Leg**: Means and ±SD for assessments T2 – T5 of both intervention groups (P–SEC<sub>IPSI-CE</sub> and P–SEC<sub>CONTRA-CE</sub>) on the untrained leg as a result of cross-education (CE). Calculated effect sizes and percentage changes are relative to baseline T2 pre-P–SEC intervention. **Key**: * = within-subjects contrasts significance (p < 0.05). EMD - electromechanical delay (ms); RF - rectus femoris muscle; VL - vastus lateralis muscle; P–SEC<sub>IPSI-CE</sub> - CE effects observed in the surgical leg; P–SEC<sub>CONTRA-CE</sub> - CE effects observed in the non–surgical leg; RFD - rate of force development (N/s); PF - peak force (N); FE - force error (%).

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<th>Outcome variable</th>
<th>T2 Mean ±SD</th>
<th>T3 Mean ±SD</th>
<th>T4 Mean ±SD</th>
<th>T5 Mean ±SD</th>
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<th>ES T2 - T4</th>
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<td>45.88 ±15.24</td>
<td>42.38 ±13.17</td>
<td>44.38 ±14.66</td>
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<td>-0.25</td>
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<td><strong>EMD&lt;sub&gt;VL&lt;/sub&gt; (ms)</strong></td>
<td>47.50 ±15.57</td>
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<td><strong>RFD (N/s)</strong></td>
<td>876.67 ±200.81</td>
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<td>889.78 ±211.24</td>
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<td><strong>RFD (N/s)</strong></td>
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<tr>
<td><strong>PF (N)</strong></td>
<td>227.56 ±92.06</td>
<td>239.22 ±95.28</td>
<td>238.00 ±96.01</td>
<td>233.11 ±92.33</td>
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<td><strong>PF (N)</strong></td>
<td>167.25 ±62.66</td>
<td>183.13 ±68.15</td>
<td>176.25 ±61.03</td>
<td>128.50 ±75.88</td>
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<tr>
<td><strong>FE (%)</strong></td>
<td>13.55 ±4.97</td>
<td>13.00 ±4.66</td>
<td>14.00 ±4.87</td>
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Table 5.4 – Continued from previous page

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<td>FE (%)</td>
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5.3.5 Changes in neuromuscular and sensorimotor outcomes due to cross-education (CE)

As alluded to within the preceding sub-sections of the thesis, factorial ANOVA showed significant group x time x leg interactions consistently for each index of neuromuscular (EMD$_{RF}$; EMD$_{VL}$; RFD; PF) and sensorimotor (FE) performance ($F(5,104)_{GG} = 2.1$ to $10.3; \ p < 0.05$) indicating that by comparison to the relatively constant performance of the knee extensor musculature in the legs of the Control patients during the experimental period (T1 – T4), the performance of the P–SEC trained leg improved to a greater extent than the corresponding performance of the leg that had not received conditioning. The patterns of improvement in performance associated with the latter findings showed importantly that significant CE-related effects had occurred for each of the neuromuscular and sensorimotor performance outcomes as a result of the unilateral limb P–SEC conditioning. Please note that full consideration of the CE-related findings for neuromuscular and sensorimotor performance of the leg that does not receive P–SEC directly, is presented within Chapter 7.

5.3.6 Confirmation of independence and mechanism of improvements amongst neuromuscular and sensorimotor outcome measures

A Pearson correlation ($r$) analysis was employed amongst all outcomes of neuromuscular (EMD$_{RF}$, EMD$_{VL}$, RFD and PF) and sensorimotor (FE) performance at baseline (T1 and T2) for both legs (surgical and non-surgical). Relationships amongst sensorimotor and neuromuscular outcome measures either did not exist or were weak at best ($r \approx 0.40$), indicating that outcomes were independent of one another and as expected, reflective of different physiological capabilities.

The extent of improvement in sensorimotor performance (FE) within the period of the P–SEC (T2 – T3) for patients undergoing P–SEC was strongly and significantly correlated ($r = 0.6 – 0.8$; Table O.1, Appendix O) with corresponding improvements in neuromuscular performance (EMD$_{RF}$, EMD$_{VL}$, RFD and PF), for both legs (surgical and non-surgical), sharing up to 64% (coefficient of determination ($r^2$)) of the pooled
Table 5.5: The following table reports the calculated effect sizes (ES) and respective percentage (%) change calculated from means and standard deviations (SD) from the 3-way ANOVA interaction. The ESs and percentage changes presented below have been calculated using pre- and post-intervention measures obtained between T2 and T3 for the respective groups on all five outcome measures. The ESs and percentage changes reported on the Right side of the table (untrained leg) include the values obtained on the untrained leg when the P–SEC intervention was delivered to the contralateral leg. The negative symbol shown next to the EMD and FE values indicates improvement for that outcome. Key: EMD - electromechanical delay; RF - rectus femoris muscle; VL - vastus lateralis muscle; P–SEC<sub>IPSI</sub> - surgical leg; P–SEC<sub>CONTRA</sub> - non-surgical leg; RFD - rate of force development; PF - peak force; FE - force error.

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<td>ES</td>
<td>% change</td>
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<td><strong>FE (%)</strong></td>
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5.4 Discussion

The main finding of this study was that the ‘novel’ P–SEC intervention elicited significantly greater improvements in neuromuscular and sensorimotor performance than current practice (control; no exercise conditioning). The study’s primary outcome (EMD: 37% improvement (baseline to immediately post-P–SEC, T3, trained leg)) and FE (24%) showed the most prominent and immediate gains in performance, with more conservative (12% to 14%) gains noted for RFD and PF in the trained leg. Therefore, a modest and brief (9 sessions (1-week); high-intensity (60% – 100% of daily MVC)) AMI-related, nociceptor averse (exercise lasting <1.5s) dosage of unilateral exercise conditioning that nevertheless adhered robustly to training principles of physiology (including specificity - neuromuscular focus), resulted in substantive and immediate improvement in neuromuscular performance. Furthermore, concomitant gains in sensorimotor performance were also observed. It was notable that these pre-habilitative improvements in performance had been achieved against an apparent conditioning-resistant background of end-stage OA, without sacrificing patient tolerance to exercise-conditioning, and with no significant or unfavourable P–SEC-related responses identified for any participant in the potentially vulnerable study population. The latter P–SEC-related gains (moderate to large ESs (0.5 - 2.0)) in neuromuscular and sensorimotor performance reflect the effects of unilateral limb conditioning in both the leg that would have been undergoing surgery and the non-surgical leg, but delivered experimentally by means of two separate groups. Given the imperative ethically to deliver a pathway of care involving bilateral limb conditioning in order to be congruent with contemporary practice, direct contemporaneous application of P–SEC to both legs is likely to have similar positive gains should it be adopted within clinical practice in the future.

The smaller magnitudes of improvement in neuromuscular and sensorimotor per-
formance (4% to 11% (baseline (T2) to immediately post-P–SEC, T3, non-trained leg; ES = 0.1 – 0.4)) were observed as simultaneous effects in the untrained leg, associated with indirect P–SEC-related cross-education (CE). These findings confirmed that significant indirect contralateral limb gains would be possible, even under conditions of clinical or practical necessity for unilateral conditioning, such as during unilateral episodes of joint inflammation associated with OA. Effects of CE associated with the P–SEC intervention are considered in detail within Chapter 7.

The sustained state of neuromuscular inhibition that these cohort of patients experience, often leads to a decrease in motor unit (MU) activation in the involved musculature (quadriceps) and a resultant decrease in muscular performance (Hurley et al. 1994, Palmieri et al. 2004). These features are enhanced even further in deconditioned and elderly individuals that are typical characteristics of those individuals waiting to undergo TKA surgery (Jones et al. 2004). The dampened activation of these MUs, have been found to favour faster muscular contractions and larger magnitude of forces delivered through dynamic movements (Henneman et al. 1965, Suchomel et al. 2018) similar to those exhibited during eccentric-concentric muscle contractions performed during the P–SEC intervention. Therefore, the improvements recorded within this study could be attributed to an increase in stimulation of the inhibited MU caused by the inherently brief muscular demands associated with the P–SEC prescribed exercises. The resultant P–SEC-related improvements in neuromuscular performance, and to its acuity of control by means of gains in sensorimotor performance, were notable and novel, and they had occurred despite an emphasis on motor-biased conditioning exercises within the P–SEC intervention. There would be a reasonable expectation that P–SEC-type interventions could be deployed successfully for performance gains amongst other similar chronic disease conditions.

The novelty of this research lies firstly in the delivery method of exercise-conditioning, favouring an individual patient-focused pre-surgery protocol as opposed to the generic pre-surgery conditioning programmes that have been delivered in previous research (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015).

The significant and immediate results achieved for pre-habilitative conditioning within this current study conflict with the conclusions of some recent reviews (Wang et al. 2016, Chesham & Shanmugam 2017) in which pre-habilitative conditioning efficacy has been considered too small for clinically effectiveness and for any possibility of adoption within routine clinical practice. The latter limited pre-habilitative responses to relatively lengthy (> 6 weeks) volumes and dosages of exercise-conditioning most likely reflect a patterning of ‘generic’ stimuli rather than the relatively greater potency of specifically focussed stimuli associated with P–SEC and its strict adherence to physiological principles. The apparent paradox associated with a successful pre-habilitative intervention would be the need for sufficient or optimised potency in a specific dose of conditioning that would also be congruent with the required expectations for logistical or cost expediency and clinical effectiveness within the care-delivery system. The P–SEC intervention appears to be capable of delivering the required efficacy in neuromuscular and sensorimotor performance outcomes (ES = 0.3 – 2.0) within a brief programme (1 week) that matches or exceeds the capabilities for efficacy shown amongst neuromuscular rehabilitative conditioning studies in patients undergoing TKA surgery (Rooks et al. 2006, Swank et al. 2011, McKay et al. 2012, Calatayud et al. 2017) and those that are not (Van Cutsem et al. 1998, Aagaard et al. 2000). It was notable that the current formulation of the P–SEC protocol typically yielded substantive improvements in neuromuscular and sensorimotor performance that were sustained until at least one week after the cessation of the conditioning for some (EMD; PF) but not all (RFD; FE) outcomes, and that all of the latter gains in performance capabilities had dissipated by six weeks after surgery. It is plausible that the complex interaction of the effects of major biological insults to the knee joint associated with surgery and
CHAPTER 5. RESULTS 1: CHANGES IN MUSCULAR PERFORMANCE FOLLOWING A PRE-SURGICAL INTERVENTION (P–SEC)

the effects of the immediate post-TKA clinical care-pathway including rehabilitative conditioning, would have had added to the heterogeneity of response amongst participants. In turn, these threats to sustained gains in neuromuscular and sensorimotor performance for the knee extensor musculature may have overwhelmed any remnant effects of the single episode of P–SEC at six weeks following TKA surgery. Results from the current analysis of data nevertheless question the capability of the P–SEC intervention in its current configuration to positively influence post-surgery outcomes, and thus the imperative for pre-habilitation to some extent. Future investigations and optimised re-configurations of P–SEC will no doubt address this issue directly.

There are several factors to take into consideration when comparing between the current and previous research studies. Although the results may be similar in the extent of effect, study’ populations were heterogeneous in characteristics and sample’ size, the mode of the intervention’s delivery was varied and often much longer in duration and prescribed dosage than the brief (1 week) delivery of the P–SEC. Furthermore, outcomes of previous studies tended to focus only on changes in strength, rather than the wider consideration of neuromuscular and sensorimotor performance, which had been achieved within the current investigation of the effects of P–SEC. The adaptation mechanisms for eliciting conditioning-related improvements are also potentially different. Strength and resistance-type training improves muscular performance ultimately by causing morphological changes in the muscular structure with concurrent increases in strength cross-sectional area (CSA) (Suetta et al. 2004). The rapid muscular activations (eccentric-concentric) used in the delivery of the P–SEC intervention have been associated with changes in the patterning of neural activation as the muscle is required to respond volitionally to serial activations (‘doublets’), causing an increase in rate of MU firing (Van Cutsem et al. 1998). An increased rate of MU firing has been associated with decreases in autogenic and arthrogeneic inhibition (e.g. AMI) and concomitant increases in muscular strength and aspects of the rapidity with which muscular activation and force delivery can occur (e.g. EMD and RFD) (Aagaard et al. 2000, Hurley et al. 1994, Suchomel et al. 2018), without the accompaniment necessarily of any changes in morphology. The larger P–SEC effects associated with EMD and FE (ES = 0.9 to 2.0;
22% to 37% gains) compared to PF (ES = 0.5; 14%) tends to support the notion that neurally-derived mechanisms rather than morphological changes underpin the stimuli for adaptation within the relatively short duration of the P–SEC intervention. Relationships amongst sensorimotor and neuromuscular outcome measures either did not exist or were weak at best \( (r \approx 0.4) \), indicating that the outcomes were independent of one another and as expected, reflective of different physiological capabilities. By contrast, the extent of improvement in sensorimotor performance for patients undergoing P–SEC was strongly and significantly correlated \( (r = 0.6 – 0.8) \) with corresponding improvements in neuromuscular performance scores, sharing up to 64% \( (r^2) \) of pooled variance. Thus conceptually, it is plausible that neuromuscular adaptations to P–SEC might be considered to be mechanistic determinants of sensorimotor performance.

The objective outcome measures of EMD, PF, RFD, FE were selected for use in this study due to their excellent psychometric properties in the assessment of patients undergoing knee surgery (Bailey et al. 2014, Peer 2017). They were matched well to a role in this study that had been designed essentially as a quantitative assessment of proof of principle for a ‘novel’ approach to conditioning in patients with chronic knee OA and undergoing TKA surgery. By contrast, patient-reported outcomes (PROs) assess the effectiveness of an intervention subjectively (Bourne 2008, Hamilton et al. 2013) and the important consideration of whether or not there was congruence between objective and subjective changes in performance as a result of the P–SEC intervention will be considered in Chapter 6.

Duration of the exercise-conditioning intervention is another essential aspect in explaining differences between current and previous research. Previous generic presurgery exercise-programmes were commonly delivered over a much longer period of time (6 – 12 weeks) (Aagaard et al. 2000, Rooks et al. 2006, Topp et al. 2009, McKay et al. 2012, Swank et al. 2011, Calatayud et al. 2017, Suchomel et al. 2018) and included a patterning of exercise delivery that commanded time- and cost-pressures on health service care providers that would be simply unavailable in routine practice.
ilar durations of conditioning have been used to elicit gains in strength (Ackerman & Bennell 2004, Suchomel et al. 2018). Within these lengthy programmes, there was a concomitant large number of sessions (18 to 24) in which participants were exposed to the intervention. The P–SEC conditioning programme by contrast, had required only 50% of the number of sessions (9 sessions) to be delivered over a much shorter period of time (1 week) in order to be efficacious. The extent of improvements in neuromuscular and sensorimotor performance have been considered statistically significant ($p < 0.05$) and meaningful physiologically ($ES > 0.5$) especially in the leg undergoing surgery ($P$–SEC$_{IPSI}$). Therefore, this study’s findings indicate the potential for a novel, focal sensorimotor, pre-surgery exercise-conditioning programme to achieve relatively large neuromuscular and sensorimotor performance improvements over a relatively much shorter period of time and smaller dosage of stimuli compared to current pre-habilitative and rehabilitative practices.

### 5.5 Limitations, clinical implications and further research

The strength of this study lies in the methodological approach adopted within a randomised controlled trial (RCT). An RCT is considered the “gold standard” of clinical research and along with the blinding and concealment processes adopted during the execution of this study, one can consider the results obtained from this study as relatively robust. Furthermore, the concealment of the data to the principal investigator prior to analysis, further increased the robustness of the study. Another strength includes the evaluation of muscular performance through repeated assessment points, providing a comprehensive analysis of the effects of the ‘novel’ (P–SEC) intervention during pre-surgical and post-surgical phase of patients electing to undergo a TKA. Furthermore, intra- and inter-day reliability analysis was performed for each outcome measure used within this study in order to establish and understand the limits of measurement precision. Several factors must be considered with respect to the conclusions that can be drawn from this study. Firstly, there were a considerable number of patients involved in ‘loss-to-follow-up’ after randomisation due to unforeseen circumstances, including
changes to the scheduled date for surgery that logistically, did not allow enough time for delivery of the P–SEC intervention or for further assessments. Patients ‘loss-to-follow-up’ led to a decreased number of data-sets for analyses and therefore possibly, a negative influence on the statistical power associated with the experimental design sensitivity using the selected measurement outcomes. Further recruitment was not possible due to restricted funding and resource limitations associated with an educational project. The main funds were allocated to allow for appropriate randomisation and blinding of the selected participants into groups and to meeting the costs of travelling in order to obtain the required data over a period of 11 months. Secondly, although baseline measures of the respective muscular performance indices were comparable in extent to those in previous research, participants were recruited at a specialist orthopaedic NHS Trust hospital (RJAH), which may reduce the ability to generalise from the results of this study. Although the sample population used within the study can be considered to be small, the experimental design sensitivity of the study was sufficient to have identified a variety of situations in which the tested null-hypothesis was not retained, with Type II error rates exceeding the prescribed levels (> 0.20).

This is the first study to evaluate the efficacy if a ‘novel’ pre-surgery exercise-conditioning (P–SEC) programme in patients electing to undergo TKA and was designed essentially as a quantitative assessment of proof of principle. As would be the case for any successful conditioning programme, the potential importance of this ‘novel’ conditioning programme (P–SEC) is its capability for expediting timely gains in neuromuscular and sensorimotor performance. The significant and immediate results achieved for enhanced performance levels will aid in protecting the surgical implant and decrease the risk of injury, whilst potentially improving patients’ pre-habilitative status, without imposing any additional logistical or cost expediency and clinical effectiveness within the care-delivery system. As a result of the randomisation process adopted in the current study, an appropriate representation of patients electing for TKA within the specialised institution (RJAH NHS Trust hospital), the sample population would not necessarily represent the wider cohort of patients undergoing TKA surgery attending other non-specialised institutions. Therefore, future research into the applicability of
this ‘novel’ approach to conditioning should include a more varied sample from different centres (multi-centre) to present a more heterogeneous population sample and improve external validity and generalisability of the results.

5.6 Conclusion

The results of this study have shown for the first time that a modest and brief (9 sessions (1 week); high-intensity (60% to 100% of daily MVC); AMI-related nociceptor averse (exercises lasting <1.5s)) dosage of unilateral exercise conditioning (P–SEC) elicited significantly greater improvements in neuromuscular and sensorimotor performance than current practice in patients electing to undergo TKA, which was maintained up to a week following the intervention. The P–SEC-related gains (moderate to large ES = 0.5 - 2.0) achieved in both neuromuscular and sensorimotor performance outcomes, reflect the effects of unilateral limb conditioning in both the legs (surgical and non-surgical). Thus, the P–SEC was endorsed for potentially being able to improve rehabilitation practices for patients electing to undergo TKA surgery. Direct contemporaneous application of P–SEC simultaneously to both legs is likely to have similar positive gains should it be adopted within clinical practice in the future. Although the results observed in this study were obtained from a relatively small sample size (n = 29), Type II error rates were contained within appropriately powered (≥ 0.9) statistical analyses, making the study and its results robust for consideration within clinical practices.
Chapter 6

Results 2 – The effects of pre-surgery exercise-conditioning (P–SEC) on patient reported outcomes

6.1 Introduction

The results reported in Chapter 5, revealed as hypothesised that the ‘novel’ P–SEC intervention elicited statistically significant changes over time in the selected objective physical performance measures (EMD, PF, RFD and FE). These changes were primarily observed as improvements in muscular performance outcomes with the biggest contributor to the overall change being observed before and after the P–SEC intervention in the pre-surgery phase. These findings indicate that objectively, the P–SEC intervention has been effective in eliciting improvements in physical performance outcomes. However, whether these physical improvements were also perceived by the individual to affect physical function, pain, self-efficacy, quality of life (QoL) and self-reported habitual physical activity (PA) can only be investigated through patients reported outcomes (PROs). For this Chapter, the main considerations are the patients’ perceptions on outcomes such as pain, physical function, PA and QoL before and after surgery.
and how these may be affected when a pre-surgical intervention is applied. For the individual, the main aims for undergoing a TKA surgery are mostly to relieve ongoing symptoms of pain, restore function and physical activity and improve QoL (Magee et al. 2015, National Joint Registry Annual Report 14th Edition 2018). One of the underlying physiological mechanisms that contribute to these symptoms and physical limitations is chronic neuromuscular inhibition (AMI). AMI is thought to contribute to decreased joint stability, balance capabilities and reduced movement control that often persists a year on from surgery (Silva et al. 2003, Piva et al. 2010, Rätsepsoo et al. 2011). These issues are not always addressed through surgery and the subsequent rehabilitation. Due to time and financial pressure within the NHS, the main focus of post-TKA rehabilitation is to restore function and alleviate pain. Although TKA surgery has been shown to be successful in doing this in the majority of patients, the lack of consideration of issues such as joint instability and reduced movement control may result in persisting function disabilities and subsequent patients’ dissatisfaction.

Pre-surgery conditioning is a growing research focus. It occurs at a time when patients generally receive no formal conditioning, and as such could potentially improve post-surgery outcomes (Topp et al. 2009, McKay et al. 2012, Desmeules et al. 2013, Huber et al. 2015). However, the patterns of patients’ adaptations to the generic exercise stimuli within these studies on pre-surgery conditioning, have not shown the gains expected considering the physiological dose-response relationships. Since the scope of this Chapter is to focus on the use of PROs, the reader is referred to Chapters 2 and 5 for further details on pre-surgery conditioning and the novel P–SEC conditioning programme used as the intervention within this study.

PROs are self-reported questionnaires that measure patients’ perceptions of constructs including pain, physical function and habitual PA and QoL. For individuals undergoing TKA, PROs have been often utilised to predict post-surgery outcomes (Stevens-Lapsley et al. 2011, Black 2013), evaluate the effectiveness of an intervention ( Bourne 2008), measure patients’ satisfaction following surgery (Hamilton et al. 2013, Black 2013) and monitor changes in perceived capabilities during the pre- and post-
surgery period (Hamilton et al. 2013, Peer 2017). Compared to objective performance measures, PROs are generally more easily administered and obtained, and are more often employed in large scale studies with repeated measures (Bellamy et al. 1997). Furthermore, PROs also provide a structural and repeatable way of obtaining information that is experienced by the patient alone and corresponds to their interpretation of their health and physical performance status at the time that is not always clearly obtained through the use objective measures (Copay et al. 2007). This is especially important with outcomes such as pain, physical function/activity and QoL, that are personal and subjective experiences of the individual. Therefore, in addition to the objective measures of physical performance that are discussed in Chapter 5, the aim of this study is to also explore the effects of the ‘novel’ intervention (P–SEC) on patients’ perceived outcomes through PROs. Data reported in this chapter will complement the results obtained in Chapter 5 and identify whether the positive effects of the (P–SEC) intervention on objective physical function also positively affect patients’ perceptions of their physical capabilities and as a result influence other outcomes such as pain self-efficacy, self-reported habitual physical activity and QoL. These are important outcomes which ultimately affect patient satisfaction with surgery (Hamilton et al. 2013, Black 2013).

A considerable number of PROs have been developed and are available to measure various aspects of knee function. Chapter 2 Section 2.6 describes and compares the most commonly employed PROs in patients undergoing TKA. Amongst these are the six main questionnaires that have been selected for this study that include: the Oxford knee score (OKS), the knee injury and osteoarthritis outcome score (KOOS), pain self efficacy questionnaire (PSEQ), the international physical activity questionnaire (IPAQ), performance profile (PP) and the general health questionnaire (SF-36v2). Amongst the selected six, the OKS and the KOOS are two of the most commonly used PROs in patients undergoing TKA surgery (Lovelock et al. 2018) both in research and the NHS. Both questionnaires exhibit clinically acceptable psychometric properties of validity, reproducibility and responsiveness to variations in the patient’s condition over time (Dunbar et al. 2001, Jenny & Diesinger 2012, Peer & Lane 2013) that have been
reported in Chapter 2. However, the constructs within these questionnaires are joint specific and do not quantify pain in relation to self-efficacy, habitual PA levels and overall health status. The PSEQ is a commonly used tool with comparable psychometric properties to other well established PROs (Nicholas 2007, Nicholas et al. 2008). In addition, the P–SEC intervention aims to improve, perceived functional capability, habitual PA levels and ultimately QoL and levels of physical activity. The PP, SF-36v2™ and IPAQ questionnaires have been successfully used to measure and quantify PA levels and perceived performance in patients undergoing TKA surgery (Peer 2017) and other knee related surgeries (Bailey et al. 2014, Yates 2016) and have appropriate psychometric properties (refer to Chapter 2 Section 2.6). Although none of the PROs’ constructs relate specifically to sensorimotor function such as joint stability, movement control or balance impairment, the constructs within the selected PROs reflect on different aspects that could be influenced through P–SEC conditioning.

The aim of including PROs in this study is to evaluate and quantify changes in patients’ perceived physical performance specifically in relation to pain, physical function/activity and QoL following the application of a ‘novel’ pre-surgical conditioning programme (P–SEC) in patients waiting for TKA. Previous literature (Nicholas 2007, Peer & Lane 2013, Blikman et al. 2013, Silsbury et al. 2015, Peer 2017) has shown that little to no change occurs during the pre-surgery phase in patients’ perceived performance for the above outcomes unless an intervention occurs during this period. Therefore, it is hypothesised that the P–SEC intervention during this time will elicit changes in PROs for pain, habitual PA, function and QoL during the pre-surgery phase (T2 – T3 – T4; refer to the detailed study timeline in Chapter 4). The secondary aim of the assessment of PROs within this study investigates whether effects of the pre-surgery conditioning (P–SEC) that might have carried over to the post-surgical phase six weeks after surgery (T5). Previous literature (Yakhdani et al. 2010, Mizner et al. 2011, Peer 2017) has used this time-point as the earliest assessment session to observe any significant changes following the surgery. Any observed changes at this time point are due to a complex interaction of events including effects of surgery and ongoing rehabilitation. Therefore, this post-surgical assessment point is primarily aimed at as-
certaining that the P–SEC intervention did not result in a deterioration in perceived physical performance and capability, pain, pain self-efficacy, habitual PA and QoL.

6.1.1 Summary

PROs have become an essential part of health care and are essential in highlighting the effects of an intervention. Although most patients report decreased pain and improved function and QoL following a TKA, some are dissatisfied with the outcome of their surgery possibly because some aspects of their function such as perceived stability are neither addressed within traditional patient reported outcome measures nor the primary focus routine clinical rehabilitation practice. Pre-surgery conditioning aimed at improving outcomes after TKA has been investigated in recent years, but the generic conditioning parameters used in these programmes have been short-lived and not clinically significant. The ‘novel’ conditioning (P–SEC) offered in this study has shown to elicit changes in objective measures of physical performance (refer to Chapter 5), while in this chapter the focus is on whether a similar improvement is shown in PROs. Therefore, the primary aim of this chapter was to evaluate the effects of the P–SEC intervention as a pre-surgical conditioning programme in patients’ perceived physical performance outcome in relation to pain, habitual PA, function and QoL during the pre-surgery period. Secondly the aim was to assess whether this intervention may affect post-surgery recovery in these outcomes.

6.2 Methods

A. Methodological procedures and P–SEC conditioning

Due to the nature of the study investigated in this doctoral research project (RCT), the methodological approach and procedures for the results discussed in this chapter (PROs), are the same as those described in Chapters 4 and 5. The reader is referred to Sections 4.4, 4.6, 4.7.3 and 5.2 for further information about study design, ethical approval and assessment procedures, and participants’ characteristics. The P–SEC intervention referred to in this Chapter is described in detail in Chapter 4 Section 4.6.
CHAPTER 6. RESULTS 2 – THE EFFECTS OF PRE-SURGERY EXERCISE-CONDITIONING (P–SEC) ON PATIENT REPORTED OUTCOMES

B. PRO scoring

The total and subsection scores of the PROs were obtained according to the guidelines provided for each outcome measure and are detailed in Chapter 4 Section 4.7.3, where the reader is directed to for further information.

C. Statistical analyses

The data was entered and analysed using IBM Statistical Package for the Social Science (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to test for normality of the data and where appropriate, parametric statistical analysis was used. Separate analyses of variances (parametric ANOVAs) for each outcomes (OKS, KOOS, IPAQ, PSEQ, PP and SF-36v2™) were used to assess changes over time. A 2-factor ANOVA involving factors of group (Experimental [P–SECIPSI] vs. Experimental [P–SECCONTRA] vs. Control [current practice/no conditioning [Control]]) by time (≈ 10 weeks pre-surgery (T1), 2 weeks pre-surgery (T2), 1 week pre-surgery (T3)) was utilised to evaluate perceived changes in pain, physical function/activity and QoL during the pre-surgical period (n = 28). A subsequent but separate 2-factor ANOVA involving factors of group (Experimental [P–SECIPSI] vs. Experimental [P–SECCONTRA] vs. Control [current practice/no conditioning [Control]]) by time (≈ 10 weeks pre-surgery (T1), 2 weeks pre-surgery (T2), 1 week pre-surgery (T3) and 6 weeks post-surgery (T5)) was used to evaluate changes in perceived physical performance outcomes in pain physical function/activity and QoL over the pre- and post-surgical period (n = 15). Due to a poor response rate for assessment time period T4 (week of surgery/ 1 week following cessation of P–SEC intervention for any retention of effects), the ANOVA did not include data obtained from the T4 assessment. The assumptions supporting the use of ANOVA with repeated measures were verified, and violations were corrected using the Greenhouse-Geisser adjustment for the degrees of freedom associated with the critical F-value (indicated by GG). In addition, reverse Helmert orthogonal a priori differences rather than post-hoc statistical analyses, were employed. Unless specified, data are presented as group mean ±SD. A Friedman ANOVA (non-parametric equivalent) was employed for data where the underlying distribution was not normal. A priori alpha
level was set at $p < 0.05$.

Recent literature using a similar methodological approach, demonstrated no statistically significant changes in the PROs (OKS, IPAQ, SF-36v2\textsuperscript{TM}, PP, KOOS except for pain subscale) were found across a 10-week pre-surgery period (Peer 2017). Therefore, adopting the assumption that the exposure of the individual did not change between T1–T2 time period, missing data was imputed using the same value. The missing data was imputed manually using the last observation carried forward (LOCF) method for single data imputations (Karahalios et al. 2012) for the scores of questionnaires missing in assessment point T1 or T2. No data was imputed for the post-intervention assessment points (T3 – T5). A per protocol analysis was subsequently performed following imputation of missing data.

6.3 Results

Per protocol analysis was reported for each outcome measure unless otherwise stated. Accounting for loss-to-follow-up and appropriate imputation of missing data, complete datasets from a total of 28\textsuperscript{1} participants were available for analysis (Control n = 9; P–SEC\textsubscript{IPSI} (Surgical leg) n = 9; and P–SEC\textsubscript{CONTRA} (Non-Surgical leg) n = 10). The first research question regarding the effect of the P–SEC intervention on the PROs for assessment time points during the pre-surgery phase (T1, T2 and T3). To answer this question a 2-factor ANOVA was employed based on the total number of responses ($N = 28$). For the second analysis the total number of responses where from a smaller number of participants (n = 15: Control n = 6; P–SEC\textsubscript{IPSI} (Surgical leg) n = 4; and P–SEC\textsubscript{CONTRA} (Non-Surgical leg) n = 5). Shapiro-Wilk test for normality indicated an overall non-significant result ($p > 0.05$) for all but one (PP) PROs during the pre-surgery phase, confirming that the data was overall normally distributed. Post-surgery, normality of data was confirmed for outcome scores of the OKS, PSEQ and KOOS (all sub-scales) (Shapiro-Wilk test non-significant result ($p > 0.05$)). The Shapiro-Wilk

\textsuperscript{1}The total number of responses differs from the objective data (n = 29) because objective measures had three trials of each outcome measured at each session therefore an average was taken as the mean value whilst PROs were only based on concealed answers from the respective questionnaire per session.
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test for the PP and the IPAQ questionnaires outcome scores was significant \( p < 0.05 \) indicating that the data was not normally distributed. For this reason, non-parametric tests were selected for the respective analysis (Refer to Table Q.2 in Appendix Q).

6.3.1 Oxford Knee Score (OKS)

Pre-surgery period
The factorial ANOVA with repeated measures indicated no statistically significant group x time interaction for the OKS questionnaire \( (F_{(4,50)} = 0.09; \ p = 0.98) \) indicating that the scores of all groups remained relatively constant during the experimental period (T1– T3) (refer to Figure 6.1). Mean responses for the three groups were (Control = 25.6 ±9.6, 27.2 ±9.1, 27.8 ±6.6; P–SECIPSI = 19.6 ±4.4, 20.9 ±6.1, 21.6 ±5.8; P–SECCONTRA = 19.4 ±8.0, 20.4 ±9.2, 20.6 ±9.4) for T1, T2 and T3 respectively.

Pre- and post-surgical period
The factorial ANOVA with repeated measures for comparisons between pre- and post-surgical assessments (T1, T2, T3 and T5) indicated a non-significant group x time interaction \( (F_{(3,16)} = 1.7; \ p = 0.2) \) for the OKS questionnaire. This per protocol analysis only included 15 participants (Control n = 6; P–SECIPSI n = 4; and P–SECCONTRA n = 5) as opposed to n = 28 that was used for the pre-surgical analysis above. The decreased sample size was a result of responses lost between follow up assessment sessions when participants were unable to attend or dropped out of the study entirely. An intention to treat (ITT) analysis was also performed across all five assessment sessions. The results of the ITT analysis also reveal a non-significant group x time interaction and further details can be found in Appendix N.

6.3.2 Pain Self-Efficacy Questionnaire (PSEQ)

Pre-surgical period
Similar to the OKS, factorial ANOVA revealed no significant group x time interaction \( (F_{(4,50)} = 0.8; \ p = 0.6) \) for the PSEQ questionnaire indicating that all the scores in each group remained relatively the same across the intervention period (T1 – T3) (refer to Figure 6.2 (a)). Interestingly a non-statistically significant decline (deterioration)
Figure 6.1: Oxford Knee Score (OKS) group means ±SD across: (a) Baseline (T1 – T2) and post-P-SEC intervention (T3 - 1 week before surgery)(b) Baseline (T1 – T3) and post-surgical assessment (T5). Key: P-SEC\textsubscript{CONTRA} (P-SEC delivered to the non-surgical leg); P-SEC\textsubscript{IPSI} (P-SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.
Figure 6.2: Pain Self Efficacy Questionnaire (PSEQ) group means ±SD across: (a) Baseline (T1 – T2) and post P–SEC intervention (T3 - 1 week before surgery)(b) Baseline (T1 – T3) and post–surgical assessment (T5). Key: P–SEC_CONTRA (P–SEC delivered to the non–surgical leg); P–SEC_IPSI (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.

was observed in the mean scores between T2 (Control = 39.4 ±8.3; P–SEC_CONTRA = 36.4 ±13.9) and T3 (Control = 37.9 ±11.3; P–SEC_CONTRA = 33.3 ±12.6) for the Control and the P–SEC_CONTRA groups whilst an increase (improvement) was observed for the P–SEC_IPSI group (T2: P–SEC_IPSI = 34.1 ±8.2; T3: P–SEC_IPSI = 35.2 ±8.0).

Pre- and post-surgical period

A factorial ANOVA revealed no significant group x time interactions (F(4,23)GG = 2.6; p = 0.7) for the PSEQ questionnaire indicating that all scores in each group remained relatively the same across the the pre- and post-surgery period (T1 – T5) (refer to Figure 6.2 (b)). Interestingly, a non-significant trend towards improvement (increase in score) was observed in the control and the non-surgical leg group (P–SEC_CONTRA) when mean scores at T5 (Control = 47.2 ±6.2; P–SEC_CONTRA = 37.2 ±18.4) were compared to T1 (Control = 42.5 ±9.6; P–SEC_CONTRA = 32.2 ±15.1) despite not being statistically significant. A general non-significant decline in scores between T2 (Control = 42.2 ±9.6; P–SEC_IPSI = 36.0 ±9.3; P–SEC_CONTRA = 37.2 ±14.4) and T3 (Control
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41.0 ±11.1; P–SEC_Ipsi = 34.5 ±11.0; P–SEC_Contra = 31.0 ±11.0) can be observed in all three groups as seen in Figure 6.2(b).

6.3.3 The Knee injury and Osteoarthritis Score (KOOS)

Pre-surgical period

Similarly to OKS and PSEQ, factorial ANOVA revealed no significant group x time interaction all subscales of the KOOS (ADLs (F(4,50) = 0.4; p = 0.8); pain (F(3,36)GG = 0.2; p = 0.9); QoL (F(4,50) = 2.0; p = 0.12) and Symptoms (F(4,50) = 0.4; p = 0.81)) indicating that the scores of each subscales across the experimental period remained constant (refer to Figures 6.3(a), 6.4(a), 6.5(a) and 6.6(a)).

Further analysis for interaction of time, revealed a significant effect for time for KOOSQoL subscale indicating an improvement mainly observed in the two intervention groups (P–SEC_Ipsi and P–SEC_Contra). A priori difference contrasts suggest that the overall interaction for time in the KOOSQoL subscale was between baseline (mean of KOOSQoL scores at T1 and T2) and immediately post-P–SEC (T3) (F(2,25) = 3.8; p = 0.03).

Pre- and post-surgical period

A factorial ANOVA revealed no significant group x time interaction for all subscales (ADLs (F(3,19)GG = 0.3; p = 0.8); pain (F(3,20)GG = 0.4; p = 0.7); QoL (F(6,42) = 1.4; p = 0.2) and symptoms (F(4,23)GG = 0.6; p(4,23)GG = 0.7) of the KOOS questionnaire indicating that the scores of each group remained relatively similar across the pre- and post-surgical period (refer to Figures 6.3(b), 6.4(b), 6.5(b) and 6.6(b)). Similarly as the pre-surgery interactions for time, a significant interaction for time was revealed for the KOOSQoL subscale (F(3,42) = 5.5; p < 0.05) indicating that compared to the other subscales, an change in score towards improvement (refer to Figure 6.5(b)) was observed. A priori difference contrasts revealed that for KOOSQoL subscale suggest that the overall interactions for time in the KOOSQoL subscale were between baseline (mean T1 and T2) scores and immediately post-P–SEC (T3) (F(2,14) = 5.6; p < 0.05) as well as between post-P–SEC (T3) (mean of KOOSQoL scores at T1, T2 and T3) and immediately post-surgery (T5) (refer to Figure 6.5(b)).
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Figure 6.3: Knee Injury and Osteoarthritis Score (KOOS) ADLs subscale group means ±SD across: (a) Baseline (T1 – T2) and post P–SEC intervention (T3 – 1 week before surgery)(b) Baseline (T1 – T3) and post-surgical assessment (T5). Key: P–SEC CONTRA (P–SEC delivered to the non-surgical leg); P–SEC IPSI (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.

The responses gathered for the sports and recreation subscale in the KOOS questionnaire were left out by the majority of the participants resulting in very few responses in order to undertake appropriate statistical analysis (< 2/3 overall responses per group) and more often scored a 0². Due to the very poor recoding of this subscale, statistical analysis was not carried out to avoid any increased risk of bias from a poorly reported outcome.

6.3.4 International Physical Activity Questionnaire (IPAQ)

Pre-surgical period

A factorial ANOVA also revealed a non-significant group x time interaction ($F_{(3,41)} = 0.4; p > 0.05$) for the IPAQ questionnaire indicating that the scores of the three groups remained relatively the same across the intervention pre-surgical period (T1

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²Due to the concealment procedure adopted over the data collection and analysis period, the assessor was not aware when participants did not respond appropriately or skipped the respective constructs when filling in the questionnaire. Therefore, any missing data was not noted prior to data extraction.
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Figure 6.4: Knee Injury and Osteoarthritis Score (KOOS) group means ±SD for pain subscale across: Baseline (T1 – T2) and post P–SEC intervention (T3 - 1 week before surgery). Key: P–SEC<sub>CONTRA</sub>(P–SEC delivered to the non-surgical leg); P–SEC<sub>IPSI</sub>(P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.

Figure 6.5: Knee Injury and Osteoarthritis Score (KOOS) group means ±SD for QoL subscale across: Baseline (T1 – T2) and post P–SEC intervention (T3 - 1 week before surgery). Key: P–SEC<sub>CONTRA</sub>(P–SEC delivered to the non-surgical leg); P–SEC<sub>IPSI</sub>(P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.
Figure 6.6: Knee Injury and Osteoarthritis Score (KOOS) group means ±SD for symptoms subscale across: Baseline (T1 – T2) and post P–SEC intervention (T3 - 1 week before surgery). Key: P–SEC_CONTRA (P–SEC delivered to the non-surgical leg); P–SEC_IPSI (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.
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– T3) (refer to Figure 6.7). In line with the most of the previous PROs (except for KOOSQoL subscale), further analysis for the effects of time revealed no significant effects for time ($F_{(2,50)} = 0.4; p > 0.05$) during the pre-surgery phase (T1 – T3).

![Graph](image)

Figure 6.7: International Physical Activity Questionnaire (IPAQ) group means ±SD across baseline (T1 – T2) and post P–SEC intervention (T3 – 1 week before surgery). Key: P–SEC<sub>CONTRA</sub> (P–SEC delivered to the non-surgical leg); P–SEC<sub>IPSI</sub> (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.

Pre- and post-surgical period

A non-parametric approach was used due to the non-normality of the T5 scores. A Kruskal Wallis test was employed to analyse the mean IPAQ scores from the three groups (P–SEC<sub>IPSI</sub>, P–SEC<sub>CONTRA</sub> and Control) were compared at for each time points (T1, T2, T3 and T5) assessment points for comparisons between pre- and post-surgery effects. This revealed a non-significant ($p > 0.05$; $\chi^2$ range = 1.18 (T1) – 0.13 (T5)) effects between groups when baseline measures (T1 – T3) where compared against post-surgery assessment point (T5). The effect of time was then analysed for each group separately using a Wilcoxon signed rank test and revealed no statistically significant effect for time for each group when Bonferroni adjustments were taken into consideration.
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\( (p > 0.02) \).

6.3.5 Performance Profile Questionnaire (PP)

Pre-surgical period

The Kruskal-Wallis test was also selected for analysis in the PP questionnaire because the data of more than one group was overall not normally distributed, therefore the assumptions underpinning the use of ANOVA were not fulfilled. Similar to the majority of the PROs the PP did not reveal a significant effect (T1: \( \chi^2 = 2.23 \) (2df), \( p = 0.34 \); T2: \( \chi^2 = 2.10 \) (2df), \( p = 0.35 \); T3: \( \chi^2 = 2.53 \) (2df), \( p = 0.28 \)) between groups (T1 – T3). This can be observed in Figure 6.8 (a). Furthermore, when the effects of time were analysed for the groups separately, a Wilcoxon signed rank test was undertaken and revealed no statistically significant effect for time for each group when Bonferroni adjustments were taken into consideration (\( p = 0.03 \)).

Pre- and post-surgical period

When pre-and post-surgical effects were analysed for changes between T1, T2, T3 and T5 a statistically significant effect was revealed (\( \chi^2 = 8.94 \) (2 df); \( p = 0.01 \)) with the analysis showing the biggest significance to occur between T3 and T5 (\( \chi^2 = 2.52 \) (2 df), \( p = 0.28 \) vs. \( \chi^2 = 8.94 \) (2df), \( p = 0.01 \) respectively). The results can be observed in Figure 6.8 and the statistical significance observed in all three groups over the T3 and T5 period shows an improvement in the P–SEC\text{CONTRA} group whilst a decline in the scores obtained by the P–SEC\text{IPSI} and Control group.

6.3.6 The 36-Item Short Form Health Survey (SF-36v2\textsuperscript{TM})

Pre-surgical period

The scores obtained from the SF-36v2\textsuperscript{TM} questionnaires were transformed into two main components: the physical (PC) and mental component (MC). Both these scores represent the data obtained from various questions across the whole questionnaire. The methods for calculating these scores is discussed in Chapter 4 Section 4.7.3. A factorial ANOVA revealed no significant group x time interaction for both the PC (F(4,28) = 1.17; \( p > 0.05 \)) nor for the MC (F(3,19)\text{GG} = 1.06; \( p > 0.05 \)) SF-36v2\textsuperscript{TM} scores indicating that
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Figure 6.8: Performance Profile questionnaire (PP) group means ±SD across: (a) Baseline (T1 – T2) and post P–SEC intervention (T3 - 1 week before surgery) and post-surgical assessment (T5). Key: P–SEC<sub>CONTRA</sub> (P–SEC delivered to the non-surgical leg); P–SEC<sub>IPSI</sub> (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery) and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post surgery.

the scores amongst the groups remained relatively similar across the pre-surgery intervention period (T1 – T3) (refer to Figure 6.9). The results of these analyses are based on a smaller number of responses (n = 17) as opposed to n = 28 that were used within the pre-surgical analyses of the other PROs despite utilising similar procedures for data imputation. The reason behind this variation in the number of responses is similarly due to the concealment procedures adopted during data capture as those reported for the KOCOSSports subscale in Section 6.3.3 that did not allow the researcher to identify whether participants where skipping or opting out of answering all the questionnaire’s constructs.

Pre- and post-surgical period

The calculated scores for post surgical analysis for both the PC and MC resulted in a total of five scores for comparisons without any scores related to the control groups at any point in time. As a result, no analysis for post-surgical effects was employed.
Figure 6.9: The 36-Item Short Form Health Survey (SF-36v2™) group means ±SD across: (a) Baseline (T1 – T2) and post P–SEC intervention (T3 - 1 week before surgery) (b) Baseline (T1–T3) and post–surgical assessment (T5). Key: P–SEC CONTRA (P–SEC delivered to the non-surgical leg); P–SEC IPSI (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery).

6.4 Discussion

A. Effects of P–SEC in the pre-surgery phase

The main finding of this study was that the ‘novel’ P–SEC intervention did not elicit statistically significant group by time improvements in patients’ perceived pain, physical function/activity and QoL as measured by the selected PROs (OKS, PSEQ, KOOS, IPAQ, PP and SF-36v2™) during the pre-surgery period, accepting the null hypothesis (Section 2.11 Hypothesis 2). This is in contrast to the objective physical performance outcomes reported in Chapter 5, where a significant effect over time was observed in all outcomes. The results observed in this Chapter essentially show that there was no real transfer of the improvements achieved in objective physical outcome measures to patients’ perception of physical function, pain, QoL and self reported PA. These results are in line with those observed in previous pre-surgery studies where PROs have also been used to measure changes in pain, physical function and QoL following a conditioning programme in patients with end stage OA and waiting for TKA surgery.
Only one study (Calatayud et al. 2017) in patients waiting for TKA found statistically significant improvements in PROs measuring pain and physical function (WOMAC, VAS, SF-36v2TM) that was also observed in the objective functional outcomes after a mixed strength and senorimotor intervention. The differences of our study with this study firstly includes the duration of the pre-surgical programme delivery (eight weeks as opposed to six weeks and one week for the P–SEC programme) that might have affected the outcomes. Similar PROs were used in previous studies (Rooks et al. 2006, Gstoettner et al. 2011, McKay et al. 2012, Huber et al. 2015) which also failed to report a statistically significant effect but whose pre- and post-intervention assessment period was less than the 8-week period reported in Calatayud et al. (2017). Secondly, there was also a substantial difference between the physiological parameters of the intervention delivery in the study by Calatayud et al. (2017) which was much more (24 sessions; an hour of supervised exercise per session; combined motor and sensory training) compared to the intervention delivered in the current (nine sessions, one hour of training across the nine sessions, motor based conditioning) and previous studies (Rooks et al. 2006, Gstoettner et al. 2011, McKay et al. 2012, Huber et al. 2015). Whilst the overall increased exposure to the pre-surgical intervention in the study by Calatayud et al. (2017) might have contributed to the significance observed, the remaining studies including the current one did not reveal any overall statistically significant effects in the selected PROs during the pre-surgical period indicating that the P–SEC intervention was not enough to elicit significant changes in patient perceived outcomes of performance. For the current study since the intervention resulted in statistically significant improvements in the objective measurements, the lack of statistically significant effects in the selected PROs could mean that the constructs (questions) evaluated by the particular PROs were not distinctly related to to performance-based criteria that reflect the patients’ perceptions following the novel P–SEC intervention at that point in time. In fact, as mentioned in the introduction, none bar one (PP) of the PROs’ construct reflects perceived sensorimotor performance which was the main aim for improvement using of the P–SEC conditioning programme.
Finally, the overall sample (n = 28) used within the current study was considerably less than the original sample size required (n = 45 – 60) for appropriate power (0.7 – 0.8) to detect a statistically significant effect in primary outcomes. This might have resulted in the overall lack of statistical significance achieved and possible Type II error. Furthermore, the sample size calculation was based on the physical performance outcomes (EMD, PF, RFD and FE) as opposed to any of the PROs. A sample size calculation based on one or more PRO may have resulted in a higher sample size required for an appropriately powered study.

B. Effects of P–SEC on post-surgery outcomes

The main objective for including a post-surgical (six weeks post-surgery assessment point - T5) was to ascertain that the P–SEC intervention, being a ‘novel’ (never tested before) conditioning programme, had not negatively affected the post-surgery recovery in the intervention groups when compared to controls. The analyses for comparisons between groups over the pre- and post-surgical phase failed to detect statistically significant group by time effect all PROs (OKS, PSEQ, KOOS, IPAQ and SF-36v2TM) except for the KOOSQoL and PP questionnaires, accepting the null hypothesis (Section 2.11 Hypothesis 2). Previous pre-surgical conditioning studies that used PROs to evaluate changes in perceived physical performance over the pre- and six weeks post-surgical period have revealed a significant effect for group over time showing an improvement (Bitterli et al. 2011, McKay et al. 2012, Huber et al. 2015, Calatayud et al. 2017) with only one study reported a lack of significance (Gstoettner et al. 2011). Therefore, the results of the current study do not fall within the exact similar patterns of change in PROs for physical performance outcomes at six weeks after surgery. The only significant results for PP and KOOSQoL were observed possibly because of the type of constructs used within the respective questionnaires and high sensitivities to changes in the post-surgical phase when compared to pre-surgery. The PP is an individually designed PRO specifically aimed at being sensitive to short term changes in the self-perceived patient-constructed physical needs (Weston et al. 2011, 2013). It is possible that the PP is therefore more sensitive to immediate changes in the knee joint structure and resulting in improved functional capability than the other PROs.
For example, it may take longer for a patient to notice improvements in ADL function and general health and increase their habitual PA levels even if there is an immediate improvement in the knee joint post surgery. However, any conclusions regarding the effects of surgery on the PROs in this study should be made with extreme caution because of the very small sample size (n = 15) in the post vs. pre-surgery resulting in a very low power to detect any statistically significant effects, hence a very high risk of Type II error.

### 6.5 Strengths and limitations of the study

The strength of this study lies in the methodological approach adopted namely a randomised controlled trial (RCT). An RCT is considered the “gold standard” of clinical research to have a relatively low risk of bias compared to other designs. Another strength includes the evaluation of self-reported pain, physical function/activity and QoL over repeated assessment points, providing a comprehensive analysis of the effects of the ‘novel’ (P–SEC) intervention during pre-surgical and post-surgical phase of people undergoing TKA surgery. However, several factors must be considered with respect to the conclusions that can be drawn from this study. Firstly, there were a considerable number of ‘lost-to-follow-up’ (n = 18) following randomisation. The ‘lost-to-follow-up’ were due to various factors including primarily a sudden change in surgery date that did not allow for appropriate allocation of follow-up assessments or intervention and secondly commuting and travelling issues experienced by both the participant and the researcher due to the remote research location. These ‘lost-to-follow-up’ resulted in a decreased number of participants which contributed to a lower statistical power output than required to detect statistically significant changes in perceived physical performance outcomes over time and between groups. Further recruitment was not possible due to restricted funding and resource limitations of an educational project. The main funds were allocated to allow for appropriate randomisation and blinding of the selected participants into groups and travel costs for the researcher to obtain the required data over a period of 11 months. Secondly, participants were recruited from a specialist orthopaedic NHS Trust hospital (RJAH) whose care pathways are similar and consistent
for all the participants and may reduce generalisability of the results to non-specialised institutions. Lastly, the IPAQ questionnaire was selected to indicate overall levels of self-reported general PA around the time of surgery. The limitations of using self-reported measures of PA have been well-documented and the use of accelerometry is considered the “gold standard” for the assessment of PA levels. However, as explained above, time and financial resources were primarily allocated towards randomisation, blinding and patient recruitment in order to deliver the best possible clinical trial, leaving little to no funds to contribute towards the necessary equipment for appropriate measures of PA. Furthermore, PA was considered a ‘less important’ aspect of the research in comparison to assessing aspects of neuromuscular and sensorimotor performance capabilities.

6.6 Clinical implications and further research

This is the first study to evaluate the effects of a ‘novel’ pre-surgery exercise-conditioning (P–SEC) programme in patients waiting for a TKA and was essentially a proof of concept study. Due to its novelty in the delivery and type of conditioning for this cohort of patients, direct comparisons with previous research assessing the effects of a similar intervention are difficult.

Patient-reported outcomes provide valuable information to orthopaedic research. The duration of the intervention, mode of delivery and type of conditioning addressed in the P–SEC intervention aimed to increase aspects of joint function and stability by improving muscular performance. The findings in Chapter 5 and Chapter 7 confirmed the effectiveness of the P–SEC intervention in improving physical performance outcomes in both the trained and untrained legs as observed in the objective measurements of muscular performance (EMD, PF, RFD and FE). The results of this chapter show that the majority of the PROs did not show any statistically significant changes (improvement or decline) over time during both the pre- and post-surgical period.
The research design and the aspects employed to ensure appropriate data concealment, randomisation and blinding, contributes to the overall robustness of the study (low risk of bias). However, the study was likely to be ‘under powered’ due to participant ‘loss-to-follow-up’ and missing items in the questionnaires. As a result, caution should be taken when interpreting the overall results observed in this study due to inflated Type II error rates.

6.7 Conclusion

The current study revealed an overall lack of statistical significant time x group interaction in perceived physical performance outcomes (PROs), during the pre- and post-surgical phase. These results are in contrast to the those in Chapter 5 where a statistically significant improvement in objective physical performance outcomes was found in the pre-surgery period. This means that there was no transference of the improvement in the objective physical performance to the individuals’ perceived physical performance. However, further appropriately powered studies are required including objective measures of PA to confirm these results. Lastly, the overall lack of significance observed in the PROs for responses between the pre- and post-surgical period, indicate the absence of any ill-effects or deterioration in physical capabilities occurring following the delivery of the ‘novel’ P–SEC conditioning.
Chapter 7

Results 3 – Cross-education effects associated with pre-surgical exercise conditioning (P–SEC)

7.1 Introduction

Patients undergoing total knee arthroplasty surgery experience a long history of ongoing pain and inflammation due to the underlying osteoarthritis of the knee joints’ surfaces. These symptoms often affect both legs and aspects of physical function negatively (Hurley et al. 1994, Mizner, Petterson, Stevens, Vandenborne & Snyder-Mackler 2005, Mizner, Petterson, Stevens, Axe & Snyder-Mackler 2005, Pietrosimone et al. 2011). The mechanisms by which physical function becomes compromised include those that elicit chronic states of inhibition, such as AMI (Hurley et al. 1994, Palmieri et al. 2004, Rice & McNair 2010, Rice et al. 2014), a phenomenon that alters muscular function through an increased neurally derived inhibitory process (Hurley et al. 1994, Palmieri et al. 2004, Rice & McNair 2010, Rice et al. 2014). The affected neural mechanisms hinder the resultant efferent muscular performance in both limbs, regardless of surgery allocation due to the sharing of spinal circuitry connections bilaterally (Carroll et al.
Cross-education (CE) is a phenomenon that is observed as an alteration in performance characteristics of the untrained limb following a period of conditioning in the contralateral limb (Scripture et al. 1894, Enoka 1988, Munn et al. 2004, 2005, Carroll et al. 2006, Manca et al. 2017, Oliveira et al. 2013, Schlenstedt et al. 2017, Harput et al. 2018). The effects of CE have been previously recorded as improvements in neuromuscular (Zhou et al. 2002, Shima et al. 2002, Jackson & Turner 2003, Munn et al. 2005, Manca et al. 2017, Harput et al. 2018) and sensorimotor performance (Oliveira et al. 2013, El-Gohary et al. 2016, Schlenstedt et al. 2017), with plausible expectations of corresponding benefits for physical function (Mizner, Petterson, Stevens, Vandeborne & Snyder-Mackler 2005, Maffiuletti et al. 2010). Effects of CE in muscular performance have also been recorded in both healthy (Munn et al. 2004, Carroll et al. 2006, Manca et al. 2017) and diseased (Anson et al. 1993, Hortobágyi et al. 1997, Harput et al. 2018) populations. However, methodological heterogeneity amongst the studies resulted in a large variation in the extent of CE-related gains. For example, early studies (Anson et al. 1993, Hortobágyi et al. 1997) reported substantial improvements in strength of the untrained leg (77% – 135%). However, subsequent reviews (Munn et al. 2004, Manca et al. 2017) concluded that more conservative CE-related gains in muscular strength in the untrained limb were possible (8% – 12%). More recently, substantive CE effects (31%) have been reported in patients undergoing anterior cruciate ligament surgery (ACL) (Harput et al. 2018) and within other studies (43%) in which conditioning had focused on gains in sensorimotor performance rather than in strength (Schlenstedt et al. 2017). Furthermore, eccentric (lengthening) based muscle strengthening programmes have been the most common type of strength based conditioning, eliciting the largest (18% – 31% increase) CE-related changes in muscular performance outcomes of the untrained limb compared to concentric (11.3%) and isometric (8.2%) muscular contractions (Anson et al. 1993, Weir et al. 1995, Hortobágyi et al. 1997, Shima et al. 2002, Zhou et al. 2002, Jackson & Turner 2003, Munn et al. 2004, 2005, Ehrensberger et al. 2016, Manca et al. 2016, 2017, Harput et al. 2018). However, the characteristics
of conditioning programmes varied amongst these studies.

There have been few focal sensorimotor conditioning studies reporting CE effects (20% – 42%) (Oliveira et al. 2013, El-Gohary et al. 2016, Schlenstedt et al. 2017) compared to those involving strength-focused conditioning (8% – 12%) (Manca et al. 2017, Harput et al. 2018), with no studies having addressed CE responses within patients awaiting TKA. In this context, exercises involving sequenced eccentric and concentric muscular actions (such as those observed during dynamic joint movements e.g. plyometric, proprioceptive training), have been considered as sensorimotor stimuli (Suchomel et al. 2018). Current research investigating the effects of sensorimotor conditioning lacks the evidence regarding optimal conditioning parameters and stimuli (Risso et al. 2018 in press; Refer to Chapter 3), which might suggest that although large performance gains for ipsilaterally-trained and CE legs may have been reported, these findings may not be maximal. This might be especially so for the study’s primary outcome for the ipsilaterally-conditioned leg (partnering study in Chapter 5 EMD (37%), FE (24%), RFD (14%) and PF (12%)), which although substantive, were associated with a focal but not yet optimised P–SEC programme. For example, the P–SEC comprised a modest and brief (9 sessions (1-week); high-intensity (60% to 100% of daily 1RM); AMI-related nociceptor averse (exercises lasting < 1.5s)) dosage of conditioning. Using approximately 50% of the dosage of conditioning sessions and even less time for exposure to conditioning stimuli (≈ 17%), the P–SEC protocol contrasted starkly with the characteristics of contemporary conditioning interventions. While the novel P–SEC protocol had adhered robustly to training principles of physiology (including specificity (neuromuscular focus), varied micro-cycles of stimulus intensity and inter-exercise energetic recovery), even greater concomitant improvements in neuromuscular and sensorimotor performance might be possible in the future, with further research-driven titration and individualised manipulations of stimuli and physiological stress.

Patients electing and awaiting TKA surgery to combat end-stage OA, present with a complex set of challenges for successful conditioning. The knee joint that has been listed for surgery should be presenting with the most severe symptomatology, with
chronic degeneration of the knee joint structure and cyclical acute flare ups of inflammation and pain, that invoke AMI and require periods of rest and decreased mobility. Nevertheless, both the leg undergoing surgery and its contralateral counterpart will inevitably be subjected to acute episodes of pain and physiological inhibitory mechanisms. As such, when trained using P–SEC, both ipsilateral and contralateral legs may offer valuable and novel evidence for the effects of CE in this clinical population.

Given potentially more pervasive effects of AMI within the leg scheduled to undergo surgery and thus, training-related headroom, it is plausible that with P–SEC training of its counterpart limb, the CE responses of the leg scheduled for surgery will be most prominent. Previously, CE effects through exercise-conditioning has aided patients in attenuating loss of function and muscle atrophy, and in restoring bilateral symmetry following a stroke (Ehrensberger et al. 2016), and in the management of severely weakened limbs due to multiple sclerosis (Manca et al. 2016, 2017). Utilising CE effects as an adjunct therapy amongst the pre-habilitative conditioning of patients awaiting TKA may offer similar novel advantages.

Therefore, the primary objective of this chapter was to investigate the effects of P–SEC on the neuromuscular and sensorimotor performance of the untrained leg in patients awaiting TKA surgery. The focus of P–SEC intervention aimed primarily at improving neuromuscular performance in patients electing TKA surgery, with plausible expectation that any gains would transfer to concomitant enhanced sensorimotor performance (the reader is referred to Chapter 2 for additional details underpinning the study’s rationale and to Chapter 5 for further details of the study’s partnering P–SEC-related findings associated with the ipsilaterally-trained leg). Indices of PF, EMD, RFD and FE are estimates of neuromuscular and sensorimotor performance, respectively, that are influenced by alterations in the peripheral spinal neural activities, including AMI (Enoka 1988, Cavanagh & Komi 1979, Minshull et al. 2007). It was hypothesised that both the untrained limb scheduled to undergo surgery and its untrained counterpart would show CE effects, but that the CE effects would be more pronounced within the performance of the leg undergoing surgery. Immediate (1-week post-cessation of P-SEC (T4)) retention of any CE effects was also scrutinised to identify the direct
influence of P–SEC on neuromuscular and sensorimotor CE-related performance, together with the complex interactive effects on any residual CE of major surgery and immediate post-TKA care-pathway including bilateral limb rehabilitative conditioning.

7.2 Methods

A. Methodological procedures, and P–SEC conditioning

Due to the nature of the study investigated in this doctoral research project (RCT), the methodological approach and procedures for the results discussed in this chapter (CE-related effects), are the same as those described in Chapters 4 and 5. The reader is referred to Sections 4.4, 4.6 and 5.2 for further information about study design, ethical approval and assessment procedures. For detailed information regarding participants’ characteristics, the reader is referred to Table 5.1. The P–SEC intervention referred to in this Chapter is described in detail in Chapter 4 Section 4.6.

The information gathered during the assessment procedures quantified and described objective measures of neuromuscular and sensorimotor performance prior to and around the time of surgery. Information gathered around the delivery of the intervention (T2 – T4) quantified the changes in neuromuscular and sensorimotor performance resulting from the P–SEC intervention. Information gathered from the post-surgery assessment point (T5) was envisaged as an end-point comparison for identifying any possible gains (although these were not anticipated due to the brevity of P–SEC and complexity of post-surgery care) or hindrance to the post-surgery recovery of patients in the intervention groups as a result of the P–SEC conditioning. Learning effect analysis reported in the partnering Chapter 5, reported no significant effect ($p > 0.05$) associated with the mean scores between baseline (T1) and pre-P–SEC intervention (T2) assessment point, indicating that there was no learning effects attributed to participant exposure to experimental assessment procedures for any of the neuromuscular or sensorimotor indices. Therefore, the measurement of CE for each outcome was calculated as the percentage change (%) and the effect size (ES) associated with group mean scores.
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at ‘baseline’ pre-P–SEC intervention (T2) and post-P–SEC intervention measures (T3) and similarly for any retention of effects 1-week after cessation of P–SEC intervention (T4) and 6-weeks post-TKA (T5).

B. Statistical analyses

Results were presented as mean ±SD, unless otherwise specified. The Shapiro-Wilk test was used to assess normality of data. If normality of the data was not confirmed, appropriate transformations (Log\({}_{10}\)) were adopted. The effects of the P–SEC programme was analysed separately for each outcome measure (neuromuscular: EMD\(_{RF}\), EMD\(_{VL}\), RFD, PF and sensorimotor: FE) using factorial (3-way) ANOVA (group [P–SEC\(_{IPSI}\); P–SEC\(_{CONTRA}\); Control] x leg [Surgical; Non-surgical] x time [T1 – T5]), with repeated measures on the latter two factors. Assumptions underpinning the use of ANOVA for repeated measures were checked. Greenhouse-Geisser (GG) was used to counter any violations. \textit{A priori} Reverse Helmert orthogonal difference testing was used in conjunction with ANOVA. The statistical alpha level was set at \(p < 0.05\). Missing or ‘outlier’ data were taken into account on a ‘case-by-case’ basis separately for each outcome measure, and the reasons for absence or abnormality of a datum point were recorded. Missing data were imputed using a multiple imputations approach (Bennett 2001) and a \textit{per protocol} analyses was performed on the resultant data set for all outcome measures, unless otherwise stated.

The results for CE are presented as percentage change scores between pre- and post-P–SEC intervention (T2 – T3) for all neuromuscular and sensorimotor data of both limbs. Furthermore, calculated effect sizes for comparisons between ‘baseline’ pre- (T2) and post-P–SEC intervention (T3) were also evaluated using \textit{Cohen’s d} for parametric tests (Cohen 1988)\(^1\) (Equation 5.1, Chapter 5). The calculated effect sizes were classified as small (≤ 0.2), medium (≤ 0.5) or large (≤ 0.8) (Cohen 1988).

For clarity and consistency, the nomenclature referred to as P–SEC\(_{IPSI}\) will be used

\(^1\)Analysis of percentage change and effect sizes for changes between pre-P–SEC intervention ‘baseline’ (T2) and retention of effects pre-surgery (T4) and between ‘baseline’ (T2) and post-surgical assessment (T5) can be found in Appendix 5.4
to describe the leg undergoing surgery (i.e. Surgical leg) and P–SEC$_{CONTRA}$ will be used to describe the non-surgical leg. Therefore, the CE observed in the respective legs will be referred to as: P–SEC$_{IPSI-CE}$ (for CE effects observed in the untrained Surgical leg) and P–SEC$_{CONTRA-CE}$ (for CE effects observed in the untrained Non-Surgical leg). The results included in this chapter are based on those obtained from a 3-way factorial ANOVAs (group x time x leg) with repeated measures for time for all five outcomes (neuromuscular: EMD$_{RF}$, EMD$_{VL}$, RFD, PF and sensorimotor: FE) reported in Chapter 5 Section 5.3.

7.3 Results

Per protocol analysis was reported for each outcome measure unless otherwise stated. Accounting for loss-to-follow-up and appropriate imputation of missing data, complete data sets from a total number of 29 participants were available for analysis (Control n = 12; P–SEC$_{IPSI}$ n = 9; and P–SEC$_{CONTRA}$ n = 8). Shapiro-Wilk test for normality indicated an overall non-significant result ($p > 0.05$) for all neuromuscular (EMD, RFD, PF) and sensorimotor performance outcomes for each assessment point, for the data in the allocated groups and overall, therefore confirming that the data was normally distributed (Refer to Table Q.1 in Appendix Q).

7.3.1 CE effects on neuromuscular outcomes for EMD, RFD and PF

Electromechanical delay (EMD)

Factorial ANOVA showed a significant group x time x leg interaction for the study’s primary outcome (EMD) of the knee extensor muscles (EMD$_{RF}$: $F_{(6,79)} = 9.6; p < 0.005$; EMD$_{VL}$: $F_{(6,77)} = 10.3; p < 0.001$) indicating that for both muscles, while performance in the legs of the control group remained relatively constant during the experimental period (T1 – T4), the CE-related performance of the untrained leg of patients undergoing surgery on the same leg (group: P–SEC$_{IPSI-CE}$) or on the contralateral leg (group: P–SEC$_{CONTRA-CE}$) improved (shorter EMD$_{RF}$ and EMD$_{VL}$ scores), but to a lesser extent (peak ES = 0.4 and 0.4 respectively; Table 7.1) than the corresponding performance of the leg that had received the P–SEC directly (peak ES = 1.8 and 1.7).
respectively; Table 5.5 and Figure 5.2) rejecting the null hypothesis (Section 2.11 Hypothesis 3). *A priori* difference contrasts suggest that there was a similar pattern of change in performance over time for both muscles, with the extent of interaction between baseline (group mean scores for EMD_{RF} and EMD_{VL} performance, respectively at T1 and T2) and immediately post-P–SEC intervention (T3) (F\((1,26) = 26.0; p < 0.01\), and F\((1,26) = 29.6; p < 0.01\), respectively), between T3 (mean of EMD_{RF} only, at T1 – T3) and 1 week post-P–SEC (T4) (F\((1,26) = 3.6; p < 0.04\) and between pre-surgery (mean T1 – T4) and 6-weeks post-surgery (T5) (F\((1,26) = 6.1; p < 0.01\), and F\((1,26) = 6.6; p < 0.01\), respectively) contributed most to the overall significant 3-factor ANOVA interaction and the patterns of relative differences over time associated with the effects of direct P–SEC training or CE. There had been no clear difference in the pattern of CE gains over time between the untrained leg undergoing surgery (P–SEC\_IPSI-CE) and the leg that hadn’t been scheduled for surgery (P–SEC\_CONTRA-CE).

Prior to surgery, P–SEC elicits substantive CE-related improvements in EMD_{RF} (peak 10.8% compared to baseline (T2)) and EMD_{VL} (peak 10.6%) performance characteristics that were sustained for EMD_{RF} in particular, until at least one week after the cessation of the conditioning within the leg undergoing direct P–SEC conditioning. It had been anticipated that there would have been similar patterns of responses to conditioning for functionally synergistic muscles such as m. rectus femoris and m. vastus lateralis. The similarly substantive CE-related gains in performance prior to surgery for EMD_{RF} and EMD_{VL} were congruent with that expectation. At six weeks after TKA surgery, CE-related effects on EMD_{RF} and EMD_{VL} performance had been dissipated amongst the complex competing interactive influences of major surgery, the immediate post-TKA care-pathway and bilateral rehabilitative conditioning, to a level that ultimately had matched the level of performance within the Control group (Figure 5.2).

**Rate of force development (RFD)**

Factorial ANOVA showed a significant group x time x leg interaction for RFD (F\((6,75)GG = 2.2; p < 0.04\) indicating that while the performance in the legs of the Control group
remained relatively constant during the experimental period, the CE-related perfor-
mance of the untrained leg of patients undergoing surgery on the same leg (group:
P–SEC\textsubscript{IPSI-CE}) or on the contralateral leg (group: P–SEC\textsubscript{CONTRA-CE}) improved (larger RFD scores), but to a lesser extent (peak ES = 0.3; Table 7.1) than the corresponding performance of the leg that had received the P–SEC directly (peak ES = 0.6) (please refer to Table 5.5 and Figure 5.3 a and b) rejecting the null hypothesis (Section 2.11 Hyper-
thesis 3). A priori difference contrasts suggest that the extent of interaction between baseline (mean RFD performance at T1 and T2) and immediately post-P–SEC (T3) \((F(1,26) = 5.5; p < 0.05)\) contributed most to the overall significant 3-factor ANOVA in-
teraction. As had been noted for EMD, there had been no clear difference in the pattern of CE gains over time between the untrained leg undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and the leg that hadn’t been scheduled for surgery (P–SEC\textsubscript{CONTRA-CE}).

Prior to surgery, P–SEC elicits substantive CE-related improvements in RFD per-
formance characteristics (peak 7% compared to baseline (T2)) that were mostly evident immediately after the cessation of the conditioning of the leg undergoing direct P–SEC conditioning. At six weeks after TKA surgery, CE-related effects on RFD performance had dissipated amongst the complex and competing interactive influences associated with \textit{inter alia}, surgery and bilateral rehabilitative conditioning, to a level that once again, had matched the level of performance within the Control group (Figure 5.3 a and b).

\textbf{Peak Force (PF)}

Similarly, P–SEC had elicited substantive CE-related improvements in PF performance characteristics \((F(5,66) = 3.6; p < 0.005)\); peak ES = 0.2; 8.7% compared to baseline (T2); group: P–SEC\textsubscript{IPSI-CE} and group: P–SEC\textsubscript{CONTRA-CE}; Figure 5.3 c and d) rejecting the null hypothesis (Section 2.11 Hypothesis 3) but that were less prominent over time compared to the leg undergoing direct P–SEC training (peak ES = 0.5), and whose effects were most evident immediately after P–SEC training (T3) \((F(1,26) = 5.9; p <
0.01)\) and subsequently partially preserved until at least one week after cessation of P–SEC \((F(1,26) = 3.4; p < 0.05; T4)\). There had been no clear difference in the pattern
of CE gains over time between the untrained leg undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and the leg that hadn’t been scheduled for surgery (P–SEC\textsubscript{CONTRA-CE}). At six weeks after TKA surgery, CE-related effects on PF performance had dissipated amongst the complex and competing interactive influences associated with \textit{inter alia}, surgery and bilateral rehabilitative conditioning, to a level that had matched that of the Control group (Figure 5.3 c and d).

### 7.3.2 CE effects on sensorimotor outcome: Force Error (FE)

Sensorimotor performance associated with the knee extensor muscles as measured by FE, showed a significant group x time x leg interaction ($F_{(8,104)} = 2.1; p < 0.05$) indicating that while performance in the legs of the Control group remained relatively constant during the experimental period (T1 – T4), the CE-related performance of the untrained leg of patients undergoing surgery on the same leg (group: P–SEC\textsubscript{IPSI-CE}) or on the contralateral leg (P–SEC\textsubscript{CONTRA-CE}) had improved, but to a lesser extent (peak ES = 0.1; Table 7.1) than the corresponding performance of the leg that had received the P–SEC conditioning directly (peak ES = 0.9; Table 5.5; Figure 5.4) rejecting the null hypothesis (Section 2.11 Hypothesis 3).

\textit{A Priori} difference contrasts suggest that the extent of interaction between baseline (mean of FE performance at T1 and T2) and immediately post-P–SEC (T3) ($F_{(1,26)} = 6.4; p < 0.01$) contributed most to the overall significant 3-factor ANOVA interaction. As had been noted for indices of neuromuscular performance, there had been no clear difference in the pattern of CE gains over time between the untrained leg undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and the leg that hadn’t been scheduled for surgery (P–SEC\textsubscript{CONTRA-CE}).

As had been noted amongst indices of neuromuscular performance, prior to surgery, P–SEC elicits substantive CE-related improvements in FE performance characteristics (less error) (peak 4.7% compared to baseline (T2)) that was prominent immediately after the cessation of the conditioning within the leg undergoing direct P–SEC, but not necessarily sustained thereafter. At six weeks after TKA surgery, CE-related effects on FE performance had dissipated amongst the complex and competing interactive influences including surgery and bilateral rehabilitative conditioning, to a level that
had matched that of the Control group (Figure 5.4).

Table 7.1: The following table reports the calculated effect sizes (ES) and respective percentage (%) change for the untrained leg calculated from means and standard deviations (SD) obtained from the 3-way ANOVA interaction in Chapter 5. The ESs and percentage changes presented below have been derived from pre- and post-intervention measures obtained between T2 and T3 for the respective groups on all five outcome measures. The negative symbol shown next to the EMD and FE values indicates improvement for that outcome. Key: EMD - electromechanical delay; RF - rectus femoris muscle; VL - vastus lateralis muscle; P–SECIPSI-CE - CE effects observed in the surgical leg; P–SECCONTRA-CE - CE effects observed in the non-surgical leg; RFD - rate of force development; PF - peak force; FE - force error.

<table>
<thead>
<tr>
<th>Outcome variable (Unit)</th>
<th>T2 Mean ±SD</th>
<th>T3 Mean ±SD</th>
<th>ES (d)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMDRT (ms) P–SECIPSI-CE</td>
<td>44.3 ±11.2</td>
<td>40.0 ±10.7</td>
<td>0.4</td>
<td>10.8</td>
</tr>
<tr>
<td>EMDRT (ms) P–SECCONTRA-CE</td>
<td>45.9 ±15.2</td>
<td>42.4 ±13.2</td>
<td>0.3</td>
<td>8.3</td>
</tr>
<tr>
<td>EMDVL (ms) P–SECIPSI-CE</td>
<td>44.0 ±11.2</td>
<td>39.8 ±10.7</td>
<td>0.4</td>
<td>10.6</td>
</tr>
<tr>
<td>EMDVL (ms) P–SECCONTRA-CE</td>
<td>47.5 ±15.6</td>
<td>43.4 ±13.9</td>
<td>0.3</td>
<td>9.5</td>
</tr>
<tr>
<td>RFD (N/s) P–SECIPSI-CE</td>
<td>876.7 ±200.8</td>
<td>908.8 ±207.8</td>
<td>0.2</td>
<td>3.5</td>
</tr>
<tr>
<td>RFD (N/s) P–SECCONTRA-CE</td>
<td>586.9 ±124.0</td>
<td>631.3 ±152.6</td>
<td>0.3</td>
<td>7.0</td>
</tr>
<tr>
<td>PF (N) P–SECIPSI-CE</td>
<td>227.6 ±92.1</td>
<td>239.2 ±95.3</td>
<td>0.1</td>
<td>4.9</td>
</tr>
<tr>
<td>PF (N) P–SECCONTRA-CE</td>
<td>167.3 ±62.7</td>
<td>183.1 ±68.2</td>
<td>0.2</td>
<td>8.7</td>
</tr>
<tr>
<td>FE (%) P–SECIPSI-CE</td>
<td>13.6 ±5.0</td>
<td>13.0 ±4.7</td>
<td>0.1</td>
<td>4.2</td>
</tr>
<tr>
<td>FE (%) P–SECCONTRA-CE</td>
<td>19.8 ±7.2</td>
<td>18.9 ±5.7</td>
<td>0.1</td>
<td>4.7</td>
</tr>
</tbody>
</table>

7.3.3 Retention of CE effects (T4) and post-surgical observations (T5)

In summary, some (EMDRT, PF) but not all (EMDVL, RFD) outcome measures of neuromuscular performance showed partial retention of CE-related performance in the untrained leg of patients undergoing surgery on the same leg (group: P–SECIPSI-CE) or on the contralateral leg (group: P–SECCONTRA-CE) until at least one week after cessation of the P–SEC intervention (T4) ($F_{(1,26)} > 3.6; p < 0.04$). There had been
no clear difference in the pattern of CE gains over time between the untrained leg undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and the leg that hadn’t been scheduled for surgery (P–SEC\textsubscript{CONTRA-CE}). For EMD\textsubscript{RF} and PF, the preservation of neuromuscular performance at T4 constituted effect sizes of 0.1 and 0.1 – 0.2, respectively (pooled effect sizes relative to pre-P–SEC intervention baseline (T2) for the untrained leg undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and contralateral leg (P–SEC\textsubscript{CONTRA-CE}); Table 5.4 Appendix ??). In general, at one week after the cessation of the P–SEC intervention, the retention of the CE-related performance in the untrained leg of TKA patients comprised of 3\% and 4 – 5\% of the gains in neuromuscular performance achieved immediately after the P–SEC (pooled percentage scores relative to T3 for the untrained leg undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and contralateral leg (P–SEC\textsubscript{CONTRA-CE}); Table 5.4 Appendix ??). Although P–SEC had elicited substantive CE-related improvements in sensorimotor performance that was prominent immediately after the cessation of the conditioning, the immediate CE-related gains in FE were not sustained thereafter.

At six weeks after TKA surgery (T5), the pattern of CE gains over time for all outcome measures of neuromuscular and sensorimotor performance for both the untrained leg undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and contralateral leg (P–SEC\textsubscript{CONTRA-CE}) had been dissipated amongst the complex and competing interactive influences of major surgery, the immediate post-TKA care-pathway and bilateral rehabilitative conditioning, to a level that ultimately had matched the level of performance within the Control group (Figures 5.2, 5.3 and 5.4; Table 5.4 Appendix ??). At T5 some (EMD\textsubscript{RF} \& VL and PF) but not all (RFD and FE) indices of neuromuscular and sensorimotor performance showed levels of performance in the untrained leg of patients undergoing surgery (P–SEC\textsubscript{IPSI-CE}) and contralateral leg (P–SEC\textsubscript{CONTRA-CE}), which were below those recorded at baseline (pooled scores, T1 and T2; Figures 5.2, 5.3 and 5.4).
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Figure 7.1: The table above represents the same figure as Figure 5.3 with group means and ±SD from the 3-way ANOVA interaction for rate of force development (RFD; N/s) and peak force (PF; N). Reference is made to the results observed graphs (c) and (d) for PF. When analysing effects of CE, the reader is referred to the blue open square graph symbol for CE effects observed in P–SEC\textsubscript{CONTRA} on the left hand side (Surgical leg). For CE effects observed in P–SEC\textsubscript{IPSI} the reader is referred to the green solid diamond shape graph on the right hand side (Non-surgical leg). Key: P–SEC\textsubscript{CONTRA} (P–SEC delivered to the non-surgical leg); P–SEC\textsubscript{IPSI} (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (≈ 11 – 12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery), T4 as time 12 weeks (week of surgery) and T5 as time 18 weeks (6 weeks post-surgery).
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Figure 7.2: Percentage of cross-education (CE) measured as percentage change pre- and post-intervention (P–SEC) (T2 – T3) for both untrained legs. The two bars represent the two untrained legs from the respective groups. Key: P–SECIPSI-CE is the CE measured in the untrained surgical leg; P–SECCONTRA-CE is the CE measured in the untrained non-surgical leg. EMD - electromechanical delay; RF - rectus femoris muscle; VL - vastus lateralis muscle; RFD - rate of force development; PF - peak force; FE - force error.

7.4 Discussion

The main finding of this study was that the ‘novel’ P–SEC intervention elicited small to moderate (4% – 11%; $d = 0.1 – 0.4$) CE-related improvements in muscular performance in the untrained limb, as measured by outcome measures of neuromuscular and sensorimotor performance (EMD, RFD, PF and FE). These novel findings indicated that the P–SEC conditioning programme used in this study was effective in eliciting CE effects in patients undergoing TKA surgery, and is the first study presenting evidence for CE in this cohort of patients. All indices of neuromuscular and sensorimotor performance showed similar patterns of CE-related gains over time for both the untrained leg undergoing surgery (P–SECIPSI-CE) and the leg that hadn’t been scheduled for surgery (P–SECCONTRA-CE). This finding suggested that a prior expectation for the study favouring greater CE-related responses being observed for the leg undergoing surgery because of a likely diminished conditioning status and a commensurately increased ‘headroom’ for responses to physiological conditioning, had been unfounded.
While inflated type-II error rates might have prevented the discrimination of subtle inter-limb differences in performance capability, this study’s findings suggested that similar CE ipsi- and contra-lateral limb dose-responses to P–SEC should be expected. Furthermore, the extent of percentage improvements associated with CE match those reported by earlier studies in healthy populations (Munn et al. 2004, Carroll et al. 2006, Manca et al. 2017), which had required much more intensive and extensive periods of conditioning to elicit those CE-related effects. For example, studies utilising progressive load intensities of $\geq 50\%$ of MVC or 1RM, similar to the current P–SEC protocol (60% – 100% of daily 1RM), have found similar ($\approx 7.8\%$; (Munn et al. 2004, Carroll et al. 2006, Manca et al. 2017)) or moderately larger percentage improvements ($> 11\%$; (Latella et al. 2012, Kidgell et al. 2015, Beyer et al. 2016, Cirer-Sastre et al. 2017)) in CE-related gains in healthy individuals but have required a much longer period (3 – 8 weeks) than the 1-week period of the P–SEC protocol delivered in this study. Therefore, this indirect comparison suggests that the P–SEC programme comprising of a modest and brief (9 sessions (1 week); high intensity (60% to 100% of daily 1RM); AMI-related nociceptor-averse (exercise lasting $< 1.5s$)) dosage of conditioning, was capable of delivering similar CE-related gains in neuromuscular (EMD, RFD, PF) and sensorimotor (FE) performance, using only $\approx 50\%$ of the dosage of contemporary conditioning sessions and even less time for direct exposure to conditioning stimuli ($\approx 17\%$). The nociceptive-averse (muscular loading lasting $< 1.5s$) approach used in the current study might have contributed to a successful re-scaling of the dose-response patterning for CE-related gains by achieving substantive extra gains over a condensed period of conditioning. In contrast to conventional progressive conditioning practices that focuses on greater numbers of sustained repetitions (Moritani et al. 1979, Suchomel et al. 2018), P–SEC was designed to minimise afferent nociceptive inhibitory signalling by avoiding in a timely manner, the peak pain-related physiological responses during mechanical loading of the joint system (Fein 2012). This interpretation of the study’s findings that brevity and intensity within muscular loading appears to be an important factor for re-scaling the dose-response relationship of CE, has been endorsed indirectly by recent evidence in the literature. A recent systematic review in healthy subjects investigating dose-response relationships for eccentric muscular training and
CE-related gains, interestingly identified that studies following exercise programmes with long-duration muscular contractions maintained to fatigue resulted in a decreased CE-related gains compared to short, discrete contractions within a set of (8 – 10) of repetitions (Cirer-Sastre et al. 2017). Increased nociceptive input that would be expected in this study’s TKA population if it had been subjected to sustained muscular contractions, has been linked to an increase in the peripheral inhibitory neuromuscular afferent input resulting in a decrease in magnitude of CE-related effects observed in the untrained limb (Lee & Carroll 2007, Hortobágyi et al. 2011, Lepley & Palmieri-Smith 2014, Kidgell et al. 2015). Confirmation of CE-related improvements in neuromuscular and sensorimotor outcomes in both limbs of this cohort of patients provides a rehabilitative tool for optimising quadriceps strength and neuromuscular capabilities towards enhanced recovery (Munn et al. 2005, Farthing et al. 2009, Manca et al. 2017), especially in the presence of pain during the acute phases of surgery.

Alongside with optimising training-load parameters, mode of training has been identified as an important factor in CE-related training adaptations (Carroll et al. 2006, Lee & Carroll 2007). For example, greater (17% – 77%) CE-related gains in muscular performance outcomes have been reported following an eccentric-type muscular strengthening programme as opposed to those programmes involving concentric muscle actions (11% – 32%) or isometric muscle actions (8.2%) (Anson et al. 1993, Weir et al. 1995, Hortobágyi et al. 1997, Shima et al. 2002, Zhou et al. 2002, Jackson & Turner 2003, Munn et al. 2004, 2005, Lepley & Palmieri-Smith 2014, Kidgell et al. 2015, Ehrensberger et al. 2016, Manca et al. 2017, Harput et al. 2018). The P–SEC programme utilised dynamic eccentric-concentric muscular contractions, similar to those experienced during ballistic and plyometric movements of activities of daily living (Suchomel et al. 2018). The predominant eccentric contraction phase within the P–SEC had been progressively delivered over a very brief (< 1.5s) period, in order to attenuate any peripherally-derived nociceptive (pain) signalling (Hurley et al. 1994, Rice & McNair 2010, Rice et al. 2014).

The magnitude of CE-related improvements associated with P–SEC for both neuromuscular (EMD, RFD, PF) and sensorimotor (FE) performance, were much less (4%
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than those achieved in the previously eccentrically-dominated strengthening programmes (17% – 77%) (Hortobágyi et al. 1997, Munn et al. 2004, 2005, Lepley & Palmieri-Smith 2014, Kidgell et al. 2015, Manca et al. 2017, Harput et al. 2018). However, the methodological approaches (non-randomised controlled studies), training-load parameters (frequency, intensity and duration), population (healthy vs. injured) and computational methods for percentage measurement of CE-related were idiosyncratic and varied both amongst the latter studies and with the methods adopted within the current study, therefore making direct comparisons amongst the studies’ outcomes difficult. Recent studies that have investigated dose-response relationships for CE-related improvements in healthy subjects (Lepley & Palmieri-Smith 2014, Cirer-Sastre et al. 2017) have revealed that lengthier (3 – 8 weeks; 3 sessions·week$^{-1}$) eccentric-based training protocols were mostly ideal to achieve CE-related improvements in muscular performance outcomes, reaching gains of $\approx 39\%$ (ES = 0.6). Nevertheless, the magnitude of CE-related improvements in the current study’s predominant primary and secondary neuromuscular outcomes ($\text{EMD}_{\text{RF&VL}}$ and RFD) compared favourably (ESs $\approx 0.4; \leq 11\%$) to previous studies (Munn et al. 2004, Carroll et al. 2006, Manca et al. 2017). This is especially so given the much smaller dosage of conditioning sessions ($\approx 50\%$) and time allotted for exposure to conditioning stimuli ($\approx 17\%$) compared to contemporary practice.

The primary mechanisms by which CE-related effects occur have been attributed to alteration in neural activities (Hortobágyi et al. 1997, Zhou 2000, Lee & Carroll 2007), that increases neuromuscular adaptations and alters muscular performance outcomes such as the muscle activation and the speed at which peak muscle strength is achieved (Lee & Carroll 2007, Frazer et al. 2018). In fact, the largest CE-related improvements ($\leq 11\%$) in the current study have been observed in the primary ($\text{EMD}_{\text{RF&VL}}$) neuromuscular performance outcomes. Along with RFD and PF, these indices of neuromuscular performance are modulated through motor-unit (MU) activity (Minshull et al. 2009, Smith et al. 2016) governed by both peripheral and central mechanisms (Cavanagh & Komi 1979, Enoka 1988, Costa et al. 2013). Recent studies have shown that neuromuscular function in the untrained limb, is modulated through training adap-
tations occurring in the trained limb at both spinal and cortical level (Hortobágyi et al. 2011, Lepley & Palmieri-Smith 2014, Kidgell et al. 2015). These adaptations cause a reduction of the inhibitory mechanism of the motor-neuron (MN) pool and the overall net excitability resulting in improved muscular performance outcomes (Kidgell et al. 2015) such as those observed in this study. Gains in strength despite a robust expectation for no measurable increases in muscle morphology because of the relatively short exposure to P–SEC, suggest a mechanism for change that would be predominantly due to neural adaptations (Hortobágyi et al. 1997, Zhou 2000, Lee & Carroll 2007). Furthermore, the neural-based mechanism of improvement for CE is further confirmed by the significant increase in PF (strength) that was observed in the untrained limb (P–SEC_{IPSI-CE} and P–SEC_{CONTRA-CE}). Muscle morphology (cross-sectional area (CSA)) was not assessed in this study because it was hypothesised that measurable improvements in muscular strength (PF) would result as a bi-product of the P–SEC’s 1-week intervention. A minimal duration of ≥ 3 weeks for detecting muscle hypertrophy has been reported previously (Moritani et al. 1979, Garber et al. 2011). Along with previous studies (Farthing et al. 2007, Latella et al. 2012, Beyer et al. 2016) that have found no change in muscle CSA of the untrained limb but a significant increase in strength and muscle activation’ characteristics, the CE-related improvements of PF observed in the current study can be attributed predominantly to the increased neural activation.

Orthopaedic related studies where CE was investigated in patients undergoing knee surgery are elusive, with only two studies being published to the author’s knowledge at the time of writing (Papandreou et al. 2013, Harput et al. 2018). Both these studies have investigated CE-related effects in patients undergoing ACL reconstruction during the post-surgery period (as opposed to pre-surgery like the present P–SEC study), where bilateral contemporary rehabilitation was routinely undertaken as part of the rehabilitative care-pathway in addition to the experimental CE-related training protocol. Larger post-surgery CE-related gains (20% – 31% respectively) (Papandreou et al. 2013, Harput et al. 2018) in muscular performance are more than twice the extent of CE-related improvements observed in the neuromuscular and sensorimotor outcomes for the current P–SEC study (4% – 11%). Contemporary rehabilitation that included
bilateral limb conditioning, might have contributed to the CE-related improvements in the untrained limb because of the the shared neural-related pathways (Lee & Carroll 2007), despite both studies included control group (no CE-related intervention) comparisons. In rehabilitation practices, bilateral limb conditioning is preferred over unilateral training (McCurdy et al. 2005, Summers et al. 2007) but CE-related effects alongside or following bilateral limb conditioning, mimicking the conditions of real-world rehabilitative care, has not been investigated to date. The magnitude of CE-related improvements in neuromuscular and sensorimotor performance achieved for the trained limbs (P–SECIPSI and P–SECCONTRA) of the current P–SEC study, were larger (≤ 37%) compared to the corresponding CE gains. Similarly, this has been the case in previous studies where CE-related improvements were compared to those on the trained leg (Munn et al. 2004, Manca et al. 2017). Therefore, the improvements in muscular performance achieved by training directly the desired limb is preferred over the CE-related improvements achieved from training the contralateral leg. However, in the presence of acute injuries (e.g. a fall, strain), immobilisation (e.g. following a fracture) and immediately post-surgery (e.g. post-ACL reconstruction or TKA) where pain is a predominant feature, immediate training on the desired limb may not be possible or indeed, it may be detrimental to patients’ physical recovery (Munn et al. 2005, Farthing et al. 2009, Manca et al. 2017). Therefore, unilateral limb conditioning, where training is applied to the contralateral limb, results in CE-related gains, which although considerably smaller in comparison to direct training, would be preferred to a scenario involving ‘no training’ at all because it can be applied to the non-injured limb to maximise the effectiveness of rehabilitation of the injured or immobilised limb, and mitigate against risk of muscle atrophy (Magnus et al. 2010).

In the current P–SEC study, some (EMD RF, PF) but not all (EMD VL, RFD) outcome measures of neuromuscular performance showed partial retention of CE-related performance in the untrained leg (P–SECIPSE-CE and P–SECCONTRA-CE) until at least one week after cessation of the P–SEC intervention, with preservation of neuromuscular performance of small but significant effects \( p < 0.05; \) ESs = 0.1 and 0.1 – 0.2 for EMD RF and PF respectively. The retention of the CE-related performance in the
untrained leg of TKA patients comprised of 3% and 4% – 5% of the gains in neuromuscular performance achieved immediately after the P–SEC. Retention of CE-related gains is not always reported, but those studies that did (Weir et al. 1995, Shima et al. 2002) showed evidence that increased CE-related strength was not lost 6 – 12 weeks after cessation of training in healthy but not age matched individuals compared to control subjects, with similar magnitude of CE-related improvements (3.9% (Shima et al. 2002). At six weeks after surgery (T5), the pattern of the CE gains over time for all outcome measures (neuromuscular and sensorimotor performance) in both untrained legs (P–SECIPSE-CE and P–SECCONTRA-CE) had been dissipated amongst the complex and competing interactive influences of major surgery, the immediate post-TKA care-pathway and bilateral rehabilitative conditioning, to a level that ultimately had matched the level of performance within the control group. Further investigation into the effects of CE-related improvements following the early staged of post-TKA will need to be researched further to be able to draw any conclusions on the matter.

7.5 Limitations, clinical implications and further research

The main strengths of the current study lie in the methodological processes used in delivering an assessor-blinded, randomised controlled trial (RCT). An RCT is considered the “gold” standard of clinical research and along with blinding and randomisation processes adopted during the execution of this study, one can consider the results obtained from this study as relatively robust. Furthermore, the concealment of the data to the principal investigator prior to analysis, further increased the robustness of the study. Another strength of the study is the methodological reporting approach adopted for observational studies based on recommendations of the CONSORT check-list. However, several factors must be considered with respect to the conclusions that can be drawn from this study. Firstly, there were a considerable number of drop-outs (n = 18)\(^2\) following randomisation that potentially increase the risk of bias. Secondly, although the P–SEC intervention was primarily designed as a unilateral limb conditioning pro-

\(^2\)The drop-outs were due to various factors and are similar to those mentioned in the previous two chapters: Chapter 5 and Chapter 6
gramme, bilateral limb movements during the muscular loading programme, although brief and submaximal in nature, might have contributed to the improvements measured as CE-related gains in the untrained limb. Physical restraint (e.g. using straps) of undesirable counteracting movements within the contralateral limb would have permitted the assessment of CE-related improvements more effectively by decreasing the bilateral contributions to the overall CE-related effects. This would have required an externally designed load delivering machinery or additional that delivered the loading weight on the desired limb without requiring the contralateral leg input. Use of further equipment was not possible due to restricted funding and resource limitations associated with an educational project. The main funds were allocated to allow for appropriate randomisation and blinding of the selected participants into groups and to meeting the costs of travelling in order to obtain the required data over a period of 11 months. Although the sample population used within the study can be considered small, the experimental design sensitivity of the study was sufficient to have identified a variety of situations in which the tested null-hypothesis was not retained, with Type II error rates which had bettered the prescribed levels (> 0.20).

This is the first study that evaluated the effects of CE-related effects in patients undergoing TKA surgery, following a period of modest and brief (9 sessions (1 week); high intensity (60% to 100% of daily 1RM); AMI-related nociceptor-averse (exercise lasting < 1.5s)) dosage of unilateral conditioning. All indices of neuromuscular (EMD, RFD and PF) and sensorimotor (FE) performance achieved significant small to moderate (4% – 11%; ES = 0.1 – 0.4; p < 0.05) CE-related gains in the untrained leg whether it was the leg undergoing surgery (P–SECIPSI-CE) or the leg that hadn’t been scheduled for surgery (P–SECCONTRA-CE). As would be the case for any successful conditioning programme, the importance of these CE-related gains is the potential for expediting timely gains in neuromuscular and sensorimotor performance in the untrained leg, especially during periods where rehabilitating the desired limb is difficult in the presence of pain or immobilisation. The significant and immediate results achieved for enhanced performance levels will aid in protecting the surgical implant and decrease the risk of injury, whilst potentially improving patients’ pre-habilitative status, without impos-
CHAPTER 7. RESULTS 3 – CROSS-EDUCATION EFFECTS ASSOCIATED WITH PRE-SURGICAL EXERCISE CONDITIONING (P–SEC)

ing any additional logistical or cost expediency and clinical effectiveness within the care-delivery system. Furthermore, the nociceptive-averse conditioning adopted in the P–SEC programme allows for its use in the very early stages of post-surgery rehabilitation, where major-surgery related pain commonly accentuates the previously reported AMI-related neuromuscular inhibition. However, further investigation regarding the effect of the P–SEC intervention during the early stages of post-surgery rehabilitation is required to further understand the CE-related improvements alongside contemporary, bilateral rehabilitation conditioning practices.

The results of the current study confirming the presence of CE in patients with chronic stage OA and who were waiting for surgery. Furthermore, data from this study also highlights the potential of reviewing CE-related training programmes for achieving neuromuscular and sensorimotor performance gains in the untrained limb using a focal and short period of conditioning then contemporary practices, which could then be meaningfully followed by conditioning associated with contemporary practices to build upon the preceding gains in performance. As a result of the randomisation process adopted in the current study, an appropriate representation of patients electing for TKA within the specialised institution (RJAH NHS Trust hospital), sample population would not necessarily represent the wider cohort of patients undergoing TKA surgery attending other non-specialised institutions. Therefore, future research into the applicability of this ‘novel’ approach to conditioning for eliciting CE-related improvements should include a more varied sample from different centres (multi-centre) to represent a more generalised population sample and improve external validity and generalisability of the results.

7.6 Conclusion

The results of the current study confirmed that a ‘novel’, physiologically-principled and brief period of focal exercise-conditioning (P–SEC) in patients awaiting TKA, requiring exposure to no more than 20% of the neuromuscular stimuli of contemporary practices, elicited small to moderate (4% – 11%; ES = 0.1 – 0.4; $p < 0.05$) CE-related
improvements in neuromuscular (EMD, RFD, PF) and sensorimotor (FE) outcomes of the knee extensor musculature. Gains were evident in the leg undergoing surgery (P–SEC<sub>IPSI-CE</sub>) and in the leg not scheduled for surgery (P–SEC<sub>CONTRA-CE</sub>). Furthermore, the evidence from this study highlights that a short period of focal conditioning with appropriate dose and neuromuscular stimuli, elicited significant CE-related improvements that can be used as a treatment adjunct for maximising effectiveness of rehabilitation and recovery of the quadriceps function during the pre-surgery phase. These findings are encouraging and further research should aim to investigate the optimal dosing parameters for CE using the P–SEC intervention in populations matching the characteristics of this study’s population, and in different cohorts of patients with other orthopaedic disorders to assess whether the positive findings from this study would be transferable elsewhere.
8.1 Introduction and purpose of this chapter

Following total knee arthroplasty (TKA) patients often experience positive outcomes for pain and quality of life (QoL). However, current research highlights the persistent physical dysfunction (e.g. joint instability and recurrent falls) that patients still experience even up to a year after surgery. As outlined in the literature review (Chapter 2), this physical dysfunction results from ongoing neuromuscular and sensorimotor inhibitory mechanisms that are known to persist in chronic disease conditions such as osteoarthritis (OA). The latter condition is generally the leading cause for patients electing to undergo TKA surgery. Inhibitory mechanisms such as autogenic inhibition ultimately affect the dynamic stability of the knee joint and may contribute to tripping and falls in patients. Current post-surgery rehabilitation programmes have focused primarily on decreasing pain and function with less emphasis on improving the underlying inhibitory mechanisms, with patients still experiencing episodes of tripping and falling one year on from surgery. Pre-surgical conditioning programmes have received a lot of attention in the past decade. The aim of pre-habilitation is to utilise a period prior to surgery in which patients do not usually undergo any specific conditioning, to instigate exercise conditioning-related gains that might lead to improved post-surgery rehabilitative outcomes. Generalised conditioning programmes, have typically been
adopted within contemporary pre-surgery conditioning research and have focused on the delivery of adaptation stimuli involving generic resistance-based exercise loading. They have resulted in small non-clinically relevant effects that have not been sufficient to warrant implementation within NHS or clinical practices.

Table 8.1: Key findings from Chapter 3

<table>
<thead>
<tr>
<th>Research questions (study/chapter)</th>
<th>Key findings</th>
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<tbody>
<tr>
<td>What is the efficacy of clinical sensorimotor training?</td>
<td>Meta-analysis results based on two studies confirmed efficacy of EB–SMT (3 times a week for 4 weeks) on dynamic balance (SEBT) ($z = 4.38$; $p &lt; 0.001$; SMD 1.114 (95% CI [0.630, 1.653]))</td>
</tr>
<tr>
<td>(Systematic review with meta-analysis Chapter 3)</td>
<td>Synthesis of the results from the remaining 24 studies revealed lack of sufficient robust and detailed information regarding the most efficacious parameters for delivering EB–SMT.</td>
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This thesis focused on a demonstrable need for developing a pre-surgical programme of exercise conditioning that would deliver targeted conditioning for neuromuscular and sensorimotor functional and performance gains, but which would not necessarily be hindered in that process by exacerbated inhibitory mechanisms or by increased time and costs within the patients’ care-pathway. As intimated earlier, parameters for muscular strength training have been more commonly reported in the ‘pre-habilitation’ literature but these conditioning programmes still do not fully address the underlying issues. Chapter 3 of this thesis alluded to the possibility that targeted pre-surgery conditioning emphasising in sensorimotor performance may be better suited to successfully address the latter issues. The P–SEC intervention investigated within this thesis was developed to address the possibility that underlying inhibitory mechanisms might be hindering gains in neuromuscular and sensorimotor performance. In order to evaluate
the effects of this ‘novel’ (P–SEC) intervention, appropriate measures of neuromuscular and sensorimotor performance were used and which reflected the best psychometric properties available for patients awaiting TKA surgery (refer to Chapter 2 Section 2.5).

Subjective patient-reported outcomes (PROs) questionnaires were used to analyse changes in patient’s perceived performance capabilities and related outcomes in the pre-surgery phase. Assessments of objective and subjective measurements at six weeks post-surgery were taken as a routine check for any detrimental changes, or indeed to check for the possibility of any remnants of gains in the performance capabilities of the intervention groups. Lastly, due to the shared neural circuitry between limbs, as discussed in Chapters 2, 5 and 7, neuromuscular and sensorimotor performance changes in the untrained leg were monitored as the contralateral limb in both the leg undergoing surgery and the non-surgical leg as each was conditioned using P–SEC. This approach was undertaken to investigate the effects of cross-education (CE) during the P–SEC intervention. Data associated with this aspect of the study will be the first of its kind in patients waiting for TKA surgery and will help identify whether CE might accumulate additional gains during the conditioning process. Figure 8.1 summarises the conceptual framework encompassed by the thesis and the known strengths of relationships amongst its key features.

The objectives of this clinical research project were to:

- Investigate the efficacy of a ‘novel’ pre-surgery exercise-conditioning programme (P–SEC) on objectively measured physical performance capabilities (neuromuscular and sensorimotor) during the pre- and post-surgery phases of the care pathway of patients electing to undergo TKA surgery (Chapter 5);

- Investigate the effectiveness of the P–SEC intervention on patients’ perception of physical performance related capabilities and related outcomes during the pre- and post-surgery phases of the care pathway of patients electing to undergo TKA surgery (Chapter 6);

- Investigate the efficacy of the P–SEC intervention on objectively measured phys-
ical performance capabilities (neuromuscular and sensorimotor) in the untrained limb associated with CE during the pre- and post-surgery phases of the care pathway of patients electing to undergo TKA surgery (Chapter 7).

This general discussion will summarise, integrate and critically evaluate the main findings following the application of a ‘novel’ pre-surgery exercise-conditioning programme (P–SEC) in patients electing to undergo TKA surgery. Understanding the physiological impairments and their effect on physical limitations and how these change following application of the P–SEC will be discussed. In addition, a further consideration of the limitations of the study, and the potential improvements towards future research, will be discussed, along with possible recommendations of use in this clinical population.
Figure 8.1: The figure above is a visual representation of the different aspects underpinning the hypotheses of the thesis and their respective relationships. The dashed lines represent the relationships that were unknown or not clearly defined in the literature prior at the start of the thesis. The solid lines represent the clearly-defined relationships that are reported within the literature and that have been discussed within the literature review (Chapter 2).
8.2 What are the neuromuscular and sensorimotor performance changes exhibited following the ‘novel’ P–SEC intervention?

The systematic review in Chapter 3 revealed a lack of appropriately quantified and physiologically-based characteristics for the successful conditioning-related dose of adaptation stimuli during a SM-based intervention. Therefore, the P–SEC utilised within this study emphasises a ‘motor-based’ delivery of conditioning stimuli, which had more clearly established parameters. The intention underpinning the P–SEC intervention was for it to overcome the reported ‘neurally derived’ inhibitory mechanisms by means of a rapid, ‘pain-free’ and eccentric/concentric muscular actions that require differentially challenging motor demands (Suchomel et al. 2018). Therefore, improvements following the P–SEC intervention were primarily expected to occur within epochs in which muscle force can be initiated (EMD - primary outcome) and in which the rapidity for meaningful level of forces are achieved (RFD - secondary outcome). Further anticipated gains in strength (PF - secondary outcome) and sensorimotor function (FE - secondary outcome) were hypothesised to occur but to a lesser extent compared to those that would be observed in the primary and secondary outcomes of EMD and RFD.

The predominant findings of Chapter 5 showed that the P–SEC intervention elicited significant improvements (23% – 37%; $d \leq 2.0$; $p < 0.05$) over time for indices of neuromuscular performance as indicated by EMD$_{RF}$, EMD$_{VL}$ in patients electing to undergo TKA surgery, and confirming the initial hypothesis. Additionally but to a lesser extent, there was a significant improvement (11% – 14%; $d = 0.3 – 0.6$; $p < 0.05$) observed for PF and RFD, also confirming the initial expectations of the study. The anticipated main improvements for the neuromuscular and sensorimotor performance outcomes (EMD$_{RF}$, EMD$_{VL}$, RFD, PF) were primarily observed immediately following the delivery of the P–SEC intervention (T3), highlighting the potential for direct benefits of the ‘novel’ intervention on neuromuscular and sensorimotor performance outcomes during the pre-surgery phase of the care pathway. A notable effect was observed in the sensorimotor outcome measure (FE) which had achieved gains in performance (22%; $d$
Table 8.2: Key findings from Chapter 5

<table>
<thead>
<tr>
<th>Research questions (study/chapter)</th>
<th>Key findings</th>
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<tr>
<td>What is the efficacy of the ‘novel’ P–SEC intervention on the selected neuromuscular (EMD (primary outcome), RFD and PF) and sensorimotor (FE) performance outcome measures in patients waiting for a TKA surgery?</td>
<td>Factorial ANOVA showed a significant ( p &lt; 0.05 ) group x time x leg interaction in all neuromuscular and sensorimotor performance outcomes.</td>
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<tr>
<td>(Randomised controlled trial Chapter 5)</td>
<td>The largest observation was reported in the primary outcome measure EMD\textsubscript{RF} and EMD\textsubscript{VL} (23% - 37% improvement; ( d = 2.0 )).</td>
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<td></td>
<td>The secondary neuromuscular outcomes (PF and RFD) also obtained a significant group x time x leg interaction ( p &lt; 0.05 ) but to a lesser extent (12% and 14%; ( d = 0.5 ) and 0.6 improvement, respectively).</td>
</tr>
<tr>
<td></td>
<td>Sensorimotor performance (FE) exhibited larger (22%; ( d = 0.9 )) improvements than expected when compared to the secondary neuromuscular performance outcomes (PF and RFD).</td>
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<tr>
<td></td>
<td>\textit{A priori} difference contrasts suggest that the extent of interaction between baseline (T1 and T2) and immediately post-P–SEC intervention (T3) contributed to most to the overall 3-factor ANOVA interaction.</td>
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<tr>
<td></td>
<td>Retention of P–SEC effects were observed one week after (T4) but to a lesser extent for all neuromuscular and sensorimotor performance outcomes.</td>
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that had been higher than those indices of performance which might have been expected to more specifically reflect the emphasis of the adaptation stimuli within the P–SEC (RFD and PF) (14% and 12%, respectively; \(d = 0.6\) and 0.5, respectively). Furthermore, evidence of relationships amongst sensorimotor and neuromuscular outcome measures that either did not exist or were weak at best (\(r \approx 0.4\)), showed that the outcomes were independent of one another and as expected, reflective of different physiological capabilities. Interestingly, the extent of improvement in sensorimotor performance for patients undergoing P–SEC was strongly and significantly correlated (\(r = 0.6 - 0.8\)) with corresponding improvements in neuromuscular performance scores, sharing up to 64% (coefficient of determination (\(r^2\))) of the pooled variance. The latter findings suggested the plausibility of neuromuscular adaptations to P–SEC being mechanistic determinants of sensorimotor performance.

Despite the study’s robust methodological approach involving a prospective random-allocation to groups, the findings will have been influenced by a number of factors that are specific to OA populations. Firstly, quadriceps morphological changes in patients suffering from knee OA have a preferential atrophy of fast-twitch type II fibres that are usually associated with faster muscular activations and greater capability to produce force (Aagaard et al. 2000, Jones et al. 2004, Suchomel et al. 2018), which may have caused neuromuscular performance characteristics in the study population to be generally inferior to age and gender-matched controls. The capacity for higher levels of neuromuscular and sensorimotor performance is limited by the recruitment of motor units (MU) associated with Type II muscle fibres. Variance amongst the degree of OA disease progression, age and conditioning levels amongst the patients within the study may have added to their heterogeneity of neuromuscular and sensorimotor performance characteristics. Secondly, although EMD is considered a valid and reliable index of neuromuscular performance (refer to Chapter 2), even with the use of the best quality of recording equipment, the quality of its measurement is nevertheless dependent to a certain extent on the environmental electrical noise inherent within the hospital setting. As such, the generally electrically-dense environment associated with the hospital, may have intruded during the measurement of EMG and added difficulty to the
discrimination of signature patterns of the initiation of physiological electrical onset and muscular force responses associated with EMD. Although measures were taken to ensure cleanliness and precision of EMG data capture, some additional residual noise within the EMG was inevitable.

Another important aspect from this study is the overall sample size (n = 29) on which the final per protocol analysis was performed for the neuromuscular and sensormotor outcomes. This sample size may be considered a relatively small sample size when compared to previous studies for pre-surgery conditioning programmes measuring outcomes of muscular performance (n ≥ 44 ≈ 2 groups) (Hurley & Scott 1998, Topp et al. 2009, Swank et al. 2011, Huber et al. 2015, Pohl et al. 2015, Calatayud et al. 2017). Irrespective of the possibility of an ‘underpowered’ experimental design compared to what had been envisaged originally if full participant recruitment had been achieved, the small sample size would be expected to restrict the extent with which the study’s findings could be generalised to wider populations and clinical settings. Nevertheless, the study’s experimental design sensitivity had been sufficient for the avoidance of the improper retention of null-hypotheses during statistical testing on multiple occasions (including for those associated with the study’s primary outcome (EMD)) and thus, the concomitant intrusion from inflated Type II error rates. In a wider consideration of factors that might have influenced the findings of the research study, randomisation associated with the selection and inclusion of a random sequence of patients from within all patients presenting for surgery at the single hospital, would have facilitated extrapolation of the study’s findings to other patients at the research site, but would be expected to offer limited application to other wider populations electing to undergo TKA surgery. Overall, the study has provided robust evidence for efficacy associated with the P–SEC intervention, despite a relatively small sample size, and for its potential deployment prior to TKA surgery.
A. For how long did the P–SEC-related improvements in neuromuscular and sensorimotor performance last?

One of the main criticisms of contemporary pre-surgery programmes has been the very small and short-termed improvements achieved in research outcomes that had been insufficient for them to have been considered clinically effective and meaningful (Wang et al. 2016, Chesham & Shanmugam 2017). The results for the current study reported in Chapter 5 show that there was an observable carry-over (i.e. the preservation of gains in performance beyond those apparent immediately after the cessation of conditioning) in the improvements achieved following the P–SEC intervention for all outcomes of neuromuscular (EMD$_{RF}$, EMD$_{VL}$, RFD, PF) and sensorimotor performance (FE). For example, the study’s primary outcome, EMD assessed by the responses of the m. rectus femoris, showed an immediate 35% performance gain (T3) that was maintained to a level of 17% (T4) higher than baseline performance of the P–SEC trained leg (at T2) for at least 1-week after the cessation of P–SEC (please refer to Table 5.3 in Chapter 5). The calculated values reported in Table 5.3 in Chapter 5 confirm that although there was a decline in performance from T3 to T4 (two weeks after commencement of the P–SEC intervention) some of the improvements were maintained until at least assessment point T4. Ethical and logistical constraints meant that the modelling of the conditioning-related immediate and preserved gains in neuromuscular and sensorimotor performance outcomes had to be limited to a single assessment after the P–SEC and prior to the TKA surgery, and a single post-surgical assessment at six weeks. Thus, while significant and clinically-relevant gains in performance are shown to have been preserved until at least 1-week after cessation of the P–SEC, the extent of the gains at this point (circa 50% of the immediate P–SEC gain) suggest that they would have been maintained for longer and would have been capable of being detected if the study had been permitted to have assessed the patterns of performance degradation formally. Direct comparisons with other longer-duration pre-habilitative studies (Aagaard et al. 2000, Rooks et al. 2006, Topp et al. 2009, McKay et al. 2012, Swank et al. 2011, Calatayud et al. 2017, Suchomel et al. 2018) is made difficult by a lack of convergence amongst the post-intervention assessment points.
Overall, the P–SEC intervention appears to be capable of delivering the required efficacy in neuromuscular and sensorimotor performance outcomes within a brief programme (1-week) that matches or exceeds the capabilities for efficacy shown amongst much longer duration (6 – 12 weeks) of neuromuscular conditioning studies in patients electing to undergo TKA surgery (Rooks et al. 2006, Swank et al. 2011, McKay et al. 2012, Calatayud et al. 2017). It was notable that the current formulation of the P–SEC protocol typically yielded substantive improvements in neuromuscular and sensorimotor performance that were sustained until at least 1-week after the cessation of the conditioning for some (EMD, PF) but not all (RFD, FE) outcomes, and that all of the latter gains in performance capabilities had dissipated by six weeks after surgery. As alluded to previously, it is possible that the gains in performance might have been preserved for much longer than that the recorded 1-week. However, it was plausible that the complex interaction of the effects of major biological insults to the knee joint associated with surgery and the effects immediately post-TKA clinical care pathway including rehabilitative conditioning, would have had added to the heterogeneity of response amongst the participants. In turn, these threats to sustained gains in neuromuscular and sensorimotor performance for the knee extensor musculature may have overwhelmed any remnant effects of the single episode of P–SEC at six weeks after TKA surgery. While future studies might confirm that a longer-duration but intermittent delivery of episodes of P–SEC offers optimal and versatile gains in neuromuscular and sensorimotor performance, results from the current analysis of data nevertheless question the capability of the P–SEC intervention in its current configuration to positively influence both pre-surgery and post-surgery outcomes.

B. How well was the P–SEC tolerated by patients, were there any ill-effects for them, and based on patient-perceptions, was the P–SEC a good idea?

As a novel intervention, participants’ feedback was essential during the delivery period, of the P–SEC intervention. No serious adverse reactions were reported during or after the conditioning period as reported in Chapter 5. Patients’ ‘loss-to-follow-up’
(n = 18) was not related to the intervention but rather to issues of commuting and shifting of surgical dates that did not allow for an appropriate delivery of the conditioning programme. The participants were asked to report any delayed onset muscle soreness (DOMS). DOMS is often experienced following unaccustomed muscular activities, especially during eccentric loading with sufficient intensity or duration (Cheung et al. 2003) and this was only reported as mild discomfort in two participants following the initial exposure to the P–SEC. The lack of DOMS being reported by any of the remaining 16 participants that had received the P–SEC intervention confirms that the participants did not experience any severe episodes of muscular damage during or after the intervention process. Interestingly, a decrease in joint stiffness was reported by one participant following every P–SEC session, along with a perceived concomitant ability to “walk better”. Stiffness was not measured in this study and it was not the target of the intervention, but in general previous studies investigating similar and other populations (LaRoche & Connolly 2006, Swank et al. 2011) have reported an increase in flexibility around the knee joint following eccentric muscular activity.

The lack of ill-effects and the significant increase in muscular performance outcomes achieved following the P–SEC intervention, shows that there is potential in utilising this novel conditioning programme on patients waiting for TKA surgery in order to enhance their physical performance capabilities without inducing further physical damage or pain. In addition, the novelty of the mode of conditioning within the P–SEC intervention in which weighted-resistance was being used alongside quick muscular reactions could be difficult to achieve without evoking pain, also probably indicated that these patients were generally capable of achieving greater physical performance than had been thought possible previously, where prior expectations would have been that such intense exercise might have proven too debilitating or painful at this stage of chronic disease condition.

Overall, the significant outcomes and physical benefits based on the evidence provided by a smaller (n = 29) but sufficiently powered (≥ 0.8) sample population, over such a short period of conditioning, should be enough to allow rehabilitation specialists
to consider the P–SEC programme as a new, helpful and adjunct tool within the array of possible interventions which might be considered for patients with end-stage OA and waiting for TKA surgery. By adopting brief (< 1.5s) nociceptor-averse muscle actions, the P–SEC approach might better address issues of autogenic and AMI-related inhibition that are suspected of limiting the potential for improvements to neuromuscular and sensorimotor performance capabilities in this clinical population.

C. Post surgical outcomes

The single post-surgical assessment point (T5) in the study protocol was aimed at measuring any detrimental effects in both objective and subjective outcomes in the intervention groups as a result of the P–SEC intervention on the usual outcomes of patients following TKA surgery. The assessment point T5 had also been placed strategically amongst issues of ethics (minimal disruption to the usual patterns of outpatient visits), logistics of patient availability, and the additional ambition to detect any remnant neuromuscular and sensorimotor performance effects of the single episode of P–SEC at six weeks after TKA surgery. It might have been possible that the gains in performance might have been preserved for much longer than the 1-week after P–SEC cessation given the recorded pattern of performance dissipation prior to surgery. However, it was also an expectation prior to the research that the complex interaction of the effects of a major biological insult to the knee joint associated with surgery and the effects of the immediate post-TKA clinical care-pathway including rehabilitative conditioning, would have been capable of overwhelming any remnant effects of the single episode of P–SEC on the knee extensor muscles after TKA surgery, with the possibility of relatively unpredictable findings at this end-stage of the research study.

Overall, the experimental findings from all three results Chapters (5, 6, 7) showed that neuromuscular and sensorimotor performance capacities and patient-reported outcomes had in general, recovered to a statistically similar level amongst the experimental and control groups (please refer to Table 5.3 in Chapter 5). Certainly, a priori difference contrast as adjunct information to the overall findings of the factorial ANOVA, showed consistently that the results at six weeks after TKA surgery offered signifi-
cantly inferior performance characteristics compared to those that had preceded it (i.e. different performance characteristics prior to and after surgery). The latter findings endorse the notion that what had been influencing the patients’ performance characteristics prior to surgery (principally, P–SEC) might have been considerably different to the complex interaction of influential factors afterwards (principally, surgery insult, post-surgery care; rehabilitation; possible remnant P–SEC effects).

Another possible physiologically-based reason for the attenuation of any residual P–SEC effects to a situation in which the performances of experimental and control groups match after surgery, is that the routine bilateral exercise conditioning characteristics associated with rehabilitation after surgery may have interfered with the effects of unilateral pre-surgery conditioning and concomitant CE effects in some interactive and unpredictable way. A further possibility would be that the retention of null-hypotheses associated with comparisons amongst group performance capabilities at T5, relates to a compromised experimental design sensitivity. It is plausible that Type II errors may have intruded in the attempted discrimination of subtle inter-group differences in neuromuscular and sensorimotor performance characteristics that might still remain after surgery. The experimental design had not accounted fully for the latter possibility, even within the study’s primary outcome (EMD) because an emphasis had been placed on discriminating pre-surgery P–SEC effects.

8.3 What are the changes in patient reported outcome (PROs) changes in relation to the novel P–SEC conditioning pre- and post-surgery?

Patients reported outcomes (PROs) are commonly used for evaluating outcomes of pain, perceived physical function and quality of life (QoL) (Black 2013) before and after TKA surgery both in research (Alviar et al. 2011, Collins & Roos 2012, Black et al. 2016) and arthroplasty registers (Prodinger & Taylor 2018). Amongst the more commonly used PROs in patients before and after TKA surgery are the WOMAC,
OKS, KOOS and SF-36v2, of which this study included the latter three. Further, in addition to pain, perceived function and quality of life, this study also included outcomes which measure other constructs that may be (directly or indirectly) influenced by the P–SEC programme of conditioning, such as self-reported habitual physical activity (IPAQ), pain self-efficacy (PSEQ) and psychophysiological fitness performance (PP). These PROs have exhibited excellent psychometric properties (refer to Chapter 2) for evaluating the study’s population (pre- and post-surgery) and to measure any effects an exercise-based programme of conditioning has on patients’ reported outcomes such as pain, physical function and QoL (Alviar et al. 2011, Baker et al. 2012, Black et al. 2016, Prodinger & Taylor 2018). The scores obtained from PROs have been used in patients electing and undergoing TKA surgery for predicting post-surgery outcomes (Stevens-Lapsley et al. 2011, Black 2013), evaluating an intervention’s effectiveness (Bourne 2008) and a measuring patients’ satisfaction following surgery (Hamilton et al. 2013, Black 2013). Therefore, in this study, PROs were included to complement the objective measures of physical performance.

The predominant findings reported in Chapter 6 indicate that there was no statistically significant (group x time) interaction \( p > 0.05 \) for any of the PROs (OKS, KOOS, PSEQ, IPAQ, PP and SF-36v2). This was the case when only analysing the pre-surgery assessments (P–SEC intervention (T1 – T3)) and when the post-surgery assessment was also included for statistical analysis (P–SEC intervention and TKA surgery (T1 – T5)). These results are in contrast to those reported in Chapter 5 where the P–SEC intervention elicited statistically significant (ES = 0.3 - 2.0; \( p < 0.05 \)) (group x time x leg) interactions in neuromuscular and sensorimotor physical performance outcomes. As alluded to previously, the main improvements in the objective performance capabilities were primarily observed immediately following the delivery of the P–SEC intervention (T3), highlighting the potential for direct benefits of the P–SEC intervention. The lack of statistical significance in the PROs means that there was no transfer of effect of the physical objective outcomes (EMD, RFD, PF and FE) of performance to the perceived physical performance related outcomes associated with the delivery of the P–SEC intervention. In other words, the improvements in neuromuscular and
Table 8.3: Key findings from Chapter 6

<table>
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<tr>
<th>Research questions</th>
<th>Key findings</th>
</tr>
</thead>
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<tr>
<td>What are the effects of the ‘novel’ P–SEC intervention on the selected patient-reported outcomes (PROs) as recorded by the OKS, KOOS, PSEQ IPAQ, PP and SF-36v2&lt;sup&gt;TM&lt;/sup&gt; in patients waiting for a TKA surgery? (Randomised controlled trial; Chapter 6)</td>
<td>Overall there was no statistically significant group x time interactions reported in PROs during the pre-surgery phase. There was no statistically significant group x time interaction during the pre- and post-surgery phase in the majority of the selected PROs except for KOOSQoL subscale and PP questionnaire. There was no overall transfer of effects from the objective outcome measures to patients perceived performance (PROs) following the P–SEC intervention.</td>
</tr>
</tbody>
</table>

Sensorimotor physical performance were not perceived by the participants or they were perceived but the PROs lacked sensitivity to reflect small changes in perceived physical performance and associated changes in the quality of life and self-reported physical activity.

The concealment procedures adopted, where the researcher was not allowed to check for questions which were not answered by the participants resulted in missing PRO data. This was the case for SF-36v2<sup>TM</sup> and the KOOS sports and recreation subscale. A high number of missing items (questions not answered) resulted in the SF-36v2<sup>TM</sup> data being only available for 16 participants for assessments across T1–T3 and even less for postsurgical assessments (T5 n = 5) and only 5 overall participants for the KOOS sports and recreation subscale, which was in contrast to the number of responses analysed (n = 28) in the remaining PROs (OKS, PSEQ, IPAQ, KOOS). Therefore, this process is likely to have resulted in an increase in Type II error in the respective analyses of the SF-36v2<sup>TM</sup> since the results obtained from KOOS sports and recreation subscale (n =
5) were too small for analysis. The overall sample (n = 28) used within the current study was considerably less than the original sample size required (n = 45 – 60) for appropriate power (0.7 – 0.8) to detect a statistically significant effect in primary outcomes. This might have resulted in the overall lack of statistical significance achieved and possible intrusion by Type II error. Furthermore, the sample size calculation was based on the physical performance outcomes (EMD, PF, RFD and FE) as opposed to any of the PROs and as such a sample size calculation based on one or more PRO might have been more suited and resulted in a higher sample size required for an appropriately powered study.

The P–SEC utilised within this study as described earlier and in Chapters 2 and 5 emphasises a ‘motor-based’ delivery of conditioning stimuli. The intention behind the P–SEC intervention was to overcome the reported ‘neurally derived’ inhibitory (AMI) mechanisms by means of a rapid, ‘pain-free’ and eccentric/concentric muscular actions that require differentially challenging motor demands. The latter aspect of the design has been considered important for effective adaptation of strength-related performance characteristics (Suchomel et al. 2018). The improvements in neuromuscular and sensorimotor outcomes (EMD, RFD, PF and FE) achieved after the application of P–SEC intervention is expected to transfer in increased joint stability and improve overall balance capabilities that have been reported to persist beyond surgery (Silva et al. 2003, Swinkels et al. 2008, Bade et al. 2010, Rätsepsoo et al. 2011). These improvements in balance capabilities were hypothesised to improve the overall perception of the patients’ stability and therefore indirectly affect perceptions of pain, function, QoL and habitual physical activity levels, but this was not reflected in the findings of this study.

Although the PROs did not reflect the physical changes that were observed in Chapter 5, this does not necessarily mean that the intervention was not effective in bringing about changes that were perceived by the participants but possibly, that either the PROs were not sensitive enough to detect the subtle changes or that the construct measured by the PROs did not match that of the objective sensorimotor and neuromuscular outcomes. Furthermore, the observed changes in physical performance capa-
bilities might have not been distinctly related to performance-based criteria that reflect the patients' perceptions following the novel P–SEC intervention at that point in time. In fact, the PP was the only questionnaire whose constructs have been reported previously to possess sufficient psychometric sensitivity to detect subtle changes in performance capabilities (Gleeson et al. 2005, Peer 2017) but nonetheless, this inventory also recorded a lack of statistical significance amongst the patients' perceptions of physical performance needs. Pre-habilitative studies in which the effects of a pre-surgical conditioning were measured using a combination of PROs (similar to the present study e.g. KOOS, SF-36v2<sup>TM</sup>) and objective measures (physical function e.g. muscular strength) have reported significant improvement in both PROs and physical objective outcomes (Desmeules et al. 2013, Huber et al. 2015, Calatayud et al. 2017). The main dissimilarities between these studies and the current study are mainly study sample-size (n > 28) and conditioning parameters (e.g. duration (> 1 week)). Furthermore, the objective outcome measures although similar (e.g. muscular strength) (Calatayud et al. 2017) also included functional outcomes of performance such as stair climb test (SCT) (Huber et al. 2015) and timed-up-and-go tests (TUGT) (Desmeules et al. 2013) rather than the more physiological but less functional measures of neuromuscular and sensorimotor performance that have been used in this study. The more functional measures used in previous studies may be more easily perceived by the participants and reported in the respective PROs. Whilst these pre-habilitative studies report significant outcomes in both subjective and objective outcomes during the pre-surgery phase, similarly to the current study, these improvements in physical performance were not maintained post-surgically (Huber et al. 2015, Calatayud et al. 2017) before (at 4 weeks) and after (at 12 and 24 weeks) the 6-week post-surgical assessment point used in the current study (Huber et al. 2015, Calatayud et al. 2017). As previously alluded for the neuromuscular and sensorimotor outcomes, it is plausible that the complex interaction of the effects of major biological insults to the knee joint associated with surgery and the effects immediately post-TKA (rehabilitative conditioning), would have added to the heterogeneity of the response amongst the participants and the results obtained at six weeks post-surgery. The latter would have resulted in greater difficulty in detecting any subtle P–SEC-related changes in perceived physical performance capabilities.
8.4 What are the CE effects exhibited by the novel P–SEC intervention and what are its potential for use in rehabilitation?

Concomitant alterations in physical performance outcomes, including neuromuscular and sensorimotor performance capabilities, have now been recorded for the first time in both limbs of those participants undergoing TKA surgery, due to the underlying shared neural connections, as described in Chapter 2 and Chapter 7. The results in Chapter 5 revealed that the P–SEC intervention was successful in eliciting statistically significant improvements in physical performance outcomes in the trained leg. Despite the experimental design of the study utilising the non-trained leg as a notional ‘control’ against which unilateral P–SEC-related changes in the performance characteristics of the trained leg could be compared over time, it also facilitated gauging the extent of potential cross-education (CE).

The predominant findings of Chapter 7 revealed that the P–SEC intervention elicited small to moderate CE effects \((d = 0.1 – 0.4; 4 – 11\%)\). The latter were comparable in magnitude to the findings of previous studies that had investigated CE-related changes in physical performance capabilities during unrelated motor-based conditioning programmes (Munn et al. 2004, Manca et al. 2017). The findings from this study confirmed the relevant thesis’ hypothesis and reflect the novel contribution to the knowledge base as the first study to report CE in patients waiting for TKA surgery following a presurgical exercise conditioning intervention. These findings potentially have important clinical applications: Firstly, the knowledge that CE occurs consistently and to a reasonable extent following the P–SEC intervention, potentially allows for maintenance and gains in the neuromuscular and sensorimotor performance within a leg for which temporarily, conditioning might be clinically contraindicated. For example, by continuing training of the contralateral limb during an episode of inflammation and pain...
associated with OA within the ipsilateral limb, the ipsilateral limb will receive conditioning indirectly.

Table 8.4: Key findings from Chapter 7

<table>
<thead>
<tr>
<th>Research questions (study/chapter)</th>
<th>Key findings</th>
</tr>
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<td>What is the efficacy of the ‘novel’ P–SEC intervention on objective outcomes of neuromuscular (EMD (primary outcome), RFD and PF) and sensorimotor (FE) performance capacities in the untrained limb resulting from CE in patients waiting for a TKA surgery? (Randomised controlled trial; Chapter 7)</td>
<td>The results of this chapter revealed small to moderate (4% – 11%; ( d = 0.1 – 0.4 )) improvements in all outcomes of neuromuscular and sensorimotor performance of both untrained limbs regardless whether that limb was the one undergoing surgery.</td>
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<tr>
<td></td>
<td>The main CE effects were observed in the pre-surgery phase.</td>
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<tr>
<td></td>
<td>Retention of CE effects (T4) was also reported in two of the objective outcomes EMD_{RF} and PF but to a much lesser extent (3% – 5%; ( d = 0.1 – 0.2 )).</td>
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</table>

Secondly, the presence of CE in both legs means that training one limb will automatically benefit the contralateral limb by further decreasing the asymmetry between the two limbs that is often found in patients undergoing TKA surgery. Lastly, the results discussed in Chapter 7 also reveal that CE was also maintained (to a lesser extent (3.1% – 5.1%; \( d = 0.1 \))) in two of the neuromuscular outcomes (EMD_{RF} and PF) for at least one week after the cessation of the P–SEC intervention (T4). These findings are again novel as no previous study investigating CE have included any retention of effects in the pre-surgery period in this cohort of patients. Information about the retention of an intervention’s effects helps to guide the practitioner on when to deliver the intervention during the rehabilitation process for optimal results.
8.5 It’s novel, it works but so what?

The results reported in this thesis highlight the potential of a ‘novel’ (P–SEC) approach to conditioning for improving aspects of physical performance in patients with ongoing and depressed performance capabilities associated with neuromuscular inhibition, such as those individuals electing to undergo TKA surgery. Statistical significant improvements (\(p < 0.05\)) in indices of neuromuscular and sensorimotor function (objective physical performance outcomes) have been achieved utilising approximately 50% of the volume and even less of the duration (9 sessions, 5 minutes/session = total 60 minutes; vs. 18 sessions, 30 – 45 minutes/session total \(\approx 540\) minutes) of contemporary conditioning practices (Gill & McBurney 2013, Suchomel et al. 2018), but involving a nociceptor-averse (<1.5s of muscle activation) physiological exercise intensities of > 60% of maximum daily strength capabilities and 17% of exposure to adaptive stimuli. These findings highlight the importance for revisiting contemporary conditioning programmes for improving neuromuscular and sensorimotor performance outcomes and ultimately, for conditioning-related improvements to the capability for and dynamic joint stability and functional control of balance. One of the aspects for improving these performance outcomes in this cohort of patients was the persistent joint instability and recurrence to falls that has been reported up to a year following surgery. As described in the literature (Chapters 2 and 5) the underlying mechanisms for recurrent joint instability and falls are attributed to ongoing inhibitory mechanisms (AMI) that affect the dynamic joint function. Current rehabilitative practices do not tend to focus specifically on improving the control and sensitivity of response within these underlying inhibitory mechanisms to facilitate conditioning-related gains in performance. Instead, contemporary practice has tended to focus on improvements to other important aspects of knee function, including increasing the joint’s range of motion (ROM) and the patient’s overall functional independence. Overly up-regulated AMI, has the potential to undermine the TKA surgery’s success. Persistent joint instability may contribute to a cascade of effects leading to balance impairment, and together with muscle weakness that also persists after surgery, may contribute to an increased risk of recurrent falls in patients. In fact, both muscle weakness and balance impairment
have been considered the most prevalent risk factors to falls according to the national guidelines (NICE). Muscle weakness and balance impairment are modifiable and are often improved through appropriate conditioning programmes. Therefore, the novel approaches to the design of relevant conditioning programmes, such as the P–SEC, provide the welcomed potential for use successfully in patients awaiting TKA surgery to improve physical performance related to the prevention of tripping and falling.

Despite the P–SEC having a significant impact and improvement on the objective measures of physical performance, this was not reflected in patient’s perceptions of their own capabilities. The lack of measurement responsiveness for PROs across the experimental period might simply reflect a compromised scaling amongst subjective and objective measures of performance and evidenced by weak correlations at best ($r < 0.3$) and independence. The latter observations have been noted within similar research populations (Bailey et al. 2014, Peer 2017). It is therefore possible that the constructs within the questionnaires were not sufficiently sensitive to detect the subtle perceived changes in performance, despite more robust P–SEC-related improvements occurring amongst the objective measures. The PROs selected for measuring aspects of perceived physical performance capabilities in this thesis exhibit good psychometric properties to justify their use with this cohort of patients. For the clinician, the lack of statistically significant changes amongst the PROs over the experimental period, including within the post-surgical phase, simply means that there was no transference of measurable effects between the objective and subjective physical performance outcomes associated with the P–SEC intervention.

Lastly, the results achieved from Chapter 5 endorse the efficacy of a ‘novel’ type of conditioning, whose effects can potentially be used and transferred to enhance the performance of other joints such as the hip, shoulder and ankle. Similar ongoing deficiencies in neuromuscular and sensorimotor characteristics, following injury, associated with synovial joint systems that are largely shared amongst these joints, would make it entirely plausible for the effects of P–SEC to be transferable amongst joint systems, once suitable research-related due-diligence had been undertaken. Future re-
search should explore these effects and incorporate different cohort of patients from non-specialised hospitals in order to achieve an increase in the ability to generalise further from any results about P–SEC. Furthermore, results for retention of effects showed that improvements started to decline two weeks following the initiation of the intervention. Given an increasing imperative amongst health care providers to deliver cost- and logistically-effective pathways of care that can be self-managed by patients, future research should also investigate whether P–SEC-type hospital-based interventions are amenable to being delivered by means of self-managed care.

The principal finding of this thesis was that patients awaiting TKA surgery and who performed the P–SEC programme unilaterally, demonstrated superior gains in neuromuscular and sensorimotor outcomes of the ipsilateral knee extensor musculature compared to controls. The leg scheduled for surgery and its contralateral counterpart responded with similar extensive gains in performance. As well as having demonstrated greater efficacy than current care pathways, the P–SEC training had been well-tolerated by patients, even when it had been initiated immediately prior to surgery. Of further potential clinical importance was the finding that a proportion of these advantages in performance were also conferred indirectly by means of neuromuscular cross-education to the leg that hadn’t received P–SEC. Thus, in an albeit modestly-sized sample of patients electing to undergo TKA, an as yet non-optimised, brief (exposure to ≈ 17% of the stimuli for adaptation compared to contemporary clinical practice) but focal dose of neuromuscular pre-habilitative training has yielded directly (Chapter 5) and indirectly (Chapter 7) significant and disproportionately greater improvements in almost all outcomes, compared to what otherwise might have been expected from findings within the relevant literature (Latella et al. 2012, Kidgell et al. 2015, Beyer et al. 2016, Cirer-Sastre et al. 2017). While minimally-important clinical differences (Sloman et al. 2006) for outcomes remain typically elusive in this clinical population (Keurentjes et al. 2012), the magnitude of the gains associated with the P–SEC, suggest that they are likely to be relevant clinically, and that the findings warrant a verification in subsequent and further well-controlled clinical trials.
Figure 8.2: Patients’ individual improvement scores for EMD (m. rectus femoris) of the leg scheduled for TKA surgery, from baseline to the end of P–SEC (absolute gain in $\text{EMD}_{\text{RF}}$ performance (vertical axis: ms) plotted relative to the corresponding mean score associated with baseline and T3 performances (horizontal axis: ms)). Minimum detectable change associated with random measurement error in EMD (MDC; Estimated as an upper 95% confidence limit at 4.5% of pooled group mean scores: 3.8 ms) is superimposed for comparison.
Figure 8.3: Patients’ individual improvement scores for EMD (m. rectus femoris) of the non-surgical leg, from baseline to the end of P–SEC (absolute gain in EMD$_{RF}$ performance (vertical axis: ms) plotted relative to the corresponding mean score associated with baseline and T3 performances (horizontal axis: ms)). Minimum detectable change associated with random measurement error in EMD (MDC; Estimated as an upper 95% confidence limit at 4.5% of pooled group mean scores: 3.7 ms) is superimposed for comparison.
One way to further explore the likely clinical relevance of the thesis’ findings would be to consider the patterning of individual patient’s responses within the context of the magnitude of group mean change in performance compared to known or anticipated errors in measurement of outcomes due to random variations in performance. For example, the patterning of patients’ individual improvement scores for the investigation’s primary outcome of EMD (illustrated using responses of m. rectus femoris) from baseline to the end of P–SEC (absolute gain in EMD$_{RF}$ performance (vertical axis) plotted relative to the corresponding mean score associated with baseline and T3 performances (horizontal axis)) and are shown in Figure 8.2 (leg scheduled for surgery) and Figure 8.3 (non-surgical leg). The graphical plots offer examples of further corroborating evidence of the potential for clinical relevance of P–SEC for which in contrast to controls, the gains for all but one of the patients who’d undertaken direct unilateral P–SEC had exceeded the MDC for EMD$_{RF}$ (3.8 ms and 3.7 ms, respectively) (estimated as an upper 95% confidence limit based on 4.5% random measurement error in EMD (Viitasalo 1980, Minshull et al. 2009) relative to pooled group mean scores). By contrast, despite P–SEC having elicited statistically-significant group mean gains in EMD$_{RF}$ indirectly by means of neuromuscular cross-education, the clinical advantages for the individual patient adopting P–SEC-related strategies for performance gains in the non-trained limb are less clearly defined. This is because the patterning of the individuals patient’s P–SEC CE-related gains for EMD$_{RF}$ partially resides within the upper limit for measurement error associated with a single estimate of this outcome, in general, appears to be less easily distinguished from that of the control group. The latter is evident in both the responses of the leg scheduled for surgery and those of the non-surgical leg. This interpretation might be considering a ‘worst-case’ scenario for CE-related gains in EMD$_{RF}$ associated with P–SEC because in this thesis, measurement of EMD$_{RF}$ has been based on the mean score of three intra-session estimates of performance with the likelihood of commensurate enhancement to precision of an individual patient’s score (i.e. a reduced MDC for a given patient), rather than utilising a single estimate of performance and a generic estimate of MDC for EMD$_{RF}$, which has been considered for this discussion. Nevertheless, interpreting individual patient’s responses in the context of group-related gains using this approach may represent a reasonable way in which to
view the relative merits clinically of direct and indirect (CE) application of the P–SEC programmes of pre-habilitation. In this case, direct conditioning of the leg targeted for improvement appears to offer decisive clinical gains for the individual patient, whereas indirect strategies would be less assured. Further well-controlled clinical studies targeting the optimal dose of P–SEC will reveal the full extent of the efficacy possible for CE-related gains in EMD_{RF}, which may counter this preliminary interpretation of CE as an underestimation of its clinical worth, as well as identify the clinical relevance that might be expected from optimal P–SEC doses for other outcome measures of neuromuscular and sensorimotor performance in this context.

### 8.6 Overall strengths and limitations of the studies

The overall strength lies in the robust methodological approach that is associated with an assessor blinded randomised controlled study (RCT). The recruitment of a random cohort of serial patients presenting for orthopaedic consultation following primary care referral, with subsequent randomisation into experimental groups, offered a realistic representation of the wider population of individuals undergoing TKA at the RJAH NHS trust hospital. Further, concealing patients’ random allocation to groups was undertaken by an independent member of staff who was not involved in the data collections and analysis. This concealment process also allowed for appropriate assessor blinding during the assessment and exercise delivery (to which experimental group the patients belonged to) period limiting assessor-related and other sources of bias. The concealment of participant randomisation into groups was kept until final stages of data analysis to further limit bias. The study also included repeated measures (five assessment points) for measurements of muscular performance outcomes and PROs. This allowed for a more comprehensive description of the effects of the ‘novel’ intervention, such as the stability of the outcome measures (T1 – T2), the effects of the P–SEC intervention (T2 – T3), possible retention of P–SEC effects before (T4) and after surgery (T5).
Prior to considering the results achieved in this study, there are some limitations that need to be appreciated. Although the ‘loss-to-follow-up’ following randomisation decreased the sample size to less than that derived from the sample size calculation, the lower sample size was still sufficient to detect statistically significant changes in the physical performance outcomes (EMD, RFD, PF and FE) that showed statistically significant group x leg x time interaction effects. Although considerable effort was focused on standardising assessment procedures, subtle variation amongst instructions and terminology might have influenced the participant responses, resulting in the decreased responses observed in the PROs. Further, concealment during data capture did not allow the assessor to ensure that the PROs were being answered fully and therefore without the possibility of retrospective completions, some of the data associated with the PROs remained missing. In addition, the P–SEC reflects just one ‘pilot’ dose of stimuli for adaptation, and thus, the studies’ findings in general do not yet reflect the outcomes of an optimised dose-response investigation for P–SEC. Future research should focus on determining the optimal dose-response parameters for delivering P–SEC.

Furthermore, participants were recruited from a specialised orthopaedic hospital, whose practices might not necessarily have reflected those in other hospitals, and as such, this scenario may limit the ability to generalise for the thesis’ findings. Furthermore, there was no set limitations for age (other than 18 years or over) and this might have played a role in increasing the heterogeneity (age range of study participants 51 – 90 years) of the results and experimental noise. Lastly, the recruited sample had not been limited to patients undergoing unilateral TKA surgery for the first time. The results in those patients who had already undergone a contralateral TKA, might have been influenced by complex neuromuscular and sensorimotor performance responses and perceptions. Nevertheless, such potential complications within the sample population reflected ‘real-world’ challenges within the health care system.
Figure 8.4: The figure above is a visual representation of the different aspects underpinning the hypotheses of the thesis and their respective relationships after completion of the thesis study. The research questions are highlighted in the blue boxes whilst the yellow boxes are the sections within the thesis that address these questions. The red box contains the main key findings. The solid lines represent the relationships that have now been confirmed from the data reported within this thesis.
8.7 Conclusion

This thesis provides a comprehensive investigation on the effect of a ‘novel’ way of conditioning for achieving improvements in physical performance outcomes (neuromuscular and sensorimotor) in the likely presence of ongoing neuromuscular inhibition, such as that experienced in patients waiting for a TKA surgery. The neuromuscular and sensorimotor performance of the P–SEC trained leg of patients undergoing surgery on the same leg or the contralateral leg, improved over the experimental period (1-week) to a greater extent than the corresponding performance of the leg that had not received conditioning, but which nevertheless, showed CE effects. The P–SEC-related improvements in neuromuscular and sensorimotor performance were generally sustained until at least one week after the cessation of the conditioning, but had dissipated by six weeks after surgery.

At the time of writing and to the best knowledge of the author, this is the first study that has confirmed the presence of CE following a period of conditioning in patients undergoing TKA surgery. These findings are essentially very important as they highlight the potential of utilising the P–SEC conditioning programme in order to elicit improvements in outcomes of physical performance (neuromuscular and sensorimotor) when training the desired (surgical) limb is clinically-contraindicated not possible due to the presence of pain and swelling.

The significant P–SEC-related improvements achieved in objective measures of neuromuscular and sensorimotor performance were not translated to patients’ perceptions of their physical capability related outcomes as measured using the PROs. The selected PROs (KOOS, OKS, IPAQ, PP, SF-36v2TM and the PSEQ) did not identify significant changes in the perceived capabilities in both the pre- and post-surgery phases of the experimental period.

The thesis’ findings highlight an important need for revisiting contemporary conditioning programmes for improving neuromuscular and sensorimotor performance out-
comes. Ultimately, the findings may contribute new knowledge towards achieving increased characteristics of joint stability and control of functional balance, which in turn, helps in the process of preventing tripping and falling and associated morbidity in patients with OA.
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Appendices
Appendix A

Search strategy example for systematic review
Table A.1: Search strategy example: Medline via EBSCOhost

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Appendix B

Research Ethics Committee

Confirmation Letter
08 March 2017

Ms Anna maria Risso
Doctoral Student
Student - Queen Margaret University
School of Health Sciences
Queen Margaret University
Musselburgh
EH21 6UU

Dear Ms Risso

Study title: Novel pre-surgery exercise-conditioning (P-SEC) in patients undergoing a total knee arthroplasty (TKA) surgery.

REC reference: 17/SS/0005
IRAS project ID: 198930

Thank you for your letter of 04 March 2017, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Sub Committee member.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

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

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).


Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites
NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)</td>
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</tr>
<tr>
<td>Letter from sponsor [Co-sponsorship letter of support]</td>
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<tr>
<td>Other [GP letter Control Group]</td>
<td>V2</td>
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<tr>
<td>Other [invitation letter to participants]</td>
<td>V2</td>
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<tr>
<td>Other [Covering letter to amendments requested on 23/2/17]</td>
<td>V2</td>
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<tr>
<td>Participant consent form</td>
<td>V2</td>
<td>09 February 2017</td>
</tr>
<tr>
<td>Participant information sheet (PIS)</td>
<td>V3</td>
<td>04 March 2017</td>
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<tr>
<td>REC Application Form [REC_Form_13122016]</td>
<td>V2</td>
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<td>Research protocol or project proposal</td>
<td>V1</td>
<td>12 December 2016</td>
</tr>
<tr>
<td>Summary CV for Chief Investigator (CI)</td>
<td>Submitted version</td>
<td>07 December 2016</td>
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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/SS/0005 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project.

Yours sincerely
Dr Sara Smith
Chair
Email: sandra.wyllie@nhslothian.scot.nhs.uk

Enclosures:
“After ethical review – guidance for researchers”

Copy to:
Prof. Nigel Gleeson
Teresa Jones, Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust
Appendix C

Research and development ethical approval RJAH
APPENDIX C. RESEARCH AND DEVELOPMENT ETHICAL APPROVAL RJAH

The Robert Jones and Agnes Hunt Orthopaedic Hospital
NHS Foundation Trust

Research Office
Oswestry
Shropshire
SY10 7AG
Telephone 01691 404143
Email: teresa.jones@rjah.nhs.uk

Ms Anna Maria Risso
PhD Student
Queen Margaret University
Musselburgh
EH21 6UU
10th May 2017

Confirmation of Readiness to Conduct Research Study (Sponsored Studies)

Dear Ms Anna Maria Risso,

Title: Novel pre-surgery exercise-conditioning (P-SEC) in patients undergoing a TKA surgery.

R&D / CLRN Reference: RL1 715 IRAS:198930
Ethics Reference: 17/89/0005
Chief Investigator: Ms Anna Maria Risso
Principal Investigator (RJAH): As Above
Sponsor: RJAH & Queen Margaret University
Funder: European Social Funds through the Endeavour Scholarship Scheme, Malta

Proposed local study end date: 31/4/2018
Target Recruitment: 45-65 patients
Documents Received:
Protocol, Version 1, 12/12/2016
PIS, Version 3, 4/3/2017
PCF, Version 3, 4/3/2017
Participant Invitation Letter, Version 2, 4/3/2017
GP Letter-Control Group, Version 2, 9/2/2017
GP Letter-Experimental Group, Version 2, 9/2/2017
Performance Profile Questionnaire, Version 1, 9/2/2017
Validated Questionnaire-KOOS
Validated Questionnaire-IPAQ
Validated Questionnaire-OKS
Validated Questionnaire-Pain Self Efficacy Questionnaire
Validated Questionnaire-SF26V2

Following receipt of the approval letter from the Health Research Authority (HRA) for the above mentioned study, I can confirm that the study can start at the Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Foundation Trust subject to:

- Study drug, IMP or study devices have been received
- Randomisation system is in place
The Robert Jones and Agnes Hunt Orthopaedic Hospital

- GCP training has been completed as necessary
- Delegation Log has been completed
- Trial Master File and or Investigator Site File has been set-up
- Unblinding procedures are in place

Once the above have been confirmed, the study will be given permission to recruit.

Please read carefully the following additional information that is applicable to this confirmation of approval.

Please note that your research study may be monitored or audited by this research office or other relevant authority as part of the requirements set out in the Research Governance Framework for Health & Social Care (2005).

In order for us to continue to meet the requirements for Research Governance you are requested to provide us with the following documents (electronic or paper) relating to this study:

- A copy of all HRA Annual progress report(s) (if applicable)
- A copy of the HRA End of Study Declaration
- A copy of the final report no more than 6 months after completion of the study

You are also requested to notify us about any of the following that are applicable:

- Amendments to any documents that require HRA approval
- Changes to the study start and end dates
- Changes in personnel / members of the research team
- Changes to details of locations of the study
- Any serious adverse events (SAE, SUSAR) within the timescale specified on the NRES website.

Wishing you every success with the study.

Yours sincerely

Mr Andrew Roberts
Research Director.
## Confirmation of Green Light

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<td>Confirmation of agreement of source data/documents</td>
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<td>Other: Receipt the Honorary Contract back fully signed</td>
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Please return to the Research Office once all the above have been completed (if applicable). Once received, the Research Office will confirm "Green Light" which will then and only then, allow you to start recruiting to your study. **Please do not start recruiting to your study until you have this Confirmation of Green Light document signed by the R&D office.**

Investigator / Study Co-ordinator signature: ___________________________
Date: 15/5/2017

Green Light confirmed:

R&D office Name: ___________________________
R&D Office signature: _______________________
Date: 15/5/2017
Appendix D

Queen Margaret University

Ethical Approval
9 March 2017

Dear Anna Maria


I am writing in relation to the above named research to acknowledge receipt, on behalf of the Queen Margaret University Research Ethics Panel, of all relevant information, including the favourable ethical opinion from the South East Scotland Research Ethics Committee.

I hope that this confirmation is helpful. Should you require any further information, please let me know.

Yours sincerely

Dawn Martin
Acting Secretary to the Research Ethics Panel
Appendix E

Patient Information Sheet
PARTICIPANT INFORMATION SHEET

NOVEL PRE-SURGERY EXERCISE CONDITIONING IN PATIENTS UNDERGOING A TOTAL KNEE REPLACEMENT (TKR)

You are being invited to take the part in a research study. Before you decide to take part, it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully. Talk to others about the study, if you wish.

Ask us if there is anything that is not clear or if you would like more information. Once you have done this, take time to decide whether you would like to take part in the study.

Background of the study
Total knee replacement (TKR) is the treatment of choice for patients suffering from long standing severe pain, functional limitation and instability caused by osteoarthritis (OA) of the knee joint’s surfaces. TKR helps to remove the cause of pain and swelling, but exercises are crucial to counteract the joint’ instability and any feeling of ‘unsteadiness’ before and after surgery. However, research hasn’t yet identified the optimum approach for delivering exercises that will help in your recovery. We have scientifically developed a new programme of exercise for the muscles of the knee that can be delivered during a single week prior to your surgery. The pre-surgery exercise-programme (P-SEC), potentially offers similar effectiveness for improving your ‘unsteadiness’ and muscle’ fitness as programmes that last much longer. Therefore, the purpose of this research study is to test the effectiveness of this new, short approach to exercising in patients such as yourself, who are waiting for a TKR surgery.

Why have I been invited?
The study is open to both men and women over the age of 18 waiting to undergo a TKR like yourself.
Do I have to take part?
No. You can refuse to take part in the study and you do not have to give a reason. You are also free to withdraw from the study at any time. If you choose not to participate, or wish to withdraw from the study, your relationship with your surgeon and the medical team involved in your care, and standard of treatment that you receive, will not be affected in any way.

What will happen if I take part?
We would like to find out whether or not the exercise-programme we have developed, works in patients like yourself, during this period leading up to your surgery. To find out, we need to make comparisons between people who perform the exercise-programme and those who don’t. In order to do so, we put people into groups. In this case, we will have three groups:

- Group 1 (exercise group)
- Group 2 (exercise group)
- Group 3 (no exercise group)

The difference between the two exercise groups is the leg which is doing the exercise. Part of the study is looking at whether the exercise also works if it is done on the opposite leg. Each group will be asked to attend between 5-8 sessions at the hospital to complete the study. Each group will follow normal standardised care and rehabilitation following the surgery. However, in addition to the normal care, the two exercise groups will attend 3 exercise sessions before surgery. Each person in the control group (Group 3) will be asked to attend 5 sessions (2 of the sessions will be non standard hospital appointments). Each person in the exercise groups (Group 1 and 2) will be asked to attend for 8 sessions (5 sessions will be non standard hospital appointments). Therefore, in order to be able to complete the study, we are asking you to attend the hospital on no more than 5 extra occasions in your own time. Your commitment to the study will end at 6-weeks after your surgery. The table below helps to explain when you will be asked to attend depending on the group you’re randomly selected.

Table 1: Highlights the study days where you will be asked to attend. The days shaded darker are the days when the exercise-programme (P-SEC) will be delivered, whilst the days lightly shaded are the days that will match your other medical appointments at the RJAH NHS Trust hospital. The rest of the days are the ones that you will be required to attend out of your own time. The letter ‘X’ marks the days where you will be asked to attend the hospital for the study according to your group allocation.

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<th>E.g. Wed.</th>
<th>E.g. Fri.</th>
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<th>Day of surgery</th>
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<td>Exercise</td>
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<td></td>
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<td></td>
<td></td>
<td>X</td>
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<td>X</td>
</tr>
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</table>
What is involved during the sessions?
The exercise-programme (P-SEC) being tested has been designed to improve your knee’s function by doing exercises with weights (see figure 1 below).

![Figure 1: Leg extensor machine that is found in the rehabilitation centre at RJAH NHS Trust. This machine will be used to deliver the P-SEC exercise-intervention protocol during the study.]

These types of exercises aim to improve the muscles that control your knee and improve its stability. You will be asked to lift weights with both legs and ‘catch’ the weight with one leg for a brief moment (no more than 2 seconds). You are asked to perform the exercises for a very short time to avoid causing pain but still be effective enough to cause changes in your muscles. The effort required during the exercises, will be within your ability. You will be asked to do these exercises over a period of 3 alternate days. You will be required to repeat the exercise for 12 times in one hour. You will have sufficient breaks in between for your own comfort. All of these exercises will be under supervision of the chief investigator of the study who is a professional physiotherapist with years of experience in this field.

In order to test the effects of this exercise-programme, a number of physical assessments need to be performed. These assessments will be done at 10-weeks, 2-weeks, 1-week before surgery, on the day of surgery and 6-weeks after surgery. During the assessment sessions, your ability to do normal daily tasks and muscle performance will be measured. Each session will take no longer than one and a half hours and will involve:

1. Completing 6 questionnaires to measure how well you feel you are progressing
2. Physical tests that will mostly be done in a seated position where measures of the strength in your knee muscles will be measured using surface electrodes by pushing for a brief moment against a stationary bar. We will also be looking at how quickly your leg muscles react by applying a brief and painless magnetic pulse. Last but not least your balance will be tested. This is the only part of the testing and assessments you will be asked to remain standing, for no longer than a few minutes on both legs and one at a time.

What are the possible benefits of taking part?
The style of the exercises being used in this study has been successful in other groups of people. Therefore, possible physical improvements in the muscles of the knee and its stability may occur following the exercise-programme (P-SEC).
What are the possible disadvantages of taking part?
You might not gain any extra benefit from the group you are in. You will have to make extra visits to the hospital on days that you would not normally have to attend, in order for us to complete the study. This will be arranged at your convenience.

What will happen when the study is completed?
The study might tell us if this ‘novel’ exercise-programme improves the knee’s physical ability during the period leading up to surgery in patients waiting for TKR. The results might also be written and published in medical/scientific journals to help other clinicians elsewhere. If you would like to know the results of the trial, we will provide you with a written report at the end of the study. This will describe the group results; your own personal data will not be published.

Will my taking part be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. In addition, all personal information collected about you during the trial will be kept strictly confidential and will be stored on our secure database as per Data Protection Act 1998. For the purposes of this study you will be identified by your initials and a unique study number. No identifiable information will be used or included when writing up the results of the study. In addition, none of your data will be passed onto any 3rd party or commercial companies. There is a possibility that anonymised data might be required to be released to a research regulatory authority, if requested. None of this data would be identified as belonging to you.

Who will know I am taking part in this study?
In addition to the researchers and clinicians involved in this study, with your consent, your GP will be informed that you have agreed to take part. You are free to discuss your inclusion in the study with anyone else you wish.

What information will be stored and why?
Your personal details (name, address, date of birth and hospital number), muscle performance, physical activity and questionnaire scores will all be kept on our secure, restricted access, password protected database. This database allows us to build a large resource of vital information to aid in future audits and improvements in clinical care. Any study documentation that identifies who you are will be stored in a lockable cabinet in a secure office. The study data will be destroyed 8 years following completion of the study as per Data Protection Act 1998.

Who has reviewed this study?
All research in the NHS is looked at by an independent group of people called a Research ethics committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by the South East Scotland Research Ethics Committee 01.
Expenses and payments
The study is part of a doctoral research programme that is currently being undertaken at the School of Health Sciences at Queen Margaret University (QMU) in Edinburgh, funded by the European Social Funds through the Endeavour Scholarship Scheme, Malta (endeavour.med@gov.mt). As you would be required to attend the hospital for treatment regardless of this study, you will not be allocated any expenses or payments. There are no allocated expenses available for the additional visits you are being asked to attend for. Transport will not be provided and you will have to see to that yourself. There is no concession being offered for parking whilst attending for the study’s sessions.

What happens if there is a problem?
In the highly unlikely event you are harmed in any way by taking part in this study, your statutory rights will not be affected. If you wish to make a complaint the normal NHS complaints procedure can be followed. This can be done through the PALS services using the details found at the end of this information sheet. If you suffer any adverse effects relating to any of the treatment you receive you can contact us or your GP directly or in the event of an emergency, you should attend A&E.

Further information and contact details
For more information, please contact us:
Ms Anna Maria Risso (Chief Investigator; Queen Margaret University Edinburgh) – tel: 0131 474 0000 or e-mail: arisso@qmu.ac.uk
Prof. Nigel Gleeson (Director of studies; Queen Margaret University, Edinburgh) – tel: 0131 474 0000 or e-mail: NGleeson@qmu.ac.uk
Teresa Jones (Research Manager; RIAH NHS Trust, Oswestry) – tel: 01691 404143 or e-mail: teresa.jones@rjah.nhs.uk
Prof. Tom Mercer (Independent advisor; Queen Margaret University, Edinburgh) – tel: 0131 474 0000 or e-mail: tmercer@qmu.ac.uk - ‘who is an experienced clinical researcher working at Queen Margaret University Edinburgh. Prof. Mercer is completely independent of this study but has the experience and expertise to offer you clarification on any queries that you might have about the procedures for this study.’

PALS
If you or your representative(s) have any questions regarding your patient rights as they relate to this study, you should contact your local Patient Advice and Liaison Services (PALS) on 01691 404606 (phone number), e-mail: PALS.office@rjah.nhs.uk

Thank you for reading this information leaflet. If you have problems or questions now or during your treatment, please do not hesitate to contact us.
Appendix F

Surgeon Contact Letter
Participant invitation letter V2 IRAS project number 198930

Dear Sir/Madam,

During your forthcoming appointment at the Robert Jones and Agnes Hunt NHS Trust hospital, you might be asked to participate in a research study entitled "NOVEL PRE-SURGERY EXERCISE CONDITIONING IN PATIENTS UNDERGOING A TOTAL KNEE REPLACEMENT (TKR)".

This request will depend on whether you will be a candidate for surgery or not following your appointment with the consultant. If you become a candidate for surgery and fulfil the criteria required to be able to participate in the study, you would be approached by one of the medical team and will be asked whether or not you would like to participate. Participation in the study is completely voluntary and you can refuse to at any time.

The study aims to investigate a new exercise programme delivered to one of your knees during the time period leading up to your TKR surgery. If you decide that you might like to take part, the first assessments for the study would be held on the same day as your appointment with the consultant. This minimises the time you'd need to spend helping with the research. The date and time for your appointment is specified within the attached letter to you from the hospital. The attached Patient Information Sheet (V3 dated 4/3/17), describes full information relating to the study and allows you to read about it prior to your consultation and to consider whether you might like to participate in the research.

Thank you very much for your time in reading this information. I will look forward to meeting you at your appointment and to answer any questions that you may have.

Thank you,

_______________________
Mr Peter Gallacher
Consultant Orthopaedic Surgeon
RJAH NHS Trust Hospital

V2 4.3.17
Appendix G

Participant Consent Form
Patient consent form v3 4.3.17 IRAS project number 198930

Centre Number: Study Number:

Participant Identification Number for this trial:

Project Title: Novel pre-surgery exercise-conditioning (P-SEC) in patients undergoing a total knee replacement (TKR).

Name of researcher: Ms Anna Maria Risso

If you consent, please write your initial in the box below next to each statement:

1. I confirm that I have read the patient information sheet dated 4.3.17 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the research team of Queen Margaret University and RJAH NHS Trust Hospital or other authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

5. I agree to my General Practitioner being informed of my participation in the study.

6. I agree to take part in the above study.

Name of Participant: ____________________________ Date: __________ Signature: ____________________________

Name of Person taking consent: ____________________________ Date: __________ Signature: ____________________________
Appendix H

Knee injury and Osteoarthritis Score Questionnaire (KOOS)
KOOS KNEE SURVEY

Today’s date: _____/_____/______ Date of birth: _____/_____/______

Name: ____________________________________________________

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities. Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the last week.

S1. Do you have swelling in your knee?
   Never ‡  Rarely ‡  Sometimes ‡  Often ‡  Always ‡

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
   Never ‡  Rarely ‡  Sometimes ‡  Often ‡  Always ‡

S3. Does your knee catch or hang up when moving?
   Never ‡  Rarely ‡  Sometimes ‡  Often ‡  Always ‡

S4. Can you straighten your knee fully?
   Always ‡  Often ‡  Sometimes ‡  Rarely ‡  Never ‡

S5. Can you bend your knee fully?
   Always ‡  Often ‡  Sometimes ‡  Rarely ‡  Never ‡

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?
   None ‡  Mild ‡  Moderate ‡  Severe ‡  Extreme ‡

S7. How severe is your knee stiffness after sitting, lying or resting later in the day?
   None ‡  Mild ‡  Moderate ‡  Severe ‡  Extreme ‡
### Pain

P1. How often do you experience knee pain?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

What amount of knee pain have you experienced the last week during the following activities?

P2. Twisting/pivoting on your knee

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

P3. Straightening knee fully

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
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<tbody>
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<td></td>
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</tbody>
</table>

P4. Bending knee fully

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tbody>
</table>

P5. Walking on flat surface

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

P6. Going up or down stairs

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

P7. At night while in bed

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

P8. Sitting or lying

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
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<tbody>
<tr>
<td></td>
<td></td>
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</table>

P9. Standing upright

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

### Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A1. Descending stairs

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

A2. Ascending stairs

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A3. Rising from sitting
   None  Mild  Moderate  Severe  Extreme
   None  Brad  

A4. Standing
   None  Mild  Moderate  Severe  Extreme
   None  Brad  

A5. Bending to floor/pick up an object
   None  Mild  Moderate  Severe  Extreme
   None  Brad  

A6. Walking on flat surface
   None  Mild  Moderate  Severe  Extreme
   None  Brad  

A7. Getting in/out of car
   None  Mild  Moderate  Severe  Extreme
   None  Brad  

A8. Going shopping
   None  Mild  Moderate  Severe  Extreme
   None  Brad  

A9. Putting on socks/stockings
   None  Mild  Moderate  Severe  Extreme
   None  Brad  

A10. Rising from bed
    None  Mild  Moderate  Severe  Extreme
    None  Brad  

A11. Taking off socks/stockings
     None  Mild  Moderate  Severe  Extreme
     None  Brad  

A12. Lying in bed (turning over, maintaining knee position)
     None  Mild  Moderate  Severe  Extreme
     None  Brad  

A13. Getting in/out of bath
     None  Mild  Moderate  Severe  Extreme
     None  Brad  

A14. Sitting
     None  Mild  Moderate  Severe  Extreme
     None  Brad  

A15. Getting on/off toilet
     None  Mild  Moderate  Severe  Extreme
     None  Brad  

APPENDIX H. KNEE INJURY AND OSTEOARTHRITIS SCORE QUESTIONNAIRE (KOOS)
For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

### A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### A17. Light domestic duties (cooking, dusting, etc)

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

### Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the last week due to your knee.

#### SP1. Squatting

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

#### SP2. Running

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
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<tbody>
<tr>
<td></td>
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</table>

#### SP3. Jumping

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

#### SP4. Twisting/pivoting on your injured knee

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

#### SP5. Kneeling

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
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<tbody>
<tr>
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</tbody>
</table>

### Quality of Life

#### Q1. How often are you aware of your knee problem?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily</th>
<th>Constantly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
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</tbody>
</table>

#### Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Mildly</th>
<th>Moderately</th>
<th>Severely</th>
<th>Totally</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### Q3. How much are you troubled with lack of confidence in your knee?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Mildly</th>
<th>Moderately</th>
<th>Severely</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### Q4. In general, how much difficulty do you have with your knee?

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Thank you very much for completing all the questions in this questionnaire.**
Appendix I

Oxford Knee Score Questionnaire (OKS)
Prior to completing the Questionnaire please complete the following:-

**Today's Date:**

| D | D | M | M | Y | Y | Y | Y |

On which side of your body is the affected joint, **for which you are receiving treatment**.

- Left  
- Right  
- Both  

If you said 'both', please complete the first questionnaire thinking about the **right side**. A second questionnaire, for the left side, will follow.
## PROBLEMS WITH YOUR KNEE

Tick (✓) one box for every question.

<table>
<thead>
<tr>
<th>Question</th>
<th>Pain Description</th>
<th>Pain Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. During the past 4 weeks...</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>How would you describe the pain you usually have from your knee?</td>
<td>Very mild</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>2. During the past 4 weeks...</td>
<td>No trouble at all</td>
<td>Very little trouble</td>
</tr>
<tr>
<td>Have you had any trouble with washing and drying yourself (all over)</td>
<td>Moderate trouble</td>
<td>Extreme difficulty</td>
</tr>
<tr>
<td>because of your knee?</td>
<td></td>
<td>Impossible to do</td>
</tr>
<tr>
<td>3. During the past 4 weeks...</td>
<td>No trouble at all</td>
<td>Very little trouble</td>
</tr>
<tr>
<td>Have you had any trouble getting in and out of a car or using public</td>
<td>Moderate trouble</td>
<td>Extreme difficulty</td>
</tr>
<tr>
<td>transport because of your knee? (whichever you would tend to use)</td>
<td></td>
<td>Impossible to do</td>
</tr>
<tr>
<td>4. During the past 4 weeks...</td>
<td>No pain/More than 30 minutes</td>
<td>16 to 30 minutes</td>
</tr>
<tr>
<td>For how long have you been able to walk before pain from your knee</td>
<td>5 to 15 minutes</td>
<td>Around the house only</td>
</tr>
<tr>
<td>becomes severe? (with or without a stick)</td>
<td>Not at all/pain severe when walking</td>
<td></td>
</tr>
<tr>
<td>5. During the past 4 weeks...</td>
<td>Not at all painful</td>
<td>Slightly painful</td>
</tr>
<tr>
<td>After a meal (sat at a table), how painful has it been for you to stand</td>
<td>Moderately painful</td>
<td>Very painful</td>
</tr>
<tr>
<td>up from a chair because of your knee?</td>
<td></td>
<td>Unbearable</td>
</tr>
<tr>
<td>6. During the past 4 weeks...</td>
<td>Rarely/never</td>
<td>Sometimes, or just at first</td>
</tr>
<tr>
<td>Have you been limping when walking, because of your knee?</td>
<td>Often, not just at first</td>
<td>Most of the time</td>
</tr>
<tr>
<td></td>
<td>All of the time</td>
<td></td>
</tr>
</tbody>
</table>
7. **During the past 4 weeks...**

*Could you kneel down and get up again afterwards?*

- Yes, easily
- With little difficulty
- With moderate difficulty
- With extreme difficulty
- No, impossible

8. **During the past 4 weeks...**

*Have you been troubled by pain from your knee in bed at night?*

- No nights
- Only 1 or 2 nights
- Some nights
- Most nights
- Every night

9. **During the past 4 weeks...**

*How much has pain from your knee interfered with your usual work (including housework)?*

- Not at all
- A little bit
- Moderately
- Greatly
- Totally

10. **During the past 4 weeks...**

*Have you felt that your knee might suddenly 'give way' or let you down?*

- Rarely/never
- Sometimes, or just at first
- Often, not just at first
- Most of the time
- All of the time

11. **During the past 4 weeks...**

*Could you do the household shopping on your own?*

- Yes, easily
- With little difficulty
- With moderate difficulty
- With extreme difficulty
- No, impossible

12. **During the past 4 weeks...**

*Could you walk down one flight of stairs?*

- Yes, easily
- With little difficulty
- With moderate difficulty
- With extreme difficulty
- No, impossible

Finally, please check back that you have answered each question.

Thank you very much.
Appendix J

The 36-Item Short Form Health Survey Questionnaire

(SF36v2™)
**SF-36 Health Survey**

**INSTRUCTIONS:** This survey asks your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

When complete, please return the questionnaire in the envelope provided.

1. **In general, would you say your health is?**
   (circle one)
   - Excellent ................................................................. 1
   - Very good ................................................................. 2
   - Good ................................................................. 3
   - Fair ................................................................. 4
   - Poor ................................................................. 5

2. **Compared to one year ago, how would you rate your health in general now?**
   (circle one)
   - Much better now than one year ago ................................................................. 1
   - Somewhat better than one year ago ................................................................. 2
   - About the same as one year ago ................................................................. 3
   - Somewhat worse than one year ago ................................................................. 4
   - Much worse now than one year ago ................................................................. 5
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (circle one number on each line)

<table>
<thead>
<tr>
<th>Activities</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects,</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>participating in strenuous sports.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate activities, such as moving a table,</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>pushing a vacuum cleaner, bowling or playing golf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bending, kneeling or stooping</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Walking half a mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Walking one hundred yards</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bathing or dressing yourself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (circle one number on each line)

<table>
<thead>
<tr>
<th>Problems</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Were limited in the kind of work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (circle one number on each line)

<table>
<thead>
<tr>
<th>Problems</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Didn’t do work or other activities as carefully as usual</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

<table>
<thead>
<tr>
<th>Interference Level</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>1</td>
</tr>
<tr>
<td>Slightly</td>
<td>2</td>
</tr>
<tr>
<td>Moderately</td>
<td>3</td>
</tr>
<tr>
<td>Quite a bit</td>
<td>4</td>
</tr>
<tr>
<td>Extremely</td>
<td>5</td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Very mild</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
</tr>
<tr>
<td>Very severe</td>
<td>6</td>
</tr>
</tbody>
</table>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Interference Level</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>1</td>
</tr>
<tr>
<td>A little bit</td>
<td>2</td>
</tr>
<tr>
<td>Moderately</td>
<td>3</td>
</tr>
<tr>
<td>Quite a bit</td>
<td>4</td>
</tr>
<tr>
<td>Extremely</td>
<td>5</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks.
For each question please give the one answer that comes closest to the way you have been feeling.
How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you feel full of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Have you been a very nervous person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Have you felt downhearted and low?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Have you been a happy person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Did you feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
(circle one)

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. How TRUE or FALSE is each of the following statements to you?
(circle one number on each line)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>I seem to get ill more easily than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Appendix K

Pain Self Efficacy Questionnaire (PSEQ)
PAIN SELF EFFICACY QUESTIONNAIRE (PSEQ)
M.K. Nicholas (1989)

NAME: __________________________________________  DATE: __________________

Please rate how confident you are that you can do the following things at present, despite the pain. To indicate your answer circle one of the numbers on the scale under each item, where 0 = not at all confident and 6 = completely confident.

For example:

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Completely confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remember, this questionnaire is not asking whether or not you have been doing these things, but rather how confident you are that you can do them at present, despite the pain.

1. I can enjoy things, despite the pain.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Completely confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Completely confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. I can socialise with my friends or family members as often as I used to do, despite the pain.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Completely confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. I can cope with my pain in most situations.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Completely confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Turn over
5. I can do some form of work, despite the pain. ("work" includes housework, paid and unpaid work).

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident</td>
<td>confident</td>
</tr>
</tbody>
</table>

6. I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite pain.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident</td>
<td>confident</td>
</tr>
</tbody>
</table>

7. I can cope with my pain without medication.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident</td>
<td>confident</td>
</tr>
</tbody>
</table>

8. I can still accomplish most of my goals in life, despite the pain.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident</td>
<td>confident</td>
</tr>
</tbody>
</table>

9. I can live a normal lifestyle, despite the pain.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident</td>
<td>confident</td>
</tr>
</tbody>
</table>

10. I can gradually become more active, despite the pain.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident</td>
<td>confident</td>
</tr>
</tbody>
</table>

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Appendix L

Performance Profile Activity

Questionnaire (PP)
PERFORMANCE PROFILE EXAMPLE

How does your injured limb feel at the present time compared with your non-injured limb, on each of the qualities you have listed?

Response scale  
(1) ‘extremely different to my non-injured limb’  
(10) ‘the same as my non-injured limb’
Appendix M

International Physical Activity Questionnaire (IPAQ)
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
(October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ
The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ
Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation
Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ
International collaboration on IPAQ is on-going and an International Physical Activity Prevalence Study is in progress. For further information see the IPAQ website.

More Information
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous and moderate activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?
   - Yes
   - No   → Skip to PART 2: TRANSPORTATION

The next questions are about all the physical activity you did in the last 7 days as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, heavy construction, or climbing up stairs as part of your work? Think about only those physical activities that you did for at least 10 minutes at a time.

   _____ days per week

   - No vigorous job-related physical activity   → Skip to question 4

3. How much time did you usually spend on one of those days doing vigorous physical activities as part of your work?

   _____ hours per day
   _____ minutes per day

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads as part of your work? Please do not include walking.

   _____ days per week

   - No moderate job-related physical activity   → Skip to question 6
5. How much time did you usually spend on one of those days doing moderate physical activities as part of your work?

_____ hours per day

_____ minutes per day

6. During the last 7 days, on how many days did you walk for at least 10 minutes at a time as part of your work? Please do not count any walking you did to travel to or from work.

_____ days per week

☐ No job-related walking  Skip to PART 2: TRANSPORTATION

7. How much time did you usually spend on one of those days walking as part of your work?

_____ hours per day

_____ minutes per day

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the last 7 days, on how many days did you travel in a motor vehicle like a train, bus, car, or tram?

_____ days per week

☐ No traveling in a motor vehicle  Skip to question 10

9. How much time did you usually spend on one of those days traveling in a train, bus, car, tram, or other kind of motor vehicle?

_____ hours per day

_____ minutes per day

Now think only about the bicycling and walking you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the last 7 days, on how many days did you bicycle for at least 10 minutes at a time to go from place to place?

_____ days per week

☐ No bicycling from place to place  Skip to question 12

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.
11. How much time did you usually spend on one of those days to bicycle from place to place?

____ hours per day
____ minutes per day

12. During the last 7 days, on how many days did you walk for at least 10 minutes at a time to go from place to place?

____ days per week

☐ No walking from place to place  ➞ Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

13. How much time did you usually spend on one of those days walking from place to place?

____ hours per day
____ minutes per day

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the last 7 days in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, chopping wood, shoveling snow, or digging in the garden or yard?

____ days per week

☐ No vigorous activity in garden or yard  ➞ Skip to question 16

15. How much time did you usually spend on one of those days doing vigorous physical activities in the garden or yard?

____ hours per day
____ minutes per day

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate activities like carrying light loads, sweeping, washing windows, and raking in the garden or yard?

____ days per week

☐ No moderate activity in garden or yard  ➞ Skip to question 18
17. How much time did you usually spend on one of those days doing moderate physical activities in the garden or yard?
   ____ hours per day
   ____ minutes per day

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate activities like carrying light loads, washing windows, scrubbing floors and sweeping inside your home?
   ____ days per week
   No moderate activity inside home → Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY

19. How much time did you usually spend on one of those days doing moderate physical activities inside your home?
   ____ hours per day
   ____ minutes per day

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the last 7 days solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the last 7 days, on how many days did you walk for at least 10 minutes at a time in your leisure time?
   ____ days per week
   No walking in leisure time → Skip to question 22

21. How much time did you usually spend on one of those days walking in your leisure time?
   ____ hours per day
   ____ minutes per day

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do vigorous physical activities like aerobics, running, fast bicycling, or fast swimming in your leisure time?
   ____ days per week
   No vigorous activity in leisure time → Skip to question 24

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.
23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ hours per day
_____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ days per week

☐ No moderate activity in leisure time  ➔ Skip to PART 5: TIME SPENT SITTING

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ hours per day
_____ minutes per day

**PART 5: TIME SPENT SITTING**

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend sitting **on a weekday**?

_____ hours per day
_____ minutes per day

27. During the **last 7 days**, how much time did you usually spend sitting **on a weekend day**?

_____ hours per day
_____ minutes per day

This is the end of the questionnaire, thank you for participating.
Appendix N

Intention to treat analyses (ITT)

A. Oxford Knee Score

Pre-surgical effects (T1 – T3)

For the ITT analysis, a 2-factor ANOVA with repeated measures for time was employed using data from all the randomised participants except for one participant whose baseline (T1 or T2) measures were missing (n = 45). ITT analysis revealed an overall non-significant group x time interaction (F(2,45) = 0.8; p > 0.05) (refer to Figure N.1) meaning that the mean OKS scores remained relatively constant for all three groups across the intervention period (T1 – T3). Further analysis of the 2-factor ANOVA results revealed a significant effect F(1,45) = 16; p < 0.05) for time interaction amongst the three groups, meaning that the mean OKS scores for the three groups varied across time but not between groups during the pre-surgery intervention period. A priori difference contrasts suggest that the extent of the significant interaction for time between baseline (mean OKS scores at T1 – T2) and immediately post-P-SEC intervention (T3) (F(2,42) = 17; p < 0.00) contributed to the overall significant time interaction.

Pre- and post-surgical effects (T1 – T5)

A 2-way factorial ANOVA for analysis showed a non-significant group x time interaction (F(5,105) = 1.5; p > 0.2) (refer to Figure N.1 (b)) meaning that the mean OKS scores remained relatively constant for all three groups across the pre- and post-surgical period (T1 – T5). Similar to pre-surgery, a significant effect for time (F(3,104) = 20.3;
Figure N.1: Intention to treat analysis for the Oxford Knee Score (OKS) questionnaire. Group means ±SD are plotted across: (a) Baseline (T1 – T2) and post P–SEC intervention (T3 - 1 week before surgery) (b) All assessment sessions (T1–T5). Key: P–SEC<sub>CONTRA</sub> (P–SEC delivered to the non–surgical leg); P–SEC<sub>IPSI</sub> (P–SEC delivered to the surgical leg); Control (current practice, no conditioning); The baseline measure T1 is taken as time 0 (12 weeks to surgery), T2 as time 10 weeks (2 weeks to surgery), T3 as time 11 weeks (1 week to surgery), T4 as week of surgery and T5 as 18 weeks from baseline assessment (T1) to 6 weeks post-surgery.
was observed, meaning that the mean OKS scores for the three groups varied across time but not between groups during the pre- and post-surgery period. A priori difference contrasts revealed that the main contributor to the overall significance was between the means of baseline (T1 and T2) scores and immediately post-P-SEC intervention (T3) \( F_{(2,42)} = 16.67; 44.90; 11.82; p = < 0.05 \), mean scores at baseline (T1 – T2 and T3) and 1 week after cessation of intervention (T4) \( F_{(2,42)} = 1.0; p = < 0.05 \) and mean scores at baseline (T1 – T2), post-P-SEC intervention (T3 and T4) and post-surgery (T5) \( F_{(2,42)} = 0.92; p = < 0.05 \) (refer to Figure N.1 (b)).
Appendix O

Pearson correlation analysis for changes between T2 – T3 (intervention period) amongst outcomes of neuromuscular and sensorimotor performance in both legs.
Table O.1: Pearson correlation (r) analysis for changes in mean scores across the P–SEC intervention period (T2 – T3) pre-surgery in the trained limb for indices of neuromuscular and sensorimotor outcomes from both intervention groups (P–SEC<sub>IPSI</sub> and P–SEC<sub>CONTRA</sub>). P–SEC<sub>IPSI</sub> refers to the values obtained from the trained Surgical leg, whilst P–SEC<sub>CONTRA</sub> are those values obtained from the trained Non–surgical leg. ** = Correlation is significant at the 0.01 level (2-tailed); * = Correlation is significant at the 0.05 level (2-tailed).  

**Key:** EMD<sub>RF</sub> - electromechanical delay for rectus femoris musculature (quadriceps); EMD<sub>VL</sub> - electromechanical delay for vastus lateralis musculature (quadriceps); FE - force error; RFD - rate of force development; PF - peak force.

<table>
<thead>
<tr>
<th>T2–T3 Differences</th>
<th>EMD&lt;sub&gt;RF&lt;/sub&gt; (P–SEC&lt;sub&gt;IPSI&lt;/sub&gt;)</th>
<th>EMD&lt;sub&gt;RF&lt;/sub&gt; (P–SEC&lt;sub&gt;CONTRA&lt;/sub&gt;)</th>
<th>EMD&lt;sub&gt;VL&lt;/sub&gt; (P–SEC&lt;sub&gt;IPSI&lt;/sub&gt;)</th>
<th>EMD&lt;sub&gt;VL&lt;/sub&gt; (P–SEC&lt;sub&gt;CONTRA&lt;/sub&gt;)</th>
<th>FE (P–SEC&lt;sub&gt;IPSI&lt;/sub&gt;)</th>
<th>FE (P–SEC&lt;sub&gt;CONTRA&lt;/sub&gt;)</th>
<th>PF (P–SEC&lt;sub&gt;IPSI&lt;/sub&gt;)</th>
<th>PF (P–SEC&lt;sub&gt;CONTRA&lt;/sub&gt;)</th>
<th>RFD (P–SEC&lt;sub&gt;IPSI&lt;/sub&gt;)</th>
<th>RFD (P–SEC&lt;sub&gt;CONTRA&lt;/sub&gt;)</th>
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<tbody>
<tr>
<td>EMD&lt;sub&gt;RF&lt;/sub&gt;</td>
<td>Pearson Correlation</td>
<td>0.268</td>
<td>0.993**</td>
<td>0.239</td>
<td>0.843**</td>
<td>0.111</td>
<td>-0.186</td>
<td>-0.171</td>
<td>-0.117</td>
<td>-0.225</td>
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<tr>
<td>P–SEC&lt;sub&gt;IPSI&lt;/sub&gt;</td>
<td>Sig. (2-tailed)</td>
<td>0.159</td>
<td>0.000</td>
<td>0.211</td>
<td>0.000</td>
<td>0.565</td>
<td>0.334</td>
<td>0.374</td>
<td>0.546</td>
<td>0.241</td>
</tr>
<tr>
<td>EMD&lt;sub&gt;RF&lt;/sub&gt;</td>
<td>Pearson Correlation</td>
<td>0.268</td>
<td>0.296</td>
<td>0.989**</td>
<td>0.139</td>
<td>0.823**</td>
<td>-0.440*</td>
<td>-0.070</td>
<td>-0.458*</td>
<td>-0.108</td>
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<tr>
<td>P–SEC&lt;sub&gt;CONTRA&lt;/sub&gt;</td>
<td>Sig. (2-tailed)</td>
<td>0.159</td>
<td>0.119</td>
<td>0.000</td>
<td>0.471</td>
<td>0.000</td>
<td>0.017</td>
<td>0.717</td>
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<td>0.993**</td>
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<td>0.836**</td>
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<td>-0.183</td>
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<td>1</td>
<td>0.157</td>
<td>0.000</td>
<td>0.517</td>
<td>0.284</td>
<td>0.342</td>
<td>0.472</td>
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<td>EMD&lt;sub&gt;VL&lt;/sub&gt;</td>
<td>Pearson Correlation</td>
<td>0.239</td>
<td>0.989**</td>
<td>0.270</td>
<td>0.115</td>
<td>0.838**</td>
<td>-0.430*</td>
<td>-0.110</td>
<td>-0.440*</td>
<td>-0.090</td>
</tr>
<tr>
<td>P–SEC&lt;sub&gt;CONTRA&lt;/sub&gt;</td>
<td>Sig. (2-tailed)</td>
<td>0.211</td>
<td>0.000</td>
<td>0.157</td>
<td>1</td>
<td>0.551</td>
<td>0.000</td>
<td>0.020</td>
<td>0.569</td>
<td>0.017</td>
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<td>0.843**</td>
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<td>0.836**</td>
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<td>-0.209</td>
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<td>0.000</td>
<td>0.551</td>
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<td>0.577</td>
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<td>0.567</td>
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</tr>
<tr>
<td>FE</td>
<td>Pearson Correlation</td>
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<td>0.838**</td>
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<td>0.517</td>
<td>0.000</td>
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<td>1</td>
<td>0.517</td>
<td>0.826</td>
<td>0.551</td>
</tr>
<tr>
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<td>-0.206</td>
<td>-0.430*</td>
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<td>-0.125</td>
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<td>0.904**</td>
<td>-0.002</td>
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<td>0.017</td>
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<td>0.020</td>
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<td>0.517</td>
<td>1</td>
<td>0.680</td>
<td>0.000</td>
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## Table O.1 – Continued from previous page

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<tr>
<td>PF</td>
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<td>-0.171</td>
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<td>-0.110</td>
<td>-0.111</td>
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<td>0.374</td>
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<td>0.567</td>
<td>0.826</td>
<td>0.680</td>
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<td>0.100</td>
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<td>-0.139</td>
<td>-0.440*</td>
<td>0.180</td>
<td>-0.116</td>
<td>0.904**</td>
<td>-0.037</td>
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<td>0.017</td>
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<td>0.000</td>
<td>0.851</td>
<td>0.812</td>
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<td>-0.225</td>
<td>0.108</td>
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<td>-0.289</td>
<td>0.100</td>
<td>-0.002</td>
<td>0.739**</td>
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<td>Sig. (2-tailed)</td>
<td>0.241</td>
<td>0.576</td>
<td>0.237</td>
<td>0.644</td>
<td>0.277</td>
<td>0.605</td>
<td>0.994</td>
<td>0.000</td>
<td>0.812</td>
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Appendix P

Correlation analysis for patient reported outcomes (PROs) against neuromuscular (EMD, PF and RFD) and sensorimotor (FE) outcomes
Table P.1: Pearson correlation (r) analysis for changes in mean scores observed across the P–SEC intervention period (T2 – T3) pre-surgery for both intervention groups (P–SEC_{IPSI} and P–SEC_{CONTRA}). Comparisons between patient perceived outcomes (PROs) against neuromuscular (EMD, PF, RFD) and sensorimotor (FE) outcomes are reported. P–SEC_{IPSI} refers to the values obtained from the trained Surgical leg, whilst P–SEC_{CONTRA} are those values obtained from the trained Non–surgical leg. * = Correlation is significant at the 0.05 level (2-tailed). Key: EMD_{RF} - electromechanical delay for rectus femoris musculature (quadriceps); EMD_{VL} - electromechanical delay for vastus lateralis musculature (quadriceps); FE - force error; RFD - rate of force development; PF - peak force; OKS - Oxford Knee Score; KOOS - The Knee Injury and Osteoarthritis questionnaire; ADLs - Activities of Daily Living; QoL - Quality of Life; Symp - Symptoms; PSEQ - Pain Self Efficacy Questionnaire; PP - Performance Profile; IPAQ - International Physical Activity Questionnaire; SF-36v2™ - 36 Short Form health survey questionnaire version 2; PC - Physical Component; MC - Mental Component.

<table>
<thead>
<tr>
<th>T2–T3 Mean Difference</th>
<th>EMD_{RF}</th>
<th>EMD_{VL}</th>
<th>FE</th>
<th>PF</th>
<th>RFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>OKS Pearson Correlation</td>
<td>-0.248</td>
<td>-0.044</td>
<td>-0.226</td>
<td>-0.040</td>
<td>-0.336</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.221</td>
<td>0.832</td>
<td>0.266</td>
<td>0.846</td>
<td>0.094</td>
</tr>
<tr>
<td>KOOSADLs Pearson Correlation</td>
<td>-0.087</td>
<td>-0.116</td>
<td>-0.044</td>
<td>-0.099</td>
<td>-0.015</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.672</td>
<td>0.573</td>
<td>0.831</td>
<td>0.630</td>
<td>0.943</td>
</tr>
<tr>
<td>KOOSPain Pearson Correlation</td>
<td>0.090</td>
<td>0.078</td>
<td>0.073</td>
<td>0.036</td>
<td>0.013</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.656</td>
<td>0.699</td>
<td>0.719</td>
<td>0.859</td>
<td>0.947</td>
</tr>
<tr>
<td>KOOSQoL Pearson Correlation</td>
<td>-0.404*</td>
<td>-0.038</td>
<td>-0.394*</td>
<td>-0.038</td>
<td>-0.335</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.037</td>
<td>0.850</td>
<td>0.042</td>
<td>0.852</td>
<td>0.088</td>
</tr>
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<td>KOOSSymp Pearson Correlation</td>
<td>-0.256</td>
<td>0.061</td>
<td>-0.227</td>
<td>0.026</td>
<td>-0.167</td>
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<td>Sig. (2-tailed)</td>
<td>0.197</td>
<td>0.763</td>
<td>0.256</td>
<td>0.897</td>
<td>0.406</td>
</tr>
<tr>
<td>KOOSSports Pearson Correlation</td>
<td>-0.177</td>
<td>-0.114</td>
<td>-0.138</td>
<td>-0.147</td>
<td>-0.041</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.443</td>
<td>0.624</td>
<td>0.550</td>
<td>0.526</td>
<td>0.859</td>
</tr>
<tr>
<td>PSEQ Pearson Correlation</td>
<td>0.148</td>
<td>-0.015</td>
<td>0.119</td>
<td>-0.019</td>
<td>0.201</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.469</td>
<td>0.942</td>
<td>0.563</td>
<td>0.926</td>
<td>0.324</td>
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<thead>
<tr>
<th>T2-T3 Mean Difference</th>
<th>EMD_{RF}</th>
<th>EMD_{RF}</th>
<th>EMD_{VL}</th>
<th>EMD_{VL}</th>
<th>FE</th>
<th>FE</th>
<th>PF</th>
<th>PF</th>
<th>RFD</th>
<th>RFD</th>
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<tbody>
<tr>
<td>IPSI</td>
<td>0.132</td>
<td>0.343</td>
<td>0.165</td>
<td>0.368</td>
<td>-0.011</td>
<td>0.320</td>
<td>0.009</td>
<td>-0.261</td>
<td>0.013</td>
<td>-0.101</td>
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<tr>
<td>CONTRA</td>
<td>0.520</td>
<td>0.086</td>
<td>0.420</td>
<td>0.064</td>
<td>0.959</td>
<td>0.111</td>
<td>0.964</td>
<td>0.197</td>
<td>0.950</td>
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<td>IPSI</td>
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<td>-0.228</td>
<td>-0.112</td>
<td>-0.178</td>
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<td>0.099</td>
<td>-0.064</td>
<td>0.113</td>
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<td>0.939</td>
<td>0.626</td>
<td>0.629</td>
<td>0.756</td>
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<td>IPSI</td>
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<td>0.132</td>
<td>-0.342</td>
<td>-0.070</td>
<td>-0.353</td>
<td>-0.105</td>
<td>-0.287</td>
<td>-0.268</td>
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<td>0.195</td>
<td>0.195</td>
<td>0.797</td>
<td>0.180</td>
<td>0.699</td>
<td>0.281</td>
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<td>0.135</td>
<td>0.138</td>
<td>-0.457</td>
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<td>0.911</td>
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<td>0.365</td>
<td>0.619</td>
<td>0.611</td>
<td>0.075</td>
<td>0.630</td>
<td>0.496</td>
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Appendix Q

Results from analysis using Shapiro-Wilk test for normal distribution

Table Q.1: Shapiro-Wilk test results for Neuromuscular and Sensorimotor data across the five assessment points (T1-T5). Data is presented as p value statistic ($p < 0.05 = \text{significant - data not normally distributed}$).

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<tr>
<th>Objective outcome</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
</tr>
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<tbody>
<tr>
<td>EMD$_{RF}$</td>
<td>0.39</td>
<td>0.40</td>
<td>0.67</td>
<td>0.61</td>
<td>0.86</td>
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<tr>
<td>EMD$_{VL}$</td>
<td>0.14</td>
<td>0.14</td>
<td>0.78</td>
<td>0.84</td>
<td>0.05</td>
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<tr>
<td>RFD</td>
<td>0.23</td>
<td>0.98</td>
<td>0.31</td>
<td>0.07</td>
<td>0.17</td>
</tr>
<tr>
<td>PF</td>
<td>0.77</td>
<td>0.35</td>
<td>0.75</td>
<td>0.69</td>
<td>0.23</td>
</tr>
<tr>
<td>FE</td>
<td>0.05</td>
<td>0.12</td>
<td>0.08</td>
<td>0.15</td>
<td>0.21</td>
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Table Q.2: Shapiro-Wilk test results for all patient reported outcomes (PRO) scores across the five assessment points (T1-T5). Data is presented as $p$ value statistic ($p < 0.05 = $ significant - data not normally distributed).

<table>
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<tr>
<th>Questionnaire (PRO)</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
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<tr>
<td>OKS</td>
<td>0.05</td>
<td>0.13</td>
<td>0.56</td>
<td>0.49</td>
<td>0.99</td>
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<td>KOOSADLs</td>
<td>0.31</td>
<td>0.49</td>
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<td>0.68</td>
<td>0.61</td>
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<tr>
<td>KOOSPain</td>
<td>0.22</td>
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<td>0.17</td>
<td>0.13</td>
<td>0.63</td>
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<td>0.63</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
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<td>0.54</td>
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<td>0.66</td>
<td>0.64</td>
<td>0.98</td>
<td>0.63</td>
<td>0.86</td>
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