The development of clinical interventions for knee injury management, using a novel cooling, heating, and compression device

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The development of clinical interventions for knee injury management, using a novel cooling, heating, and compression device

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Abstract

Background: Cryotherapy and compression are advised within guidelines for injury management. However, optimum methods of applying cryotherapy have not been defined and authors have advocated a 'personalised' intervention approach. With a novel cooling, heating, and compression device (CHCD) offering control of temperature and compression, it is possible to explore the effect of a range of interventions for knee injury management.

Methods & Results: Study 1 explored four 20-minute CHCD interventions on skin surface temperature (T_{sk}), oxygenation, thermal sensation/comfort, muscle strength, pressure pain threshold (PPT) and joint position sense (JPS), in a randomised crossover design on 26 healthy male subjects. The four interventions were: *1) 10 °C & 50 mmHg 2) 15 °C & 50 mmHg 3) 10 °C & 32 mmHg 4) alternating 10-40 °C & 25-50 mmHg*. Interventions set at 10 °C achieved T_{sk} within the therapeutic range. Despite no significant differences in T_{sk} between the two compression settings, intervention 1 was perceived to be the coldest.

Study 2 investigated the effects of two 20-minute interventions, *A) wetted ice* and *B) CHCD (10 °C & 50 mmHg)*, on quadriceps strength, PPT, JPS and participant-perceived pain, in 10 healthy participants with experimentally induced knee pain. Complete pain relief (≥93% reduction) was achieved immediately post-cooling in 7 participants for the CHCD and in 4 participants for ice. Significant increases in PPT were found following the CHCD, up to 20-minutes post-cooling. Ice reduced strength by 13% immediately post-cooling, however the CHCD had a negligible effect on strength post-cooling (+0.3%). Significant increases were found in range of motion in the coronal plane following ice, indicating increased instability.

Study 3 investigated the effects of *A) wetted ice* and *B) CHCD (10 °C & 50 mmHg)*, on participant-reported pain, swelling and stability, through a series of 11 single-case experiments, using an alternating treatment design. The CHCD intervention achieved clinically important changes more frequently than the ice intervention for patient-reported pain (by 9%), swelling (by 21%) and patient-reported stability (by 3%).

Conclusion: Compressive cryotherapy using the CHCD at 10 °C with 50 mmHg, appeared more beneficial for the majority (82%) of individuals with knee injuries, for reducing swelling and pain, compared to ice. Targeted compressive cryotherapy, using the novel CHCD, may contribute to greater clinical management of knee injuries.

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Glossary of Abbreviations and Definitions

ACL - Anterior Cruciate Ligament

ACPSM - Association of Chartered Physiotherapists in Sports and Exercise Medicine

ASIS - Anterior Superior iliac Spine

BMI – Body Mass Index

CAST – Calibrated Anatomical Systems Technique

CI – Confidence Interval

CCM - Chronic care model

CHCD – Cooling, Heating and Compression Device

CWI – Cold Water Immersion

FDA - Food and Drug Administration

GRADE - Grading of Recommendations, Assessment, Development and Evaluation

ICC – Intraclass/Interclass Correlation Coefficient

JPS – Joint Position Sense

KTP – Knowledge Transfer Partnership

LCL - Lateral Collateral Ligament

LM - Lateral Meniscus

MCIC – Minimal Clinically Important Change

MCL - Medial Collateral Ligament

MDC – Minimal Detectable Change

MHRA - Medicines and Healthcare products Regulatory Agency

MM – Medial Meniscus

MMU - Manchester Metropolitan University

MRI - Magnetic Resonance Imaging

NCAA - National Collegiate Athletic Association

NCV – Nerve Conduction Velocity

NHS – National Health Service

NICE – National Institute for Health Care Excellence

NPRS – Numeric Pain Rating Scale

OA – Osteoarthritis

PCL - Posterior Cruciate Ligament

PPT – Pressure Pain Threshold

PEACE & LOVE - Protection, Elevation, Avoid Anti-Inflammatories, Compression, Education & Load, Optimism, Vascularisation, Exercise).

POLICE – Protection, Optimal Loading, Ice, Compression, Elevation

PRICE – Protection, Rest, Ice, Compression, Elevation

PSIS - Posterior Superior Iliac Spine

QTM - Qualisys Track Manager

ROI – Region of Interest

ROM – Range of Motion

SD – Standard Deviation

SKB – Small Knee Bend

SmO_2 - Muscle Oxygenation Saturation

TENS - Transcutaneous Electrical Nerve Stimulation

TI – Thermal Imaging

TISEM - Thermographic Imaging in Sports and Exercise Medicine

T_{sk} – Skin Surface Temperature

T_{im} – Intramuscular Temperature

UCLan - University of Central Lancashire

WBC – Whole Body Cryotherapy

Chapter 1: Introduction

This chapter will briefly introduce the research topic, highlighting the rationale for the research undertaken. This introductory chapter also outlines the aims, objectives, and structure of the thesis.

1.1 Background

Knee injuries are a significant burden to people of all ages in the UK (Moore *et al.*, 2011) and worldwide (Swenson *et al.*, 2013), with the knee being one of the most common sites of injury in sport (Arendt and Dick, 1995; Bahr, Kannus and van Mechelen, 2003; López-Valenciano *et al.*, 2020). In addition, 48% of knee injuries in sport are classed as 'severe', meaning they lead to at least 10 consecutive days of restricted/no participation (Agel *et al.*, 2007). For this reason, the knee was the focus of the studies within this thesis.

The Association of Chartered Physiotherapists in Sports and Exercise Medicine (ACPSM) published the '**PRICE**' (Protection, Rest, Ice, Compression and Elevation) guidelines for acute soft tissue injury management in 2011 (Bleakley *et al.*, 2011). These guidelines have since been updated to '**POLICE'** (Protection, Optimal Loading, Ice, Compression, Elevation) (Bleakley, Glasgow and MacAuley, 2012). Cryotherapy and compression are both advised within clinical guidelines and are often applied simultaneously in clinical practice (Alexander *et al.*, 2021a). However, the complex interactions between temperature, compression and dose time/frequency are yet to be understood and optimal clinical protocols have not been defined (Selfe *et al.*, 2020). A number of factors remain unknown in regard to the optimum method of applying cryotherapy (Figure 1.1).

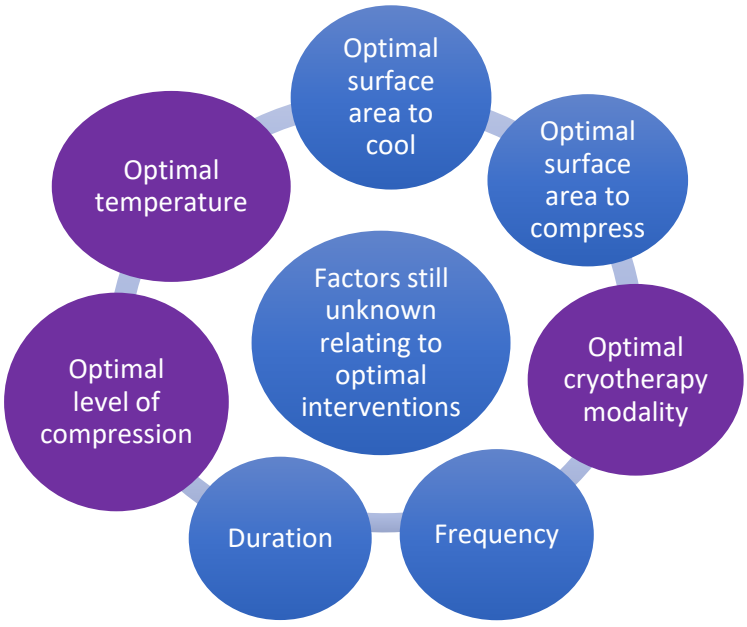


Figure 1.1: The many unknowns relating to optimal interventions

A recent review by Alexander, Allan & Rhodes (2021) highlighted that optimal cryotherapy interventions are important in sport to ensure a competitive advantage for performance and to maximise the physiological effects which are desirable for injury management. The consequence of sub-optimal clinical protocols could have many significant consequences. For example, in professional football, the cost of a premier league first team player being injured for 1 month can range from £100,000 to £2,000,000. Injuries also have a negative effect on team performance as player availability has a strong correlation with team success (Ekstrand, Hägglund and Waldén, 2011; López-Valenciano *et al.*, 2020).

In addition to the uncertainty regarding optimal applications of cryotherapy, Dubois and Esculier (2019) have recently questioned the efficacy of cryotherapy for injury management and introduced the acronym '**PEACE & LOVE'** (Protection, Elevation, Avoid Anti-Inflammatories, Compression, Education & Load, Optimism, Vascularisation, Exercise). This new acronym was proposed to take into account the sub-acute and chronic stages of tissue healing, with the previous acronyms (**PRICE** and **POLICE**) solely focusing on acute injury phases. The authors state that cryotherapy was removed due to a lack of high-quality evidence on the efficacy for treating soft tissue injury. Despite acknowledging the evidence supporting the analgesic effect, the authors suggest there may be potential disruption to tissue repair and collagen synthesis following ice. This has led to discussions amongst clinicians suggesting that cryotherapy may have a potential negative impact in a sports healthcare setting (Long and Jutte, 2020). However, as the editorial blog by Dubois & Esculier (2019) is yet to be supported by empirical data, further research is required to support or refute this proposed change in guidelines. Long and Jutte (2020) highlight that the literature supporting the argument expressed by Dubois & Esculier (2019) to remove cryotherapy is based upon studies that lack credibility and adequate study designs.

Similarly, to acute injury management, a lack of clarity for optimal clinical protocols also exists for chronic knee injuries and conditions. The use of local cooling or heating is also advocated as a self-management tool for chronic knee conditions such as knee osteoarthritis (OA) by the National Institute for Health Care Excellence (NICE) (NICE, 2014; NICE, 2020) (Figure 1.2). Knee OA is a condition contributing to reduced function, quality of life and substantial socioeconomic burden, mainly because of pain (Neogi, 2013). Currently, the lifetime risk of developing knee OA is approximately 45% (Murphy *et al.*, 2008), which is likely to rise due to an aging population. London, Miller and Block (2011)

identify that approximately 3.6 million Americans are in a knee OA treatment gap as they are unwilling to undergo invasive knee surgery. This common knee OA treatment gap can extend for as long as 20 years. Younger OA patients are faced with a treatment gap throughout the majority of their adult life (London, Miller and Block, 2011). With this significant predicted prevalence of the population suffering from knee pain, the ability to self-administer treatments to alleviate symptoms will help to fill a treatment gap in which a patient may potentially suffer a prolonged period of debilitating pain and reduced quality of life (London, Miller and Block, 2011). The ability to self-administer interventions would also reduce the increasing demand on healthcare (London, Miller and Block, 2011).

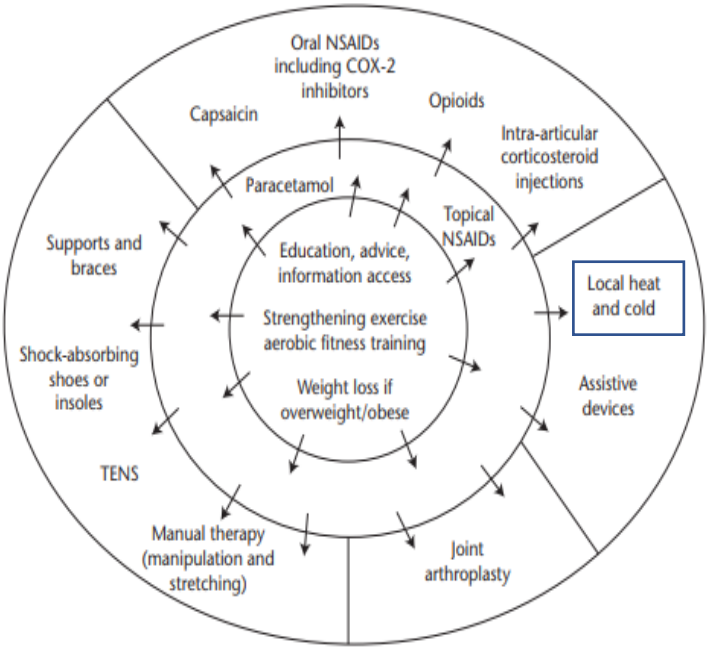


Figure 1.2: NICE guidance for self-management of knee osteoarthritis (NICE, 2014)

As injuries vary, authors have highlighted that a 'panacea' or 'one size fits all' clinical cooling and compression protocol is unlikely to exist for soft tissue injury management across the entire injury spectrum (Bleakley *et al.*, 2011; Bleakley, Glasgow and MacAuley, 2012). Additionally, an individual's response to thermal stress can differ dependent on several physiological factors (Figure 1.3). Fu et al. (2016) outlined physiological characteristics such as gender, skin type and adiposity, which affect thermal response to an environment. For this reason, there is a growing realisation that a 'personalised' intervention approach may be more effective (Bleakley *et al.*, 2011; Alexander *et al.*, 2020; Selfe *et al.*, 2020). The importance of individualising local cryotherapy interventions was stressed by Alexander et al. (2020) after investigating differences in the cooling ability of cryotherapy modalities in a rugby union population, including players of varied positions and physical characteristics. Significant variations amongst skin surface

temperature (T_{sk}) were reported between rugby playing positions (Alexander *et al.*, 2020), with 'forwards' demonstrating lower T_{sk} compared to 'backs'. Typically, 'forwards' present with higher body mass and adipose tissue than the 'backs', due to the nature of their position requiring high levels of force-generation within a scrum (La Monica *et al.*, 2016; Alexander *et al.*, 2020). As indicated in Figure 1.3, adipose tissue is a factor affecting an individual's response to thermal stress and studies have shown the effect of adipose tissue on deeper tissues, as the adipose tissue insulates the deeper tissues and has a higher the resistance to heat transfer than normal skin and muscle (Zemke *et al.*, 1998). However, the findings reported in Alexander et al. (2020) highlight that increased adipose tissue also affects superficial T_{sk} responses.

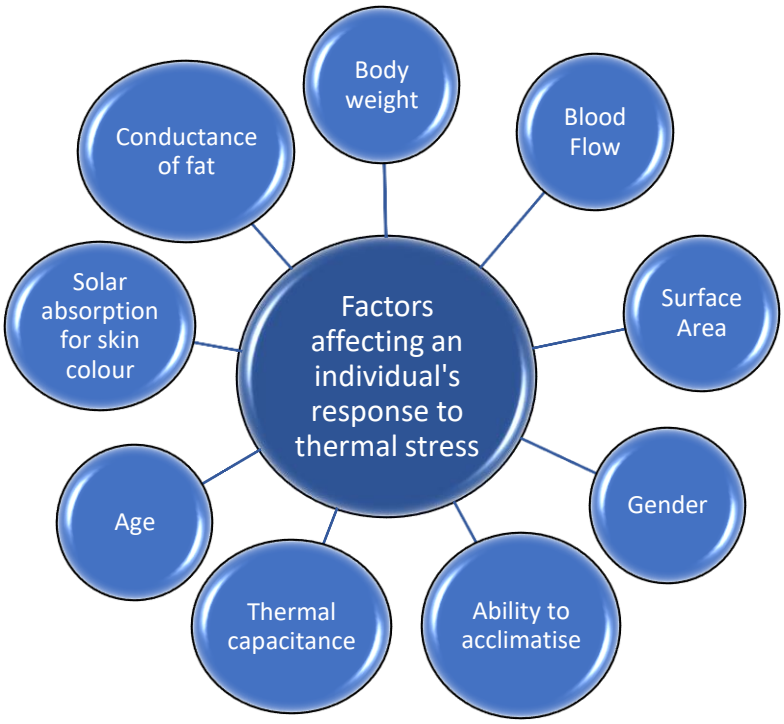


Figure 1.3: Physiological factors affecting thermal response (Fu et al., 2016)

Long and Jutte (2020) also highlighted the importance of considering the goal of the intervention in order to establish which therapeutic modality may be most effective. There is a growing research interest into the effects of cryotherapy on proprioception and more specifically joint position sense. Studies have demonstrated a decrease in dynamic stability following 20-minute ice interventions (Uchio *et al.*, 2003; Surenkok *et al.*, 2008; Alexander *et al.*, 2016; Alexander *et al.*, 2018). It is well accepted in literature that cryotherapy can significantly reduce muscle strength (Ruiz *et al.*, 1993; Rhodes and Alexander, 2018; Alexander *et al.*, 2021b) and authors have expressed caution about

players returning to play immediately after cryotherapy due to the increased risk of re-injury (Costello and Donnelly, 2010; Bleakley, Costello and Glasgow, 2012; Alexander *et al.*, 2016; Alexander *et al.*, 2018).

Therefore, it is important to consider the aim of the cooling intervention prior to the application. Bleakley, Costello and Glasgow (2012) advised that shorter applications of cryotherapy, as well as a warm-up prior to returning to weight bearing activity, could minimise the increased risk of injury post cryotherapy. More recently, Alexander et al. (2021b) highlighted that a more targeted cryotherapy approach, may minimise the adverse effects to muscle strength, whilst achieving the desired T_{sk}. This highlights that more research is required to establish the relationship between dosages of cryotherapy and the adverse effects reported following traditional cryotherapy interventions.

1.2 Thesis Rationale & Company Involvement

The ideal therapeutic range for T_{sk} of between 10 to 15 °C, is recognised in the literature due to known physiological responses to specific skin and tissue temperatures (Rivenburgh, 1992; Kennet *et al.*, 2007). However, with traditional cryotherapy modalities such as ice, it is not possible to precisely control and maintain temperatures applied to the skin surface. As discussed, optimal combinations of time, temperature and compression have not been defined. The limited accessibility to technology which can control temperatures is likely to have been a contributing factor to the lack of research establishing the dose-response relationships, in order to define optimal cryotherapy applications. A scoping review by Alexander et al. (2021a) highlighted that defining contemporary protocols of simultaneous cryotherapy and compression applications is required to enhance understanding in current practice of compressive cryotherapy modalities.

With the advancement in technology, Swellaway Ltd developed a cooling, heating, and compression device (CHCD). One of the unique features of the CHCD is the use of Peltier cell technology which facilitates the ability to control and maintain temperature, pressure, and time parameters. Peltier cell technology is used in consumer products such as refrigerators and thermoelectric air conditioners or coolers. Peltier technology is currently used in healthcare for Quantitative Sensory Testing (QST) but purely for testing

purposes rather than applying therapy (Sermeus *et al.*, 2016). This is the first device in the UK to use Peltier technology for cooling and heating for therapeutic purposes.

A technical evaluation of an early prototype of the CHCD was carried out at the University of Central Lancashire (UCLan) in 2017 (Selfe *et al.*, 2017), which led to an application to Innovate UK for a Knowledge Transfer Partnership (KTP) to support further research and development. A 3-year KTP was successfully granted by Innovate UK in 2018 (KTP11103), supporting the tripartite collaboration between Swellaway Ltd, UCLan and Manchester Metropolitan University (MMU). This is a unique Innovate UK KTP partnership as there is typically one commercial partner and one university partner. The aim of the KTP was to develop human use protocols based on a robust evidence base, to enhance usability, and inform purchasing of Swellaway. Despite the KTP and PhD focussing on the same research projects, it is important to note that the aims of the KTP and the PhD were separate; the thesis did not have a commercial focus. Some tasks carried out during the KTP were however driven by commercial influences to maintain relevance to the evolution of the product and marketing campaigns. Although the device developed by Swellaway Ltd was used within studies in this thesis, it merely facilitated the investigation of optimal combinations of temperature, compression, and time to establish new knowledge in this field. It is also important to note that prototypes were used for all studies outlined in this thesis as the device was not commercially available during data collection and analysis.

From a clinical perspective, the ability to control and maintain these parameters allows healthcare professionals, athletes, and patients to tailor their therapeutic intervention to desired settings, depending on the aim of the treatment. From a research perspective, the ability to control and maintain these parameters facilitates further exploration into optimal interventions, in order to inform clinical practice.

1.3 Contributions to Knowledge

As previously discussed, despite the knee being one of the most common sites of injury in sport, there is a significant lack of evidence surrounding the use of cooling, heating, and compression for knee injury management. A number of factors relating to optimal clinical interventions for different soft tissue injuries are still unknown (Figure 1.1).

The CHCD offers full control on temperature (from 6 to 40 °C), compression (from 20 to 75 mmHg) and time (from 1 to 20 minutes), enabling detailed exploration into the unknowns highlighted in purple in Figure 1.1. The device provides the opportunity to investigate a range of parameters of temperature, compression and time applied simultaneously to identify optimal combinations of temperature and compression, to inform the development of evidence-based clinical interventions for knee injury management. There is a significant lack of knowledge surrounding the use of contrast therapy for injury management. Therapists have not fully explored this treatment option possibly due to accessibility. In turn, the limited literature available has used either water immersion or ice packs and hot packs (hydrocollator packs) to provide and explore contrast therapy. The novel CHCD provides an opportunity to apply, control and assess the effects of contrast therapy on the knee joint, to provide a greater understanding of the effectiveness of contrast therapy for knee injury management. The development of these evidence-based clinical interventions is likely to have clinical, academic, and commercial impact.

1.4 Aims, Objectives & Hypotheses

Aim

The aim of this thesis is to explore parameters of temperature and compression, to inform the development of evidence-based interventions, using the CHCD.

Objectives:

- **Objective 1**: To identify whether the CHCD can achieve and control skin surface temperatures within the therapeutic range (10-15 °C T_{sk}), whilst minimising physiological adverse effects, on healthy participants, through a series of validation studies
- **Objective 2**: Collate the current consensus of the use of contrast therapy in soft tissue injury management and post-exercise recovery, through the creation of a scoping review and publish these findings in a peer-review journal
- **Objective 3:** To explore parameters of temperature and compression to inform the development of optimal interventions on healthy participants with experimentally induced knee pain, using the CHCD
- **Objective 4:** To explore relevant parameters of temperature and compression to inform the development of optimal interventions to use for knee injury management, using the CHCD, through a series of single-case experiments

These objectives will be achieved through three intervention studies exploring a range of outcome measures on three participant groups:

1) Healthy participants (Chapter 4)
2) Healthy participants with experimentally induced knee pain (Chapter 5)
3) Participants with knee injuries and degenerative knee conditions (Chapter 6)

This thesis uses a number of quantitative methods, through biomechanical analysis, clinical questionnaires and analysis of clinical signs and symptoms. Tables 1.1-1.3 detail the hypotheses for each outcome measure in each intervention study.

Study 1: An exploration of targeted cryotherapy interventions using a cooling, heating, and compression device on healthy male participants

Table 1.1: A summary of the hypotheses for Study 1

Outcome Measure	**Null Hypothesis (H_0) and hypothesis (H_1)**	**Statistical Analysis**
Skin Surface Temperature (T_{sk})	**H_0:** There will be no significant differences in medial and lateral knee skin surface temperature between the two temperature settings, immediately post intervention or over a 20-minute rewarming period. **H_1:** There will be significant differences in medial and lateral knee skin surface temperature between the two temperature settings, immediately post intervention or over a 20-minute rewarming period.	To test this hypothesis, two factor repeated measures ANOVAs with post-hoc pairwise comparisons were used to assess the following for T_{sk}: 1) Immediate effects of compression on medial and lateral knee $T_{sk.}$ The two factors were low/high compression and medial/lateral knee $T_{sk.}$ 2) Immediate effects of temperature settings on medial and lateral knee $T_{sk.}$ The two factors were 10/15 °C temperature settings and medial/lateral knee $T_{sk.}$ 3) How the interventions performed over a 20-minute rewarming period. The two factors were time (time points) and interventions (interventions). If any interactions were found between factors, further post-hoc analyses were carried out on medial and lateral sides of the knee separately.

Muscle Oxygenation	**H_0:** There will be no significant differences in tibialis anterior oxygenation between interventions, over a 20-minute rewarming period. **H_1:** There will be a significant difference in tibialis anterior oxygenation between interventions, over a 20-minute rewarming period.	To test this hypothesis, interventions were assessed over a 20-minute rewarming period, using repeated measures ANOVAs (6 x 4 - time points by interventions).
Thermal Sensation & Comfort	**H_0:** There will be no significant differences in thermal sensation or comfort between interventions, over a 20-minute rewarming period. **H_1:** There will be a significant difference in thermal sensation or comfort between interventions, over a 20-minute rewarming period	To test this hypothesis, Friedman Tests were used to analyse nominal questionnaire data, to explore differences between time points and interventions.
Joint Position Sense	**H_0:** There will be no significant differences in knee joint angles between interventions, over a 20-minute rewarming period. **H_1:** There will be significant differences in knee joint	To test this hypothesis, interventions were assessed over a 20-minute rewarming period, using repeated measures ANOVAs (3 x 4 - time points by interventions).

	angles between interventions, over a 20-minute rewarming period	
Muscle Strength	**H_0:** There will be no significant differences in quadriceps strength between interventions, over a 20-minute rewarming period **H_1:** There will be significant differences in quadriceps strength between interventions, over a 20-minute rewarming period	To test this hypothesis, interventions were assessed over a 20-minute rewarming period, using repeated measures ANOVAs (3 x 4 - time points by interventions).
Pressure Pain Threshold (PPT)	**H_0:** There will be no significant differences in PPT between interventions, over a 20-minute rewarming period **H_1:** There will be significant differences in PPT between interventions, over a 20-minute rewarming period	To test this hypothesis, interventions were assessed over a 20-minute rewarming period, using repeated measures ANOVAs (3 x 4 - time points by interventions).

Study 2: Exploring the effects of cryotherapy modalities on pain, muscle strength and joint position sense in healthy participants with experimentally induced knee pain

Table 1.2: A summary of the hypotheses for Study 2

Outcome Measure	**Null Hypothesis (H_0) and hypothesis (H_1)**	**Statistical Analysis**
Joint Position Sense	Outlined in Table 1.1	Outlined in Table 1.1
Muscle Strength	Outlined in Table 1.1	Outlined in Table 1.1
PPT	Outlined in Table 1.1	Outlined in Table 1.1
Participant perceived pain using the NPRS	**H_0:** There will be no significant differences in NPRS scores between interventions, over a 20-minute rewarming period. **H_1:** There will be significant differences in NPRS scores between interventions, over a 20-minute rewarming period.	To test this hypothesis, interventions were assessed over a 20-minute rewarming period, using repeated measures ANOVAs (3 x 2 - time points by interventions).

Study 3: An exploration into the effectiveness of cryotherapy modalities on participants with knee injuries, through a series of single-case experiments

The analysis within the single-case experiments focussed on assessing the clinical relevance of the changes for each individual (Table 1.3) using the relevant minimal clinically important changes (MCIC), which is a common analysis approach for this research design (Barker *et al.*, 2011).

Table 1.3: A summary of the hypotheses for Study 3

Outcome Measure	**Null Hypothesis (H_0) and hypothesis (H_1)**	**Statistical Analysis**
Numeric Pain Rating Scale (NPRS)	**H_0:** There will be no significant differences in NPRS changes between interventions, over a three-day intervention period. **H_1:** There will be significant differences in NPRS changes between interventions, over a three-day intervention period.	The MCIC for chronic musculoskeletal pain has been reported as 1-point change on the NPRS scale and 1.3-points for acute pain (emergency room population), therefore these were used in analyses.
Stability (Patient-perceived)	**H_0:** There will be no significant differences in perceived stability changes between interventions, over a three-day intervention period. **H_1:** There will be significant differences in perceived stability changes between interventions, over a three-day intervention period.	The global rate of change for an 11-point numeric rating scale of 2-points (Jaeschke, Singer and Guyatt, 1989) was used to assess the stability scores, as there is currently no defined MCIC for this outcome measure to date.
Knee Circumference (swelling)	**H_0:** There will be no significant differences in knee circumference changes between interventions, over a three-day intervention period.	With no defined MCIC explicitly reported for swelling reduction, a reduction of 0.5 cm in knee circumference was required to deem an intervention a clinically relevant

	H_1: There will be significant differences in knee circumference changes between interventions, over a three-day intervention period.	treatment, as Sari et al. (2019) reported this figure following a standard clinical cold-pack treatment on patients with knee osteoarthritis.

1.5 Thesis Structure

This thesis consists of eight chapters. This introductory chapter (**Chapter 1**) outlines the rationale for the research and the aims and objectives of the thesis.

Chapter 2 presents a review of the relevant literature surrounding knee injury management, cryotherapy, compression, and contrast therapy. Within this review the evidence underpinning the current clinical guidelines for injury management is discussed. A scoping review titled 'The use of contrast therapy in soft tissue injury management and post-exercise recovery: a scoping review' was published as part of this chapter.

Chapter 3 details the basic methodology and equipment used in the intervention studies. The validity and reliability of the equipment and outcome measures investigated are discussed along with the minimal clinically important changes (MCIC) and minimal detectable changes (MDC) for each outcome measure.

Chapter 4 presents the preliminary studies which investigated potential temperature and pressure combinations through four different interventions, on a healthy male population. The study outlined in this chapter is split into two parts, in order to explore a range of outcome measures (see Chapter 4). Part A explored the effects of the four CHCD interventions on the tissue response. Whilst Part B explored the effects of the same interventions on pressure pain threshold, muscle strength and joint position sense. The same interventions were used for both parts of the study.

Chapter 5 explores the effects of two interventions (ice and CHCD) on muscle strength, joint position sense and pain in a population with experimentally induced knee pain, through a randomised crossover pilot trial. The optimal intervention identified in Chapter 4 was compared to ice, which is the cryotherapy modality currently advised within the clinical guidelines.

Chapter 6 presents a series of single-case experiments exploring the effectiveness of two cryotherapy modalities (ice and CHCD) at reducing pain, swelling and instability in people with a range of knee injuries.

Chapter 7 summarises the main research findings and discusses the potential clinical implications. Conclusions of the thesis are discussed in this chapter, in relation to the original aims and objectives. This chapter also discusses the limitations of the research undertaken.

Chapter 8 provides recommendations for optimal CHCD interventions for knee injury management based on the research undertaken, in the form of an acronym 'OPTIMISE'. Recommendations for future research as also discussed in this chapter.

The appendices include: -

Appendix A – Consent forms & PARQ+ screening form

Appendix B – Ethical Approval

Appendix C – Single-Case Experiment Figures

Appendix D – Peer reviewed publications relating to this thesis

Appendix E – Additional supporting documentation

1.6 Publications

As part of this thesis, the following peer-reviewed publications were published and/or presented at national conferences:

Peer-reviewed publication

Relevant to Chapter 2:

> Greenhalgh, O., Alexander, J., Richards, J., Selfe, J. and McCarthy, C. (2021) 'The use of contrast therapy in soft tissue injury management and post-exercise recovery: a scoping review', Physical Therapy Reviews, 26(1), pp. 64-72.

National conference presentations (2020 & 2021)

Relevant to Chapter 4:

> Greenhalgh, O., Alexander, J., Richards, J., Selfe, J. and McCarthy, C. (2020) 'An exploration of targeted cryotherapy protocols, using the Swellaway Knee Unit, on healthy male subjects' Physiotherapy UK.

Relevant to Chapter 5:

> Greenhalgh, O., Alexander, J., Richards, J., Selfe, J. and McCarthy, C. (2021) Exploring effects of cryotherapy modalities on pain, muscle strength and joint position sense in healthy participants with induced knee pain. Physiotherapy UK.

Relevant to Chapter 6:

> Greenhalgh, O., Alexander, J., Richards, J., Jones, M., Selfe, J. and McCarthy, C. (2020) 'An exploration into the effectiveness of cryotherapy modalities on patients with degenerative knee conditions, through a series of single-case experiments' Physiotherapy UK.

Chapter 2: Literature Review

This chapter reviews the literature relevant to the use of cold, hot and compression therapy for knee injury management. As discussed in Chapter 1, this thesis focuses on the knee due to the frequency and severity of knee injuries and degenerative conditions.

The review is split into two parts. Firstly, the prevalence of knee injuries and common chronic knee conditions are explored, in addition to the current guidelines for knee injury management. Following this, the rationale behind the use of cryotherapy and contrast therapy for injury management is examined.

2.1 Search Strategy

Comprehensive literature searches were carried out using the search terms listed in Table 2.1, using the following electronic databases (from 2018-2021): Cochrane, CINHAL, EBSCO, SPORTDiscus, MEDLINE (via OVID) and PubMed. This review was conducted using the Arksey & O'Malley framework for scoping reviews reported in Arksey & O'Malley (2005). Hand searches of reference lists were also carried out.

Table 2.1: Key terms used for literature searching

Review Section	Key Words
1	Knee injury, knee osteoarthritis, acute soft tissue injury, degenerative knee conditions
2	Cryotherapy, cold therapy, contrast therapy, thermotherapy, heat therapy, ice, cooling, heating

A wide set of key words was adopted during literature searching as suggested by Arksey & O'Malley (2005), in order to provide a comprehensive coverage of the literature available. Table 2.2 details the inclusion/exclusion criteria for the literature review.

Table 2.2: Review inclusion/exclusion criteria

Inclusion	Exclusion
Published in a peer-review journal	Not related to knee or soft tissue injury management or thermotherapy interventions
Written in English	Written in a language other than English
Relevant to knee or soft tissue injury management or thermotherapy interventions	

2.2 Knee Injuries

The knee is the largest joint in the human body; it has a complex structure enabling flexion and extension, whilst maintaining stability (Elkin, Zamora and Gallo, 2019). The major ligaments of the knee joint consist of the Anterior Cruciate Ligament (ACL), Posterior Cruciate Ligament (PCL), Lateral Collateral Ligament (LCL) and the Medial Collateral Ligament (MCL). The cruciate ligaments provide anteroposterior stability in the sagittal plane. The collateral ligaments prevent excessive valgus/varus in the coronal plane. Injury to these ligaments leads to instability and reduced function (Elkin, Zamora and Gallo, 2019).

2.2.1 Prevalence of knee injuries

Previous studies have identified that 10-19% of all acute injuries in emergency rooms are sports injuries, with knee and ankle injuries being the most common (Bahr et al., 2003; Arendt & Dick, 1995). Agel et al. (2007) reviewed injury surveillance data reported for women's basketball in the US National Collegiate Athletic Association (NCAA) and found knee injuries were one of the most common injuries occurring during games and training. Forty-eight percent of these knee injuries resulted in at least 10 consecutive days of restricted/no participation meaning they were classed as 'severe' (Agel *et al.*, 2007).

Table 2.3: Incidence of knee injuries over a 10-year period as reported by Majewski et al. (2006), Swenson et al. (2013) and Awwad et al. (2019)

	Majewski et al. (2006)	*Swenson et al. (2013)*	*Awwad et al. (2019)*
Knee Injury	**Incidence (%)**	**Incidence (%)**	**Incidence (%)**
ACL	20.3	25.4	3.4
PCL	0.65	2.4	9.0
MCL	7.9	36.1	28.1
LCL	1.1	7.9	n/a
Meniscus:	14.5:	23	28.1
Lateral Meniscus (LM)	3.7	n/a	n/a
Medial Meniscus (MM)	10.8	n/a	n/a
Patella Tendon	n/a	29.5	n/a

Table 2.3 details the incidence of knee injuries in three epidemiology studies. Majewski et al. (2006) recorded knee injuries in sport over 10 years and Swenson et al. (2013) documented knee injuries amongst high school athletes in the US between 2005/06-

2010/11. More recently, Awwad et al. (2019) analysed knee injuries in a professional rugby league team. As Table 2.3 illustrates, the most common knee injuries across these epidemiology studies were ACL, MCL, meniscus and patella tendon. Despite ACL injuries being less common in the study by Awwad et al (2019), they were found to be the most severe injury, accounting for the most time missed from sport. Majewski et al. (2006) found that more knee injuries occurred during soccer (35%) and skiing (26%) than any other sports in this study. Whereas American football, girls' soccer and girls' gymnastics all presented the highest knee injury rates in Swenson et al. (2013).

Ibeachu et al. (2019) found a high prevalence of knee problems in young adults in a university cohort, with nearly a third having a knee problem in the previous 12 months (12-month period prevalence of 31.8%). Pain was reported as the predominant symptom in the majority of participants with knee pain (69.9%) (Ibeachu *et al.*, 2019). Other symptoms included giving way (22.5%) and locking (7.5%). Interestingly, only 52% had previously sought medical advice on the knee problem (Ibeachu *et al.*, 2019). The authors highlighted that the high prevalence of knee injuries in young adults appears to be associated with high physical activity levels. As populations are being encouraged to become more active, the importance of prevention and self-management of knee problems is becoming increasingly vital.

Surprisingly, there is a significant lack of epidemiological studies reporting knee injuries in the last decade.

2.2.2 Pathophysiology

2.2.2.1 Grades of Injury

There are three grades of soft tissue injury dependent on severity which are described in Table 2.4. These grades are established through clinical examination and imaging such as magnetic resonance imaging (MRI) and ultrasound (Mueller-Wohlfahrt *et al.*, 2012).

Grades I and II are the most common grades of injuries and can be treated with bracing and progressive rehabilitation programmes (Shankman & Manske, 2014). Only 15% of all knee sprains are grade III and typically require surgical repair with a few exceptions, for example, all three grades of MCL tears can repair without surgery (Shankman & Manske, 2014).

Table 2.4: Summary of grades of injury

Grade of Injury	*Sprain*	*Strain*
1	Grade I mild sprains involve microscopic tearing of the ligament, without joint laxity (Shankman and Manske, 2014).	Grade I strain injuries involves the stretching or minor tearing of muscle fibres, with pain and tenderness with movement but full ROM possible (Puddu, Giombini and Selvanetti, 2001).
2	Grade II ligament injuries are moderate sprains involving some ligament fibre tears with moderate joint laxity (Shankman & Manske, 2014). Ligament stiffness and strength decrease by 50% during this phase (Robi *et al.*, 2013).	Grade II strains involve torn muscle or tendon fibres, with palpable depression of torn fibres and a decrease in ROM due to swelling and bleeding (Puddu, Giombini and Selvanetti, 2001).
3	Grade III injuries consist of a complete ligament rupture, with severe laxity, instability (Shankman & Manske, 2014) and total loss of function.	Grade III strains involve a complete rupture of the muscle belly, tendon junction/insertion with intense pain and significant impairment to ROM (Puddu, Giombini and Selvanetti, 2001).

2.2.2.2 Phases of Healing

All connective soft tissue injuries undergo the same healing process. It is believed that healing consists of a series of overlapping phases; the reaction phase, the regeneration phase, and the remodelling phase (van der Meulen, 1982). Table 2.5 describes the characteristics of each phase of healing.

Table 2.5: Phases of Soft Tissue Healing

Phase of Healing	*Characteristics*	*Onset of phase after trauma*
Reaction	Bleeding and inflammation occur during this first phase. Redness and warmth, caused by dilation of the vessels and swelling via exudation. Pain is also a symptom during this phase, due to a number of factors including pressure on nerves, ischaemia, and action of chemical products. Typically following trauma, vasoconstriction occurs for approximately 10 minutes to close off the damaged vessels and initiate the inflammatory response via chemical signals (van der Meulen, 1982). *Bleeding* Platelets combine at the site of the injury and create a fibrin clot. The clot releases a variety of molecules which cause an acute inflammation locally.	Occurs immediately
	Acute Inflammation: Inflammation occurs between days 1-10 (Michlovitz, 1990). The 'cardinal signs of inflammation' are swelling, heat, pain, redness, and loss of function (Michlovitz, 1990). Oedema occurs due increased permeability of micro-vessels and the osmotic gradient produced following the escape of cells and macromolecules allowing fluid to move into interstitial spaces (Michlovitz, 1990). This inflammatory phase prepares the wound for the proliferation/regeneration phase	Occurs between 3-72 hours.

	(Hunter, 1998). The acute inflammatory reaction is characterised by pain, an increase in temperature, increase in oedema formation, peripheral muscle fibre contraction and cell damage/death (Robi *et al.*, 2013) due to the hypoxia caused by damaged blood vessels bleeding. The acute inflammation reaction is normally complete in two weeks; if it continues for 1 month it is then classed as 'sub-acute inflammation' and if it continues for longer than this it is classed as 'chronic inflammation' (Michlovitz, 1990).	
Regeneration/ Proliferation	During the regeneration or proliferation phase, the damaged structures are rebuilt involving both epithelial and connective tissues (Michlovitz, 1990) and the debris is eliminated (van der Meulen, 1982). This phase usually occurs within days 3-20 (Michlovitz, 1990). Collagen is deposited to the injury site and fibroblasts infiltrate the injury after four days. This phase lasts up to 6-8 weeks (Robi et al., 2013).	72 hours to 6-8 weeks
Remodelling	Following the proliferation phase, the remodelling phase can be split into two stages, a consolidation, and a maturation phase (Robi et al., 2013). This phase usually begins around day 9 (Michlovitz, 1990) but the length of the remodelling phase can vary massively between 3 weeks to 12 months in order to restore anatomic structures and regenerate tissue.	Up to 12 months

2.3 Current Clinical Guidelines

2.3.1 Acute Knee Injury Management

As mentioned in Chapter 1, the current ACPSM guidelines for acute injury management have been updated from '**PRICE**' (Protection, Rest, Ice, Compression and Elevation) to '**POLICE'** (Protection, Optimal Loading, Ice, Compression, Elevation) (Bleakley, Glasgow and MacAuley, 2012). These guidelines were formed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) sequential process, which assesses the quality of the evidence on the design, consistency, directness, and quality of the study (using the Cochrane risk of bias tool).

It is important to note that these guidelines are aimed at the entire acute soft tissue injury spectrum; no guidelines currently exist for the management of acute knee injuries specifically. This section will discuss the clinical reasoning which supports the **POLICE** guidelines presented in Bleakley et al. (2011) and Bleakley, Glasgow and MacAluley (2012).

Protection

The ACPSM guidelines advise to unload in the acute injury phase, at least in the plane of injury; with the duration of the unloading dependent upon injury severity (Bleakley *et al.*, 2011). The authors do not recommend complete unloading after the acute stage of injury, for the majority of soft tissue injuries and highlight moderate quality evidence for functional treatment being more effective than immobilisation (cast), for ankle sprains and semi-rigid structures being more effective than elastic bandages (Bleakley *et al.*, 2011).

Optimal **L**oading

The update to change **PRICE** to **POLICE** was considered not only a guideline but also a reminder to clinicians to consider optimal loading for different patients and stimulus for new research. Optimal loading involves replacing rest with a balanced and progressive rehabilitation programme which aims to promote early recovery with early activity (Bleakley, Glasgow and MacAuley, 2012). Finding an effective level of loading for each injury when tissues are healing is often the difficulty, as too much rest or unloading can inhibit recovery but too much loading can lead to re-bleeding or further injury damage (Bleakley, Glasgow and MacAuley, 2012).

Despite originally being a mechanism for rest, crutches, braces, and supports may be an effective rehabilitation tool for adjusting and controlling loading during the early stages of an acute injury (Bleakley, Glasgow and MacAuley, 2012). With the evidence of functional treatment methods including early mobilisation and weight bearing being more effective than immobilisation, 'tissue loading' is considered an essential part of soft tissue injury management (Bleakley *et al.*, 2011). However, the guidelines advise practitioners to be conscious of a careful transition from complete unloading/rest to tissue loading, considering the nature and injury severity and avoiding movement in the plane of the injury during the acute phases (Bleakley *et al.*, 2011).

Ice

Ice is an easy and cheap form of cryotherapy, that is widely used in a number of forms (e.g., cubed, crushed, and wetted). The guidelines identify moderate clinical evidence for cryotherapy being effective at reducing short term pain for soft tissue contusions and acute ankle injuries and recognise high quality evidence of cryotherapy offering a short-term analgesic effect post-surgery, but states little effect on other relevant key outcome measures (Bleakley *et al.*, 2011). Further to this, the guidelines acknowledge low quality evidence that shorter durations of cryotherapy treatment applied intermittently are sufficient to provide the cold-induced short-term analgesic effect (Bleakley *et al.*, 2011).

Compression

Bleakley et al. (2011) states that a primary reason behind using compression and elevation following an acute injury is the restoration of pressure gradients within the injured tissue via mechanical pressure (compression) or gravity (elevation).

There is little evidence surrounding optimal compression pressure values or type (intermittent or static) and the cooling and compression dosage relationship combined. Bleakley et al. (2011) notes that one dosage or approach of compression is unlikely to be equally effective across the entire soft tissue spectrum. The authors advocate considering factors such as; distance of the injury from the heart, time after injury, injury severity, tissue vascularity and depth of the injured tissue when selecting compression and elevation dosages (Bleakley *et al.*, 2011). Compression bandages which are commonly used, often exert compression levels between 15-60 mmHg (Bleakley *et al.*, 2011).

The guidelines recommend the use of compression after an acute soft tissue injury but suggest to avoid using high levels of compression in conjunction with simultaneous elevation (Bleakley *et al.*, 2011). The guidelines also recommend that the compressive modality provides a graduated compression and moulds to the shape of the body part, with focal compression around bony protuberances (Bleakley *et al.*, 2011).

Elevation

Similar to compression, elevation aims to restore the injured tissues pressure gradient. Compression alters pressure via applied mechanical pressure and elevation achieves this through gravitational force. The guidelines recommend avoiding the use of high levels of compression in conjunction with simultaneous elevation (Bleakley *et al.*, 2011). Despite having a clear physiological rationale, Bleakley et al. (2011) highlights that there is little evidence supporting the use of elevation.

2.3.2 Management of Chronic Knee Injuries & Conditions

The use of local cooling or heating is also advocated as a self-management tool for chronic knee conditions such as knee osteoarthritis (OA) by the National Institute for Health Care Excellence (NICE) (NICE, 2014). Knee OA is a condition contributing to reduced function, quality of life and substantial socioeconomic burden, mainly because of pain (Neogi, 2013). The NICE guidelines for knee OA advocate the use of local thermotherapy (heat or cold) as a self-management tool to be used alongside core treatments (information, exercise, and weight loss) (NICE, 2008; NICE, 2020). However, optimal thermotherapy protocols are yet to be established. Currently, the lifetime risk of developing knee OA is approximately 45% (Murphy *et al.*, 2008), which is likely to rise due to an aging population. Therefore, self-administered interventions to alleviate symptoms of OA would be beneficial.

PEACE & LOVE

As discussed in Chapter 1, Dubois & Esculier (2019) presented the acronym **PEACE & LOVE** (Protection, Elevation, Avoid Anti-Inflammatories, Compression, Education & Load, Optimism, Vascularisation, Exercise). This new acronym was proposed to take into account the sub-acute and chronic stages of tissue healing, with the previous acronyms (**PRICE** and **POLICE**) solely focusing on acute injury phases. The authors state that cryotherapy was removed due to a lack of high-quality evidence on the efficacy for treating more soft tissue injury. Despite acknowledging the evidence supporting the analgesic effect, the authors suggest there may be potential disruption to tissue repair and collagen synthesis following the application of ice. This has led to discussions amongst clinicians suggesting that cryotherapy may have a potential negative impact in a sports healthcare setting (Long and Jutte, 2020). However, as the editorial blog by Dubois & Esculier (2019) is yet to be supported by empirical data, further research is required to support or refute this proposed change in guidelines. Long and Jutte (2020) highlight that the literature supporting the claims that cryotherapy impedes healing lack credibility, relevance and adequate study designs. For example, Long and Jutte (2020) state that in some cases, those who do not support cryotherapy have referenced research based on a population with a rare condition (haemophilia), which cannot be generalised to the majority of the population.

2.4 Cryotherapy

2.4.1 Introduction to Cryotherapy

Cold therapy, also known as 'cryotherapy', is defined as a therapeutic application which removes heat energy from the body causing tissue temperature to decrease (Michlovitz, 1990; Nadler, Weingand and Kruse, 2004). Cryotherapy is an umbrella term which covers various methods of cooling, from local applications (i.e., partial body applications) to whole-body cryotherapy (WBC) (Allan *et al.*, 2022). WBC has a primary purpose of recovery, although has been shown to reduce pain scores related to post-exercise soreness (Selfe et al., 2020). Whereas, local cryotherapy applied directly to the skin is most commonly used for injury management (Alexander *et al.*, 2021a). The CHCD used in this thesis provides a local application of temperature to the knee, in addition to circumferential compression around the full joint. Therefore, this review will focus on local cryotherapy as a self-management tool for acute injuries and chronic conditions.

Cryotherapy is underpinned by heat transfer. Heat transfer is defined as the physical exchange of thermal energy between two systems which have different temperatures (Selfe *et al.*, 2020). There are five methods of heat transfer in humans: convection, conduction, radiation, evaporation, and conversion. The three types of heat transfer that occur during cryotherapy are conduction, convection and evaporation (Hardaker *et al.*, 2007). Conduction involves heat transfer by the direct interaction of the molecules from areas of high kinetic energy to low kinetic energy; it is the main form of energy transfer when a cold modality is placed on the skin (Halliday and Resnick, 1988; Michlovitz, 1990; Merrick, Jutte and Smith, 2003). Merrick, Jutte and Smith (2003) emphasised that cryotherapy modalities do not transfer cold energy, as it is not possible to transfer cold (low kinetic energy) but instead, cold modalities absorb heat from their environment (Kennet *et al.*, 2007). Based on Fourier's law of heat conduction, during cryotherapy application deeper tissues lose heat by warming the superficial tissues (Merrick, Jutte and Smith, 2003). The rate of heat transfer via conduction is affected by surface area, thermal conductivity, temperature of the surfaces and tissue thickness (Michlovitz, 1990).

Contemporary research has shown that cooling a smaller surface area, through a targeted cooling approach, may have therapeutic benefits (Alexander *et al.*, 2021b). This is discussed further in Section 2.4.5. This thesis explores the use of a novel CHCD, which

adopts a targeted cryotherapy approach, by providing controlled cooling over a smaller surface area than traditional methods of cryotherapy.

2.4.1.1 Pathophysiological rationale

The pathophysiological rationale for using cryotherapy for soft tissue injury management is based upon on the knowledge of the body's response to cold producing desirable physiological effects and the clinical evaluation of the effectiveness of cold as a therapeutic modality (Lehmann, 1990). Cryotherapy is still one of the simplest, oldest and cheapest modalities for treating soft tissue injuries (Bleakley and Davison, 2010).

2.4.1.1.1 Secondary Damage

Animal models have demonstrated that cryotherapy can affect key inflammatory events at a cellular level following an acute soft tissue injury (Karunakara, Lephart and Pincivero, 1999; Nadler, Weingand and Kruse, 2004; Bleakley and Davison, 2010). However, the relative effects in human tissue are not yet known (Bleakley and Davison, 2010) and authors continue to debate the effect of cryotherapy on inflammation and the healing process following an acute injury (Bleakley and Davison, 2010; Dubois and Esculier, 2019; Long and Jutte, 2020), in order to establish whether cryotherapy is optimising or hindering the natural inflammatory healing process. On a physiological level, when cold is applied, vasoconstriction occurs which reduces local tissue blood flow and subsequently, tissue metabolism, inflammation and muscle spasm are reduced (Nadler, Weingand and Kruse, 2004).

According to Van't Hoff's law, every 10 °C decrease in tissue temperature decreases the rate of chemical reactions by 2-to-3-fold (Bleakley and Hopkins, 2010). The current best evidence surrounding the effect of metabolic activity at different temperatures is limited to animal studies and are yet to be repeated in human tissue (Bleakley and Hopkins, 2010; Selfe *et al.*, 2020). Animal studies have demonstrated that metabolism is reduced when tissue temperature is reduced to 5-15 °C and this range has since been acknowledged by other authors (Kennet *et al.*, 2007; Bleakley and Hopkins, 2010; Bleakley *et al.*, 2011). However, Bleakley et al. (2011) suggests that this is based on the best current evidence and is subject to change, as new knowledge of the body's response to an acute injury may emerge over time. A reduction of tissue metabolism is beneficial for acute soft tissue injury as it reduces the rate of oxygen consumption and in turn assists tissue survival during a period of hypoxia after the injury (Knight, 1995; Nadler, Weingand

and Kruse, 2004). This period of trauma after the injury is believed to cause further trauma, termed 'secondary damage' (Merrick *et al.*, 1999). Essentially, a reduction in tissue temperature may reduce cellular metabolic demand, helping the cells to tolerate the ischaemic environment following an acute injury, and in turn can minimise secondary cell injury and cell death (Bleakley and Davison, 2010). It is generally accepted that the quicker the application of cryotherapy following an injury, the sooner the metabolic rate is reduced in order to minimise secondary damage to healthy cells not injured in the primary damage, thus minimising the overall extent of tissue damage (Merrick, Jutte and Smith, 2003; Bleakley and Hopkins, 2010; Bleakley *et al.*, 2011). Animal studies have highlighted that there is a window of opportunity within the first 30 minutes of an injury occurring, in order to minimise the secondary damage (Merrick and McBrier, 2010). The secondary injury model is possibly the most commonly cited pathophysiological rationales for applying cryotherapy for acute soft tissue injury management (Bleakley *et al.*, 2011). In clinical practice, this means immediate cryotherapy is deemed more beneficial than delayed cryotherapy. Equally, cryotherapy modalities that can provide efficient cooling quickly are more beneficial than products that are slower to reduce tissue temperature. However, it is important to note that rodent tissue has differing metabolic properties than human tissue in response to environmental stimuli, which indicates that the findings may not be generalisable to human tissue (Kowalski and Bruce, 2014). Therefore, it is difficult to conclude whether such large reductions in tissue temperature are required to minimise secondary damage in human tissue. Authors have stressed the importance of human studies in this area to provide a greater understanding (Bleakley and Hopkins, 2010; Bleakley and Davison, 2010).

In addition, authors have questioned whether it is possible to achieve optimal levels of tissue cooling through local cryotherapy applications on the skin surface, in order to affect metabolic activity (Merrick *et al.*, 1999; Bleakley and Hopkins, 2010). Uncertainty exists regarding the magnitude and rate of cooling which can be achieved through local cryotherapy in order to significantly reduce deeper tissue temperature (Zemke *et al.*, 1998; Jutte *et al.*, 2001) and this will be discussed further in section 2.4.3 within this chapter.

2.4.1.1.2 Cold Induced Analgesia

Despite the uncertainty regarding the effects of cryotherapy on the inflammatory process, moderate evidence exists which supports the use of cryotherapy as a short-term pain relief for soft tissue injury management (Nadler, Weingand and Kruse, 2004; Bleakley *et al.*, 2007; Algafly and George, 2007; Bleakley *et al.*, 2011). A cold-induced analgesic effect has been established to occur only after a localised region had been cooled to, and maintained below, 13.6 °C (Bugai, 1975). This evidence is based upon healthy human subjects.

The pathophysiological science surrounding pain relief is complex and not yet fully understood. 'Gate control theory', 'specificity theory', 'intensity theory' and 'pattern theory' are all theoretical models for pain (Melzack and Wall, 1965; Moayedi and Davis, 2013). Pain gate theory, counterirritant to pain through diffused noxious inhibitory controls, alteration in nerve conduction velocity, suppressed nociceptive receptor sensitivity or via the analgesic descending pathway of the central nervous system (for example, endorphins) have all been linked with potentially explaining the pain relief observed following cooling.

Firstly, the 'pain gate theory' refers to a gate control system which modulates sensory stimuli from the skin prior to registering a pain response (Melzack and Wall, 1965). This theory was first presented in 1965 but remains clinically relevant as a possible plausible explanation for the reduction of pain following cryotherapy.

Another plausible explanation for pain relief following cryotherapy is suppressed nociceptive receptor sensitivity, which relates to the specificity theory of pain. When a tissue injury occurs, specialised nerve endings called nociceptors, transmit signals through the spinal cord to the brain where pain is then recognised (Saeki, 2002; Nadler, Weingand and Kruse, 2004; Algafly and George, 2007).

NCV is thought to limit muscle spasm and pain sensation and is influenced by several factors including skin temperature, age and gender; meaning reduction in NCV is a plausible explanation for pain relief (Algafly and George, 2007). Interestingly, Algafly & George (2007) reported changes in both pain tolerance and pressure pain threshold in areas remote to the area cooled by ice. Selfe et al. (2020) highlighted that this challenges the concept that cryotherapy achieves pain relief through the mechanism of pain gate theory.

Figure 2.1 provides a timeline of the history of some key cryotherapy research and guideline updates to date, to illustrate some of the research discussed in this chapter in chronological order.

Figure 2.1: A timeline of the history of key cryotherapy research and guideline updates to date.

2.4.2 Skin Surface Temperatures

Thermal receptors within the skin monitor external temperatures and thermal receptors in the hypothalamus monitor core body temperature (Selfe *et al.*, 2020). Therefore, following an exposure to cold temperatures, the skin is the first site to respond (Chesterton *et al.*, 2002).

Rivenburgh (1992) first proposed an ideal therapeutic range for T_{sk} as 10-15 °C, due to the recognition of physiological responses to different skin and tissue temperatures. For example, a cold-induced analgesic effect has been established to occur only after a localised region had been cooled to, and maintained below, 13.6 °C (Bugai, 1975). Additionally, T_{sk} between 10-11 °C produces a reduction in metabolism of 50% and a reduction in NCV occurs at a T_{sk} of 12.5 °C (Jutte et al., 2001). This range has since been acknowledged by other authors and is reported in contemporary literature, despite first being established in 1992 (Bleakley, McDonough and MacAuley, 2006; Kennet *et al.*, 2007; Hing *et al.*, 2008; Selfe *et al.*, 2020; Alexander *et al.*, 2021a).

Costello et al. (2014) demonstrated that WBC (110 °C for 3 minutes, 40 seconds) reduced anterior knee T_{sk} in a healthy male population significantly greater than cold water immersion (CWI) (8 °C for 4 minutes) and exceeded the minimum clinically importance difference of 0.5 °C suggested by Selfe, Whitaker and Hardaker (2008). However, anterior knee temperature was not reduced below 13 °C for either intervention (WBC: 19.0 °C and CWI: 20.5 °C) and therefore these interventions were not sufficient to induce an analgesic effect (Bugai, 1975; Costello *et al.*, 2014).

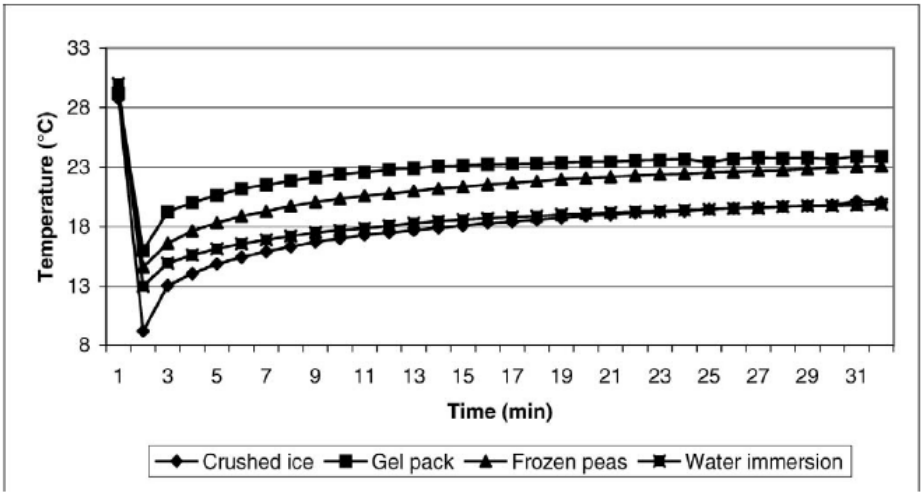


Figure 2.2: Rewarming curves following 20-minute cryotherapy applications presented in Kennet et al. (2007)

Skin surface rewarming curves presented in literature have shown that T_{sk} begins to plateau below baseline by 30 minutes post-cryotherapy treatments (Figure 2.2) (Kennet et al., 2007). Further to this, Khoshnevis, Craik and Diller (2015) reported that standard cryotherapy modalities produced a significant state of vasoconstriction locally during active cooling and rewarming; meaning that even after the cooling has stopped and local temperatures returned to baseline, reduced blood flow was still present.

2.4.3 Intramuscular and Intraarticular Temperatures

The skin reduces deeper tissues via unidirectional heat transfer (Kennet et al., 2007). Essentially, when cryotherapy is applied, heat is lost from the superficial tissues to warm the cold modality. Merrick et al. (2003) highlighted that the deeper tissues are consequentially cooled by losing heat to more superficial tissues which have lost heat to the cold modality application. Once the cold modality has been removed, the deeper soft tissues continue to cool as heat is transferred to superficial tissues to rewarm the skin (Zemke et al., 1998; Jutte et al., 2001; Kennet et al., 2007).

Previous research has shown changes to knee joint intra-articular temperature following local cryotherapy and WBC interventions (Oosterveld and Rasker, 1994; Dahlstedt, Samuelson and Dalén, 1996; Kim *et al.*, 2002). Dahlstedt, Samuelson and Dalén (1996) reported that knee T_{sk} needs to be reduced to 20 °C or less to produce a demonstrable decrease in knee joint intra-articular temperature. Oosterveld and Rasker (1994) reported a T_{sk} of 16 °C immediately after a 30-minute application of ice chips, which corresponded to a 6.4 °C decrease in intra-articular temperature to 29.1 °C in patients with arthritis. Oosterveld and Rasker (1994) also reported a T_{sk} of 9.8 °C immediately after a 6.5-minute application of nitrogen cold air (-160 °C), which corresponded to a 3.3 °C decrease in intra-articular temperature to 32.5 °C. Kim et al. (2002) also explored the effects of cold air on T_{sk} and intra-articular temperature but over a longer period of 2 hours, at a lower temperature of -30 °C and recorded minimum temperatures of 9.7 °C (T_{sk}) and 30 °C (intra-articular). The decrease in temperatures were reported as 3.9 °C (T_{sk}) and 22.1 °C (intra-articular), which were comparable to Oosterveld and Rasker (1994).

The relationship between skin surface temperature (T_{sk}) and intramuscular temperatures (T_{im}) has previously been debated amongst literature (Zemke *et al.*, 1998; Merrick, Jutte and Smith, 2003; Hardaker *et al.*, 2007). Hardaker et al. (2007) reported a negative quadratic relationship between T_{sk} and T_{im} so as T_{sk} increases, T_{im} decrease. It is believed

that the deeper the tissue, the longer the treatment time required to lower the temperature (Michlovitz, 1990). Therefore, the majority of studies exploring temperatures following cryotherapy treatments have focussed on T_{sk} readings opposed to T_{im} readings, as it is easier to access and less invasive (Jutte *et al.*, 2001).

With the skin being the first site to respond to a cold stimulus, the response is immediate and T_{sk} begins to decrease even during a brief application of cryotherapy (Chesterton *et al.*, 2002; Kennet *et al.*, 2007). However, once the cold stimulus is removed, the skin surface begins to rewarm so the effect on T_{sk} is short-lived (Figure 2.2). Contrastingly, the response within T_{im} is slow and believed to be also influenced by hormone release (Zemke et al., 1998). Zemke et al. (1998) reported that 1cm intramuscular temperatures achieved their lowest temperatures at 17.9 ± 2.4 minutes with a 15-minute ice massage and 28.2 ± 12.5 minutes with a 15-minute application of an ice bag. This highlighted that the deeper tissues continued to cool for approximately 14 minutes after the removal of the ice bag (Zemke et al., 1998). Therefore, researchers have advised cryotherapy application to extend beyond the point of surface analgesia in order to decrease T_{im} (Zemke et al., 1998). Previous studies have highlighted that T_{im} can remain cool for up to 4 hours after 30-minute cold bath at 10^{o}C; 3 hours for a 20-minute cold bath at 10^{o}C and 1.5 hours after a 20-minute application of an ice pack (Michlovitz, 1990). Costello et al. (2012) found that T_{im} (at 3cm) continued to decline up to 60 minutes post cold-water immersion and whole-body cryotherapy and T_{im} did not return to baseline within the 60 minutes observed post treatment.

Johnson et al. (1979) found that if the participant remained stationary during that period, T_{im} would still not return to baseline temperatures 4 hours post-treatment. However, with the addition of an active washout period such as moderate walking (10 minutes at a pace of 5.63 km/h), T_{im} can return close to baseline 50 minutes post-treatment (Myrer, Measom and Fellingham, 2000). This emphasises the importance of the rewarming curves and the effect on muscle function post application.

There has also been a debate over the influence of subcutaneous adipose layer thickness on T_{im} *(Zemke et al., 1998; Jutte et al., 2001; Otte et al., 2002).* Subcutaneous fat has a lower thermal conductivity than normal skin and muscle which means it produces a higher the resistance to heat transfer (Zemke *et al.*, 1998). Studies have proposed that the greater the thickness of subcutaneous fat, the lower the thermal conductivity;

meaning that a greater subcutaneous tissue thickness requires a longer treatment period to get down to the desired temperature (Lowdon and Moore, 1975; Johnson *et al.*, 1979). Previous literature has published relatively strong inverse relationships between skinfold thickness and T_{im} (Lowdon and Moore, 1975) and percentage of body fat and T_{im} (Johnson *et al.*, 1979). In contrast, Jutte et al. (2001) found that skinfold thickness was a poor indicator of T_{im} so therefore advised that subcutaneous adipose thickness may not play a significant role in cryotherapy. Similarly, Zemke et al. (1998) found a weak relationship between T_{im} and subcutaneous thickness. However, these studies examined the calf (Johnson et al., 1979), biceps brachii (Lowdon and Moore, 1975), anterior thigh (Jutte *et al.*, 2001) so the difference in subcutaneous adipose at these anatomical locations may explain the variation in the findings. Jutte et al. (2001) proposed that time was the strongest single predictor of T_{im}.

2.4.4 Dose Response

As discussed in Chapter 1, there is a lack of consensus on the optimum method of applying cryotherapy for injury management or dose-response relationships between key parameters such as temperature, duration, frequency of applications and additional level of compression (Bleakley *et al.*, 2011; Selfe *et al.*, 2020; Alexander *et al.*, 2021a). Table 2.6 presents the key variable to consider in relation to optimising compressive cryotherapy intervention as presented in Alexander et al. (2021a):

Table 2.6: The key variables in regard to optimising cryotherapy interventions and understanding dose-response relationships.

Dose	**Aim of Intervention**	**Adipose Tissue**
Dose (frequency)	Biomechanical response	Location
Dose (volume/mass)	Physiological response	Sex
Timings	Perceptual/psychological/ wellbeing response	Depth of immersion
Surface area (Targeted or global cooling)	Biomechanical response	Mode of cooling (in isolation)
Temperature	Individual response	Mode of compression (in isolation)
Phase change capability	Compression type (static/ intermittent/continuous)	Mode of cooling and compression simultaneously

In addition to the variables presented in Table 2.6, external factors affecting an individual's response to thermal stress (Figure 1.3) should also be considered when tailoring a 'personalised' local cryotherapy intervention (Bleakley *et al.*, 2011; Alexander *et al.*, 2020; Selfe *et al.*, 2020; Alexander *et al.*, 2021a).

2.4.4.1 Dose Time

Algafly & George (2007) reported the average time for T_{sk} to reach 10 °C was 26 minutes (range from 20-31 mins) with an application of ice. Interestingly, some individuals took up to 50% longer than others to achieve a T_{sk} of 10 °C which emphasises the importance of considering the other factors that affect an individual's response to thermal stress, identified in Chapter 1 (Figure 1.3).

Ho et al. (1995) reported that a 20-minute application of a standard ice wrap decreased soft tissue blood flow by approximately 26% and skeletal blood flow and metabolism by approximately 19%. When comparing the effect of different dosage times on a) soft tissue blood flow and b) skeletal blood flow and metabolism, the following reductions were found; 5 minutes (a. 11.1%, b. 5.1%), 10 minutes (a. 11.3%, b. 9.1), 15 minutes (a. 16.3%, b. 14%), 20 minutes (a. 25.5%, b. 15%) and finally 25 minutes (a. 29.5%, b. 20.9%) (Ho, et al., 1995). This study indicated that even a 5-minute application produced a physiological response to blood flow and metabolism, but a 25-minute application produced a reduction nearly 3 times greater.

Hawkins & Hawkins (2016) explored the use of clinical applications of cryotherapy among sports physiotherapists. This study found that 49% of therapists selected a cryotherapy treatment time between 11-15 minutes; with 38% selecting 16-20 minutes (Hawkins & Hawkins, 2016). Further to this, when ice was used, an elastic wrap was the selected attachment choice 57% of the time, as the elastic wrap compresses underlying tissue closer together and facilitated a greater tissue temperature decrease compared to the 'flexi wrap' (plastic film) (Hawkins & Hawkins, 2016).

2.4.4.2 Cryotherapy Agents

The greater the temperature difference between the skin and the cold modality, the faster the rate of energy transference and ultimately a greater change in the resulting tissue temperature (Kennet et al., 2007). Kennet et al. (2007) emphasised that the cold modality's capability to absorb heat is paramount in the overall effectiveness of the cold modality. Cooling modalities range from crushed ice, frozen peas, cold water immersion, gel packs, cold sprays to whole body cryotherapy. However, the current commercial market has several devices (Figure 2.3) which offer cooling using a variety of technologies such as ProMOTION EV1 (Swellaway), Game Ready, Cryocuff, Kelvi, Squid, PhysioLab and RecoverX.

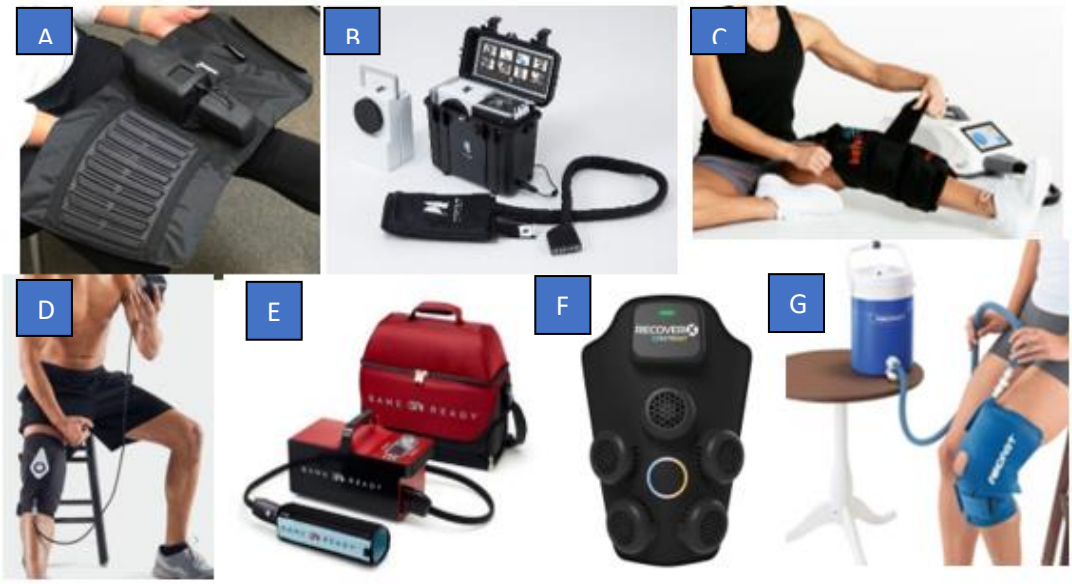


Figure 2.3: Cryotherapy devices a) ProMOTION EV1 (Swellaway) b) Physiolab c) Kelvi d) Squid e) Game Ready f) RecoverX g) Cryocuff

When comparing 4 cryotherapy agents, Kennet et al. (2007) found that crushed ice produced the lowest T_{sk} and gel packs produced the highest T_{sk}, when comparing gel packs, crushed ice, frozen peas, and water immersion.

Interestingly, the crushed ice had a preapplication temperature 10°C higher than gel packs and frozen peas but still managed to produce the lowest skin surface temperature. The authors discussed that this is due to ability of crushed ice to undergo phase change to water (see Figure 2.4), so the latent heat of fusion must be overcome (i.e., the ice melting) before warming occurs. The latent heat of fusion is defined as the energy

required for a system to complete phase transformation (Garai, 2004). The heat of fusion of water at 0°C is 334 joules (J), which means 1kg of ice absorbs 334 J of energy as it melts (Whitten et al., 2007). The heat absorbed from the skin by the crushed ice is used to as part of the phase change to melt the crushed ice into water, opposed to warming agent (Kennet *et al.*, 2007). Thus, ice remains at approximately 0°C until it is melted.

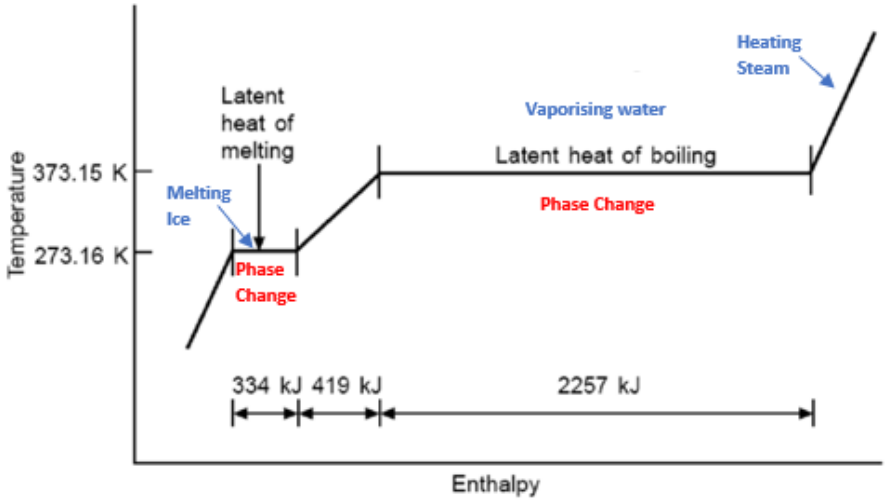


Figure 2.4: Diagram to illustrate phase change of ice to water (Almenas, 2014)

Similarly, the frozen peas will remain at approximately 0°C until the water content within the peas has melted, whereas the gel packs begin to warm as soon as they are applied to the skin (Chesterton et al., 2002). However, once all the ice is melted, the temperature of the water would begin to increase, meaning that the volume of ice used in each treatment would be essential in maintaining a constant temperature throughout the application (Kennet *et al.*, 2007).

Dykstra et al. (2009) compared crushed, wetted and cubed ice and found that wetted ice was the most effective at reducing skin surface temperature and maintaining the low temperature during treatment and recovery. An explanation for the wetted ice being the most effective form of ice for lowering skin temperature, could be because the ice goes through a phase change, but the water also allows a more malleable fit to the contact area of the skin compared to the other forms of ice. This is in agreement with Alexander et al. (2020) who demonstrated that physiological responses to cooling varied across modalities (wetted ice, crushed ice or CryoCuff®), with WI producing the greatest T_{sk} decrease.

With that being said, there are no specific recommendations regarding the optimal size of area in contact with the cryotherapy modality. Previous studies have investigated the effect of quantity of ice and the size of area in contact with an ice pack on T_{sk} (Janwantanakul, 2009). Two ice pack sizes (contact areas: 414 and 500 cm^2) and three quantities of ice (0.3, 0.6 and 0.8 kg) were used during this study. The results from Janwantanakul (2009) suggested that the quantity of ice used affects the magnitude of T_{sk} decrease but not the rate of cooling. Further to this, Janwantanakul (2009) reported that no benefit was apparent using the larger ice pack with a larger surface area. However, more evidence is required to make any conclusions surrounding the effect of contact surface area on the effectiveness of the treatment. Belitsky et al. (1987) found cooling only occurred superficially, within the surface area of the skin in contact with the cold modality; meaning that the cooling did not spread across the skin beyond this area. This could be due to the unidirectional manner of heat transfer, causing heat to spread into the deeper tissues directly underneath the application area, as opposed to across the surface of the skin. However, it is believed that cryotherapy not only affects the body locally to the site of the application but also the spinal cord via neurologic and vascular mechanisms (Nadler, Weingand and Kruse, 2004).

2.4.5 Adverse Effects

2.4.5.1 Nerve Damage

Case studies have reported cryotherapy-induced nerve damage (Collins, Storey and Peterson, 1986; Covington and Bassett, 1993; Moeller, Monroe and McKeag, 1997). Moeller et al. (1997) reported common peroneal nerve palsy causing foot drop and sensory changes following a 20-minute application of ice to the distal hamstring of a 22-year-old American football player. The authors advised that individuals should be cautious applying ice treatment in areas where a nerve is superficial and not well protected by subcutaneous tissue and for patients with low body fat (Moeller, Monroe and McKeag, 1997). Collins, Storey and Peterson (1986) also reported similar findings, with the athlete still recovering four months later.

Covington & Bassett (1993) published six cases of peripheral nerve damage following prolonged cryotherapy in athletes. All athletes recovered within 6 months (Covington & Bassett, 1993). However, it is important to note that all these athletes had minimal subcutaneous fat, which has been shown to significantly affect an individual's response to thermal stress (Fu *et al.*, 2016)

2.4.5.2 Frostbite

Previous studies have reported cases of frostbite following prolonged cryotherapy applications (Lee *et al.*, 2007; Brown and Hahn, 2009). Consequently, authors caution against unsupervised and continuous cryotherapy (Brown & Hahn, 2009).

2.4.5.3 Ice Burns

Bleakley et al. (2011) advised that skin surface temperature should not be reduced below 5 °C in order to avoid skin burns and cell damage. There have been cases of ice burns reported in case studies in the literature following local cryotherapy applications (Cuthill and Cuthill, 2006; Selfe *et al.*, 2007). Selfe et al. (2007) described a mild ice burn during a clinically relevant application of cryotherapy during a clinical research study. The cryotherapy intervention used in this case study consisted of a 20 minute application of a gel pack to a healthy male participant.

2.4.5.4 Dynamic Stability

There is a growing trend for athletes to apply hot or cold therapy before exercise or during half time (Bleakley, Costello and Glasgow, 2012). However, authors have expressed caution for athletes returning to weight bearing activity following cryotherapy,

due to the possible adverse effects to proprioception and dynamic stability (Michlovitz, 1990; Costello and Donnelly, 2010; Bleakley, Costello and Glasgow, 2012; Alexander *et al.*, 2016; Alexander *et al.*, 2018). Proprioception has been defined in literature as a specialised variation of the sensory modality of touch (Lephart et al., 1997); including joint position sense (JPS), kinesthesia, and a sense of force (Furmanek et al., 2018). JPS is the most frequently investigated component of proprioception as it is perceived as one of the more functional tests to evaluate proprioception (Furmanek *et al.*, 2018) and provides an indication of dynamic stability (Alexander *et al.*, 2018).

Michlovitz (1990) advises players to avoid stresses that may reinjure or aggravate the injury for an hour or two following an application of cryotherapy due to the analgesia causing a possible false sense of security.

Costello & Donnelly (2010) highlighted the abundance of conflicting evidence reporting the effects of cryotherapy on JPS. Some studies have published no significant effect of cryotherapy on knee JPS (Ozmun *et al.*, 1996; Aboeleneen *et al.*, 2018), whereas other studies have reported short-term negative effects on JPS following cryotherapy (Uchio *et al.*, 2003; Surenkok *et al.*, 2008; Alexander *et al.*, 2016; Alexander *et al.*, 2018).

Aboeleneen et al. (2018) found that a 20-minute application of a cold pack on the knee joint did not impair proprioceptive accuracy or isometric muscle strength in healthy young females and therefore suggested that cryotherapy could be used safely during exercise programmes. This is in agreement with Ozmun et al. (1996), who reported that cooling the knee joint for 20 minutes using ice, did not have an adverse effect on proprioception.

Uchio et al. (2003) demonstrated that a 15-minute application of a cooling pad on the knee joint caused an increase in stiffness and a decrease in sensitivity of joint position sense. The authors suggested that this should be taken into account when individuals are returning to exercise immediately after a cooling intervention. These findings are in agreement with Surenkok et al. (2008), who reported adverse effects to JPS and postural control following cold-pack and cold spray applications on the knee. More recently, Alexander et al. (2016) published adverse effects on knee joint repositioning following a 20-minute application of crushed ice. Alexander et al. (2018) also presented evidence of adverse effects on dynamic stability 20 minutes after removing ice. The authors proposed that delayed neuromuscular responses in deeper tissues, affecting sensorimotor and

mechanoreceptor mechanisms through a reduction in proprioception control as a potential cause (Alexander et al., 2018).

It is clear that the cryotherapy applications within these studies vary significantly, for both dosage time and modality, which may contribute to the conflicting conclusions presented. Further research is required to provide a greater understanding of the effects of different cryotherapy modalities and dosage on knee joint position sense and dynamic stability.

2.4.5.5 Muscle Strength

It is well accepted that local muscle cooling reduces strength. Previous studies have identified reduced intramuscular temperature was associated with reduced muscle strength. Bergh & Ekblom (1979) presented decreases of approximately 5% in both extension torque and power for every 1 °C decrease in intramuscular temperature. However, this 1979 study was only carried out on male subjects, which makes conclusions drawn from this study difficult to generalise to a wider population.

More recently, Dewhurst et al. (2010) has shown decreases of approximately 6-10% in torque during isokinetic contractions following cooling in 15 young (21.5 +/- 2.2 years; mean +/- SD) and 12 older (73.6 +/- 3.2 years) women. The authors highlighted that cooling had a greater effect on motor performance in young female adults compared to older female adults (Dewhurst et al., 2010). Although it is interesting to compare Bergh & Ekblom (1979) and Dewhurst et al. (2010), it is important to consider the gender difference in reponse to a thermal stress, as gender is a known factor affecting an individuals response (Figure 1.3). Ruiz et al. (1993) investigated the effect of cryotherapy on concentric and eccentric strength of the quadriceps in 19 male subjects and reported significant reductions in both eccentric (5-9%) and concentric (10-12%) strength immediately following a 25-minute application of ice. Interestingly, Ruiz et al. (1993) highlighted that the observed strength deficit only lasted less than 20 minutes following the ice intervention. More recently, Rhodes & Alexander (2018) explored the effects of knee joint cooling on quadriceps concentric isokinetic moment production on healthy male subjects. The authors reported decreases of approximately 16% in peak moment (35.6N.m) and average peak moment (26.1N.m) immediately post a 20-minute crushed ice application. In relation to the risk of knee injury, reduced quadriceps function and control may increase the likelihood of excessive or abnormal movements occurring (Shultz *et al.*, 2015; Rhodes and Alexander, 2018). Therefore, it is important to

understand the magnitude of inhibition of different cryotherapy interventions in order to ensure a safe return to weight-bearing activities.

Authors have advised that shorter applications of cryotherapy, as well as a warm-up prior to returning to weight bearing activity, could minimise the increased risk of injury post cryotherapy (Bleakley et al., 2012). As highlighted earlier in this chapter, emerging research suggests that a targeted cooling approach, which involves cooling a smaller surface area, may minimise the reduction to muscle strength (Alexander *et al.*, 2021b). Alexander et al. (2021b) compared a compressive cryotherapy device, Game Ready® and wetted ice to the novel cooling, heating and compression device tested in this thesis, to explore the effects on concentric knee extensor strength over a rewarming period. The authors reported that wetted ice reduced strength most significantly and this trend continued 20 minutes post intervention. One possible explanation suggested by the authors is that wetted ice interventions may have affected intramuscular temperature more than the other interventions, however this is purely a hypothesis, T_{im} was not measured (Alexander *et al.*, 2021b). Following these initial findings, Alexander et al. (2021b) highlighted that further investigation is required to optimise cryotherapy interventions using contemporary cooling devices compared to traditional methods for sport injury and recovery strategies. It is important to note that this study was carried out on healthy male subjects only and therefore cannot be generalised to a female or injured population.

2.5 Compression

Compression is used in acute injury to restore pressure gradients in the capillary beds within the injured tissue via lymphatic and venous return (Michlovitz, 1990). Michlovitz (1990) promoted the use of mechanical intermittent-compression devices to help maintain osmotic and hydrostatic pressures in the capillary beds via lymphatic and venous return. Landis (1930) found that the average capillary pressure in healthy volunteers was approximately 32mmHg at its arterial inflow as measured in the fingernail bed (arteriolar end of a capillary loop). Therefore, it was suggested if pressure exceeds 32 mmHg, then capillary occlusion (closure of the capillaries) would occur. This reflects findings from other studies which have reported 'ischaemia' between 30-35 mmHg, (Reswick and Rogers, 1976; Bradbury, 2005). In 1941 however, Landis revised this threshold for capillary occlusion to a higher range of 46-50 mmHg using a different technique (Kapp, Friedland and Landis, 1941) but 32mmHg is still the most commonly quoted value used, especially with manufacturers of body supports (Silber and Then, 2012). It has been cautioned that if a pressure of 70 mmHg is applied for 2 hours, it can cause dermal damage and pressure applied for 2 hours exceeding 80 mmHg could cause necrosis (Parish and Witkowski, 1994).

Bleakley et al. (2004) discussed that there is little evidence suggesting any significant effect of using ice and compression in comparison to compression alone. However, this evidence is limited to hospital patients only. Yet, there is evidence demonstrating that the addition of compression to cryotherapy provides more therapeutic benefit than cryotherapy alone (Capps and Mayberry, 2009; Holwerda *et al.*, 2013; Song *et al.*, 2016). Reported benefits include greater cooling to the skin surface and deeper tissues and a reduction in pain and swelling for patients undergoing knee surgery (Holwerda et al., 2013; Capps & Mayberry, 2009). Janwantanakul (2006) demonstrated that the greater the level of compression, the less time required to reduce skin temperature to the lowest temperature recorded. Hawkins et al. (2012) reported that static compression used with ice is more effective at cooling skin temperatures than a device using intermittent pneumatic compression with cooling.

The effectiveness of compressive cryotherapy compared to cryotherapy alone for patients undergoing knee surgery was assessed by Song et al. (2016), through a meta-analysis of

the available literature. Compressive cryotherapy and cryotherapy alone were both deemed safe treatments for these patients (Song *et al.*, 2016). The study concluded that compressive cryotherapy offered more therapeutic benefit than cryotherapy alone, producing a better analgesic effect, reduction in pain and better effect on swelling for patients undergoing knee surgery during the early stage of rehabilitation (Song *et al.*, 2016). The benefits were found particularly within the first three days post-surgery, with moderate quality evidence demonstrating that compressive cryotherapy is more effective at reducing pain between days 1-3 post knee surgery and for reducing swelling for days 1-2 post knee surgery. Therefore, novel cold compression devices were considered useful therapy adjuncts for post-operative management (Song et al., 2016). The compressive cryotherapy devices that were included in the review consisted of the Cryo Cuff® system, Game Ready® and Ever-Cryo® system, which have differing temperature and compression settings. Game Ready® offers target temperatures between 1-10 °C and low (5-15 mmHg), medium (5-50 mmHg) and high (5-75 mmHg) intermittent compression. Whereas the Cryo Cuff® system and Ever-Cryo® systems have less control on temperature and pressure settings as they consist of knee wraps connected to an ice/water tank, which circulates cold water. Compression is achieved through a manual air pump (Ever-Cryo®) and manually tightening the knee wrap (Cryo Cuff®); the exact magnitude of compression has not been reported. In the context of this thesis, it is important to mention that Game Ready® system offers control on temperature, compression, and time, however the target temperature is based on a sensor within the ice tank, opposed to the temperature being applied directly to the skin. The CHCD used in this thesis measures the temperature on the aluminium plate being applied directly to the skin, which offers greater accuracy for investigating different temperatures within cryotherapy interventions.

Tomchuk et al. (2010) observed that compression in the form of an elastic wrap provided a greater magnitude of cooling than a Flex-I-Wrap (self-adhering plastic film) and no compression. However, Tomchuk et al. (2010) did not measure the exact compression applied by the Flex-I-Wrap and the elastic wrap. Therefore, it is difficult to compare the two compression methods used and ultimately determine the effect of the magnitude of compression on tissue cooling.

2.6 Contrast Therapy

Contrast therapy is the alternation of heat (thermotherapy) and cold therapy (cryotherapy) (Myrer et al., 1997). Despite a general consensus within the literature of the main physiological effects of cryotherapy and thermotherapy separately (Lehmann, 1990; Lane and Latham, 2009; Malanga, Yan and Stark, 2015), the physiological basis of contrast therapy is not fully understood (Hing et al., 2008).

One theory suggests contrast therapy protocols promote a vasodilation/vasoconstriction 'pumping' action in order to reduce swelling and remove waste products (Cochrane, 2004). However, others argue that contrast therapy does not affect deep tissues enough to create the 'pumping action' of vasodilation and vasoconstriction (Myrer et al., 1997). Traditionally contrast therapy was used for soft tissue injury management but for the past few decades, it has been used for recovery post-exercise (Cochrane, 2004).

The most recently available systematic review by Hing et al. (2008) established a consensus from previous studies regarding temperature applications for contrast therapy protocols (cold = 10-15 ^{o}C and hot = 38-40 ^{o}C). However, the time of application varied amongst the studies significantly, ranging from 6 to 31 minutes (Hing et al., 2008). Previous studies surrounding contrast therapy have used hot/cold water immersion or hot/cold packs as the contrast therapy medium (Hing et al., 2008). Myrer et al. (1997) found that contrast therapy using ice packs and a hydrocollator pack produced no significant effect on the intramuscular temperature 1cm below the skin and subcutaneous fat after a 20-minute application. However, Hing et al. (2008) suggested contrast therapy may offer beneficial effects functionally (such as ROM, soreness, muscle power and perceived soreness) rather than the physiological outcome measures commonly evaluated in these studies. Gill et al. (2006) found that physiological recovery was significantly improved, with a greater creatine kinase removal, in elite male rugby players when either wearing compression garments, undertaking contrast water therapy or carrying out low impact exercise immediately post-competition compared to passive recovery.

It is clear that more evidence is required regarding the efficacy and effectiveness of contrast therapy in acute injury management and post-exercise recovery using different modalities.

2.7 The use of cryotherapy, compressive cryotherapy, and contrast therapy in the management of knee injuries and conditions

2.7.1 Acute Knee Injuries

Acute injuries are defined as an injury occurring within the last 48 hours. Therapeutic applications of cryotherapy are commonly used in both sport and clinical settings, due to the desired reduction of tissue temperature and reduction of cell metabolism (Jutte et al., 2001). It is often used pre, during (e.g., half-time) and post participation in sport, for injury prevention and to promote recovery but it is also used clinically to treat acute soft tissue injuries and for patients' post-surgery.

Astonishingly, there is currently no published research specifically on the use of cryotherapy on acute knee injuries. The guidance for acute soft tissue injury management is predominately supported by moderate evidence on the treatment of acute ankle sprains (Wilkerson and Horn-Kingery, 1993; Bleakley, McDonough and MacAuley, 2006; Collins, 2008), in addition to the pathophysiological rationale outlined earlier in this chapter. The majority of research in cryotherapy around the knee joint have explored effects on healthy participants or post-operative patients (mainly ACL repairs and knee/hip replacements) (Hubbard and Denegar, 2004).

Despite the evidence being mainly based on ankle injuries, as soft tissues undertake the same healing process, these guidelines have been applied to the entire soft tissue injury spectrum (Watson, 2003). Bleakley et al. (2011) identify moderate clinical evidence that local cryotherapy is effective at reducing short term pain in injuries such as acute ankle injuries and soft tissue contusions (Bleakley et al., 2011). Low quality evidence exists which presenting findings that shorter intermittent applications of cold therapy are sufficient to cause a cold-induced analgesic effect (Bleakley, McDonough and MacAuley, 2006). Bleakley, McDonough and MacAuley (2006) found that an intermittent application of cryotherapy after an ankle sprain (mild or moderate) significantly reduced subjective pain compared to a standard protocol but there were no differences found for function or swelling. Therefore, it was advised that intermittent applications of ice could enhance the therapeutic effect for acute soft tissue injury in regard to pain relief only (Bleakley, et al., 2006). There is a significant lack of evidence specifically investigating the use of cryotherapy on acute knee injuries.

There is currently no published research on the use of contrast therapy with acute injury as the primary intervention aim. The current best evidence for contrast therapy uses cold and hot water immersion, with a primary aim of post-exercise recovery (Greenhalgh *et al.*, 2021). A scoping review (Appendix D) addressing this gap in knowledge titled 'The Use of Contrast Therapy in Soft Tissue Injury Management and Post-Exercise Recovery: A Scoping Review' has been published in Physical Therapy Reviews, as part of this PhD.

The scoping review identified that there is a significant lack of research surrounding the efficacy of contrast therapy in regard to soft tissue injury management and the influence on physiological measures and performance. This could be due to the preference of the use of cold therapy for acute injuries to achieve the desired physiological changes occurring during the bleed phase of healing. Heat therapy is typically used in sub-acute and chronic stages.

2.7.2 Chronic Knee Conditions

Sari et al. (2019) compared the effects of intermittent pneumatic compression (45 mmHg) and cold-pack treatments on clinical outcomes in patients with knee OA. Significant improvements in range of motion, muscle strength, pain intensity, and functional status were reported for both treatment groups but interestingly, greater swelling reduction was observed in the intermittent pneumatic compression group compared to the cold-pack treatment group. Sari et al. (2019) reported an average reduction in knee swelling from pre-to-post treatment of 2cm (intermittent pneumatic compression) and 0.5cm (cold pack). However, it is important to note that both groups were also treated with ultrasound, TENS, electrical stimulation, and exercise, in addition to one of the interventions (either a cold-pack or the intermittent pneumatic compression). Therefore, it is difficult to conclude the effect of the cooling and compression interventions alone, due to the combination of treatments used. In contrast, Dantas et al. (2019) found that short-term cryotherapy (20 minutes over a 4-day period) did not significantly improve pain, function, and quality of life more than a sham intervention, as a non-pharmacological treatment for people with knee OA.

Denegar et al. (2010) recommended the use of contrast therapy in the early stages of managing patients with knee OA after investigating the use of cold, heat and contrast therapy using a wrap-around water-circulating garment and an electric heating pad. The authors concluded that the selection of heat, cold or contrast on knee OA patients was

dependent on individual preference. Greater pain relief and functional improvements were observed when patients were using their preferred modality. The wrap-around garment was commonly preferred to the heat pack. Interestingly, this is currently the only study in literature that uses contrast therapy on the knee. This may be due to the practicality of applying and alternating traditional cold and heat therapy modalities to the knee.

2.7.3 Overview

Despite an abundance of publications on cryotherapy for post-exercise recovery or soft-tissue injury management, Table 2.8 highlights that there is a lack of research on the use of cryotherapy for knee injury management specifically. Post-operative studies have been included in Table 2.8 due to the lack of literature available on acute and chronic injury populations.

Table 2.8: A summary of the key peer-reviewed articles relating to the use of cryotherapy for knee injury management, including post-operative management

Study	**No. and Gender of Participants**		**Age**	**BMI, Height, or Weight**	**Acute/Chronic or Post-Operative**	**Temperature Modality**	**Key Findings**
	Male	*Female*					
(Ohkoshi *et al.*, 1999)	10	11	22.1±6.5 years	Height: 165.0±8.0cm Weight: 63.1± 6.8kg Subcutaneous fat layer at the anterior patella: 6.8±3.4mm	Post-Operative	Icing System 2000 (Ice water circulating system)	Intraarticular knee joint temperature was reduced by cryotherapy after ACL reconstruction. This temperature decrease showed a three-phase pattern of change over time: 1) low-temperature phase, 2) temperature-rising phase and 3) thermostatic phase. Cryotherapy at 10 °C was effective in alleviating the patients' pain, while cooling at 5 °C was effective in reducing the volume of postoperative blood loss

(Kullenberg *et al.*, 2006)	Group 1: 18 Group 2: 16	Group 1: 25 Group 2: 24	Group 1: 68.1±6.0 Group 2: 68.9±6.8	Group 1: 64.61±13kg Group 2: 65.4±12.6kg	Post-Operative	Cryocuff® (Ice water circulating system) vs epidural analgesia	Range of movement at discharge was 75° in the compressive cryotherapy group, compared to 63° in the control group. At the 3 weeks' follow-up, ROM was 99° vs 88°. Mean time in hospital of patients with cold compression averaged 4.8 days, 1.4 days less than the control group. The study shows that cold compression therapy improves the control of pain which may lead to improvement in ROM and reduce the length of hospital stays.
(Woolf *et al.*, 2008)	29	24	42.4 years (range: 14-73 years)	n/a	Post-Operative	Continuous cryotherapy system (Polar Care 500) vs an ice pack	Significant reduction in knee pain and less night-time awakening, 48 hours post-surgery occurred following the use of compressive cryotherapy devices compared to cryotherapy alone.
(Denegar *et al.*, 2010)	11	23	62 ± 14 years	n/a	Chronic – Knee OA	Ice pack, heat pack, contrast therapy	The selection of heat, cold or contrast on knee OA patients was dependent on individual preference. Greater pain relief and functional improvements were

							observed when patients were using their preferred modality. The wrap-around garment was commonly preferred to the heat pack.
(Waterman *et al.*, 2012)	30	6	Mean: 30.9 years (control) 28.7 years (compressive cryotherapy)	68.5 inches, 179.2ibs (control) 69 inches, 188.1ibs compressive cryotherapy)	Post-operative	cryotherapy/compression device vs ice pack	Compressive cryotherapy in the improved, short-term pain relief and a greater likelihood of independence from narcotic use compared with cryotherapy alone, in the postoperative period after ACL reconstruction
(Kang, Kim and Choi, 2014)	46 (gender not specified)	n/a	Group 1: 66.6±3.9 Group 2: 68.5±4.7 Group 3: 67.6±3.5	Group 1: H - 155.4±4.7cm W - 56.6±3.7kg Group 2: H - 156.2±4.6cm W - 59.1±8.2kg	Post-operative	Crushed ice	A combination of low-intensity pulsed ultrasound and cryotherapy together can relieve inflammation and enhance joint function, for total knee replacement patients.

				Group 3: H - 157.1±3.6cm W -58.9±5.1kg			
(**Wittig-Wells *et al.*, 2015)**	11	18	64 ± 9.3 years	n/a	Post-operative	Crushed ice	A 30-minute application of crushed ice with analgesic medication administration did not significantly decrease pain or improve patient satisfaction with pain management compared with analgesic medication administration only.
(Kuyucu *et al.*, 2015)	60 (gender not specified)	n/a	Ranged between 57-78 yrs (mean 68.4 yrs)	n/a	Post-operative	CryoCuff®	After knee arthroplasty, the preoperative and postoperative use of cryotherapy (cryocuff) is effective for pain relief and functional knee scores without a significant change in surgical blood loss.
(Ruffilli *et al.*, 2017)	7 (study) 9 (control)	17 (study) 9 (control)	n/a	78.9±12.6kg 164.7±8.7 (study) 78.1±11.5kg 163.7± 8.0cm (control)	Post-operative	Hilotherm (Hilotherm GmbH, Germany) continuous cooling device vs crushed ice	Continuous cold flow device did not show superiority in reducing oedema, pain, and blood loss, compared with crushed ice, in the acute post-operative. setting after a total knee replacement

(Dantas *et al.*, 2019)	30	30	60±7 years	Weight: 83.5 - 85kg Height: 164-166cm 30.7-31.0 kg/m2	Chronic – Knee OA	Crushed ice	Short-term cryotherapy (20 minutes over a 4-day period) did not significantly improve pain, function, and quality of life more than a sham intervention, as a non-pharmacological treatment.
(Sari *et al.*, 2019)	68	13	50.77 ± 9.49 (IPC group) 52.25 ± 6.95 (cold pack)	28.90 ± 5.78 kg/m2 (IPC group) 28.72 ± 5.65 kg/m2 (cold pack)	Chronic – Knee OA	Intermittent pneumatic compression vs cold packs	Significant improvements in range of motion, muscle strength, pain intensity, and functional status were reported for both treatment groups but interestingly, greater swelling reduction was observed in the intermittent pneumatic compression group compared to the cold-pack treatment group. An average reduction in knee swelling from pre-to-post treatment of 2cm (intermittent pneumatic compression) and 0.5cm (cold pack).

Chapter 3: General Methods, Validation and Reliability

3.1 Research Design Overview

Figure 3.1 summarises the three intervention studies within this thesis, using the PICO model for clinical questions (patients/population, intervention, comparison and outcome) (Leonardo, 2018; Richardson *et al.*, 1995).

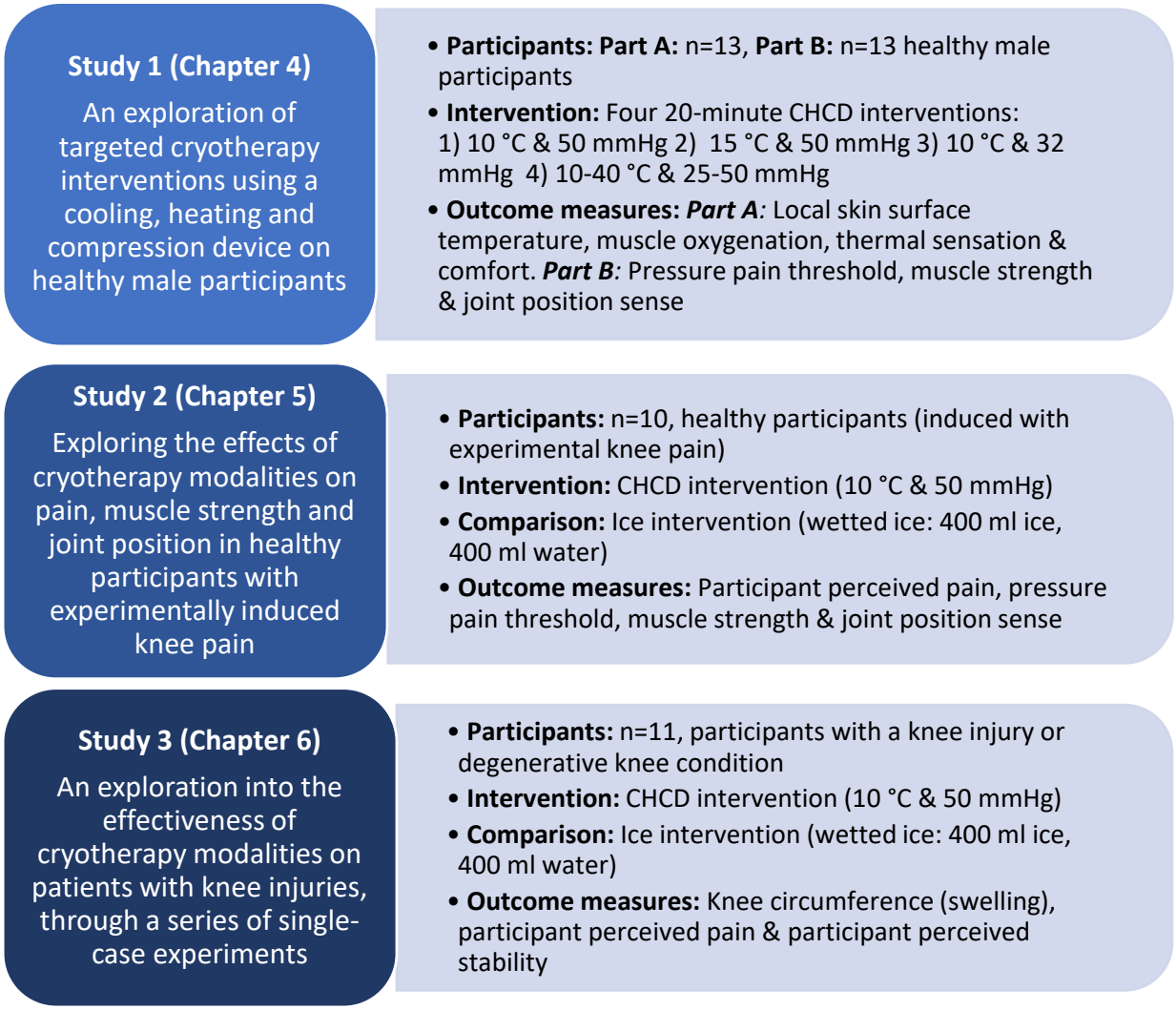


Figure 3.1: Summary of the intervention studies included in this thesis, using the PICO model

3.2 Ethical approval

All studies were approved by the Faculty of Health, Psychology and Social Care Ethics committee of Manchester Metropolitan University and by STEMH (Science, Technology, Engineering, Medicine, and Health) Ethics committee of University of Central Lancashire. The details of the ethical approvals granted for each study are reported in the relevant study chapters (Chapters 4-6) and Appendix B. Written informed consent was obtained from all participants, prior to data collection (Appendix A).

3.3 Outcome Measures

3.3.1 Skin surface temperature (Chapter 4)

Local skin surface temperature (T_{sk}) was explored during Study 1A outlined in Chapter 4. T_{sk} data was collected using thermal imaging (TI). A ThermoVision A40M TI camera (FLIR Systems, Danderyd, Sweden) was mounted on a tripod (set at 53cm), perpendicular to the defined region of interest (ROI) over the anterior, medial, and lateral aspects of the knee, whilst the participants remained in a long sitting position on a clinical plinth. The TI camera was set with an emissivity of 0.97-0.98 and was connected to a computer with the corresponding TI software (Thermacam Researcher Pro 2.8, FLIR systems, Danderyd, Sweden).

The ROI was defined using thermally inert markers placed on the non-dominant leg of the following anatomical landmarks:

- tibial tuberosity
- lateral and medial border of patella in line with the tibiofemoral joint line
- medial and lateral epicondyles of the femur
- medial and lateral condyles of the tibia

This ROI was also used in Alexander et al. (2021b). The minimum T_{sk} within this ROI on both the medial and lateral aspect of the participants non-dominant knee were manually recorded pre-intervention, immediately post intervention and for every 5 minutes thereafter until 20 minutes-post intervention.

In line with Thermographic Imaging in Sports and Exercise Medicine (TISEM) guidelines (Moreira *et al.*, 2017), the participants completed a 20-minute acclimatisation period prior to data collection. Additionally, participants were asked to avoid significant alcohol or caffeine consumption, smoking , large meals, ointments, cosmetics, sunbathing and showering for 4 hours prior to the testing sessions (Moreira *et al.*, 2017).

The current best evidence in the literature suggests that TI is an accurate and reliable method of collecting T_{sk} data following cryotherapy (Costello *et al.*, 2012b). A systematic review by Selfe et al., (2008) suggested that a temperature asymmetry >0.5 °C at the anterior knee is a clinically important difference. The reliability of this method of measuring TI is presented in more detail in Table 3.2.

3.3.2 Muscle strength (Chapters 4 & 5)

Muscle strength was measured using a handheld dynamometer (HHD) (Model 01165, Lafayette Instrument Co, Lafayette, IN) to obtain an isometric measure of quadriceps extension strength.

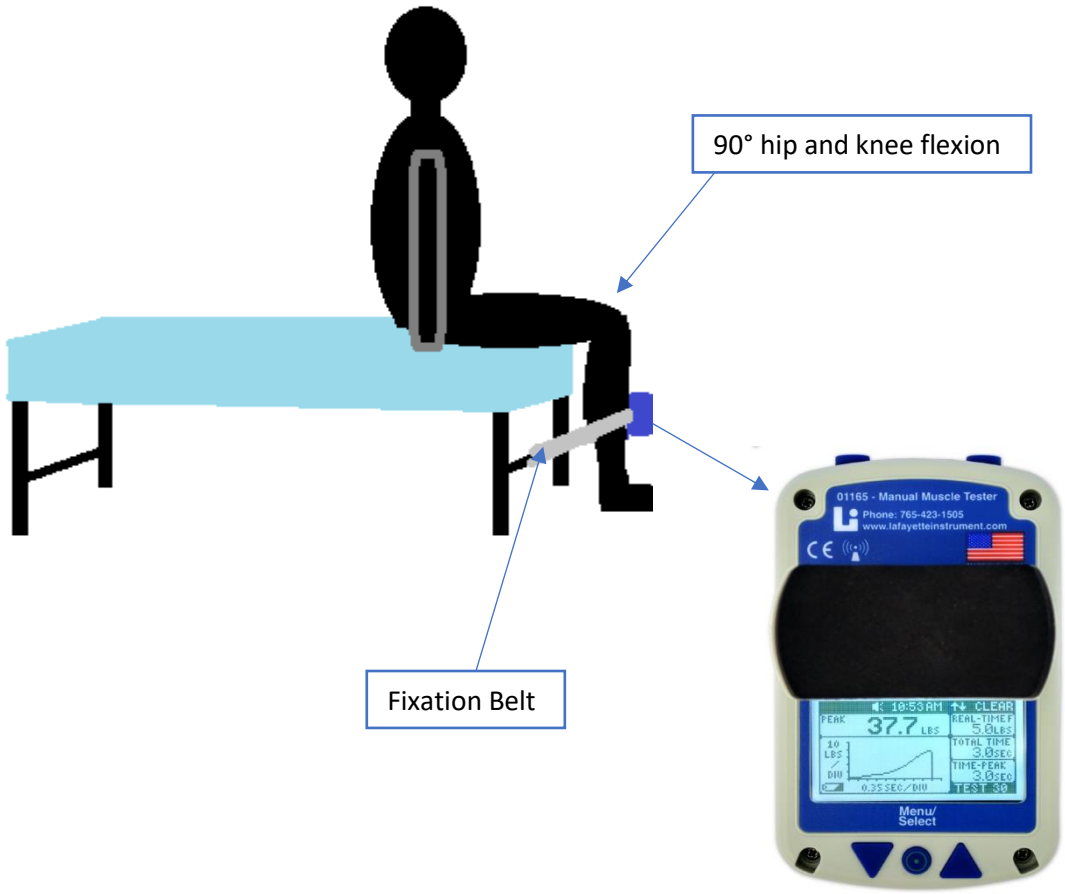


Figure 3.2: The experimental set up for measuring quadriceps strength using the HHD.

The HHD device was fixed to a belt and placed on the anterior aspect of the participants tibia on their non-dominant leg. The non-dominant leg was used as the weight-bearing limb in the studies outlined in Chapters 4 & 5, due to the increased injury rates (Krajnc *et al.*, 2010).

Participants were seated on the end of the clinic plinth, with a starting position of 90° hip and knee flexion (Figure 3.2). The tibial pad on the HHD was securely placed on the tibia, approximately 3cm superior to the lateral malleolus (Selfe *et al.*, 2006). The tester ensured that the HHD device was stable on the participants tibia during the assessments.

Participants were asked to perform a 'make test' applying maximum force to extend the knee joint for 5 seconds, resisting against the fixation belt. This was repeated three times with 60 seconds' rest. The mean of three trials was used to calculate quadriceps peak

moment. Quadriceps peak moment (Nm) was calculated using the average muscle force (N) multiplied by the lever arm length (m). This was then normalised to obtain an index of quadriceps strength independent to body size reported in Nm/Kg (Almeida, Albano and Melo, 2019).

Literature highlighted that a fixation belt increases the reliability of measuring knee extension strength using a HHD (Bohannon *et al.*, 2012; Katoh and Yamasaki, 2009; Katoh, Hiiragi and Uchida, 2011). HHD measurements without a belt can be significantly affected by tester strength (Wikholm and Bohannon, 1991). It is important to note that studies within Chapter 4 & 5 used the same tester for all participants. Isometric knee extension assessments using a HHD with a belt are equally reliable as measurements using an isokinetic dynamometer, in healthy subjects (Katoh, Hiiragi and Uchida, 2011; Katoh and Yamasaki, 2009).

Currently, there is no MCIC published for isometric quadriceps strength. However, reductions of 4% in isometric quadriceps strength and 6% in quadriceps strength normalised to body mass have been associated with clinically important changes in WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) functional disability scores in subjects with knee OA (Ruhdorfer, Wirth and Eckstein, 2015). The reliability of this method of measuring strength using a HHD is presented in Table 3.2

3.3.3 Joint position sense (Chapter 4 & 5)

3.3.3.1 Qualisys Camera System

The Qualisys motion capture system (Qualisys medical AB, Gothenburg, Sweden) in the Movement Laboratory at Manchester Metropolitan University was used for data collection of 3D kinematic motion. Three-dimensional motion was assessed within two studies (Study 1B and 2) outlined in this thesis to explore knee joint ROM. The reliability of this method of measuring 3D kinematic motion is presented in more detail in Table 3.2.

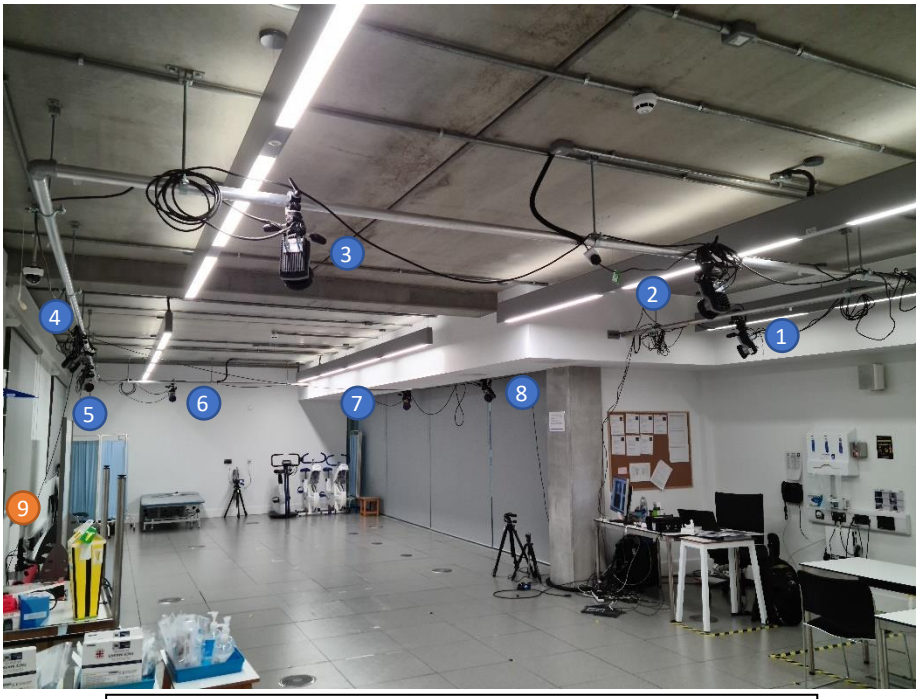


Figure 3.3: The Qualisys motion capture system in the Movement Laboratory at Manchester Metropolitan University

Oqus 210c Vector camera, in the configuration illustrated in Figure 3.3. The Qualisys motion capture system uses software called Qualisys Track Manager (QTM). Prior to 3D motion capture data collection, a thorough calibration was carried out. The calibration consisted of both static and dynamic calibration. Static calibration involved placement of a Qualisys 'L' shape, with four retroreflective markers (Calibration Kit, Qualisys Medical AB, Gothenburg) (Figure 3.4) on the origin point (force plate seen in Figure 3.4), where the small knee bend was being performed. Dynamic calibration consisted of a calibration wand (Calibration Kit, Qualisys Medical AB, Gothenburg) (Figure 3.4), with two

retroreflective fixed markers, being rotated to cover all of the volume of interest, through all three planes of motion. This is recommended in the manufacturer's guidelines (Qualisys, 2017). Dynamic calibration was sampled at 100Hz, for a period of 30 seconds.

Calibration of this system was to ensure the accuracy of the data collected and to identify average residual values of the camera system. On the calibration results report, average residual values (mm) and 'points' were checked for consistency between cameras. The standard deviation of wand length refers to the length of the measurements recorded during calibration compared to the known length of the calibration wand. Therefore, in the manufacturer's guidance (Qualisys, 2017), it's recommended to have this value as low as possible. For this study, calibration results with a standard deviation of wand length of 0.4mm and average residual values of <1 mm for each camera were accepted. Calibrations with a standard deviation of wand length over 0.4mm or residual values of >1 mm were repeated.

Figure 3.4: Qualisys calibration kit used in dynamic calibration

3.3.3.2 Marker Placement

Retroreflective markers (Super-spherical markers, Qualisys Medical AB, Gothenburg) were used to achieve segment modelling in Visual 3D (Version 2020 10.3, C-Motion, USA) (Figure 3.5). The Calibrated Anatomical Systems Technique (CAST) was adopted for segment tracking and modelling, using a 6 degree-of-freedom model (Cappozzo *et al.*, 1995). CAST is a widely used technique in clinical research, which involves the estimation of anatomical landmarks positioning based on the position of other markers (Cappozzo *et al.*, 1995; Ceccon *et al.*, 2013). A static recording of the participant in the anatomical position was obtained, in order to reference the position of the anatomical markers in relation to the cluster markers.

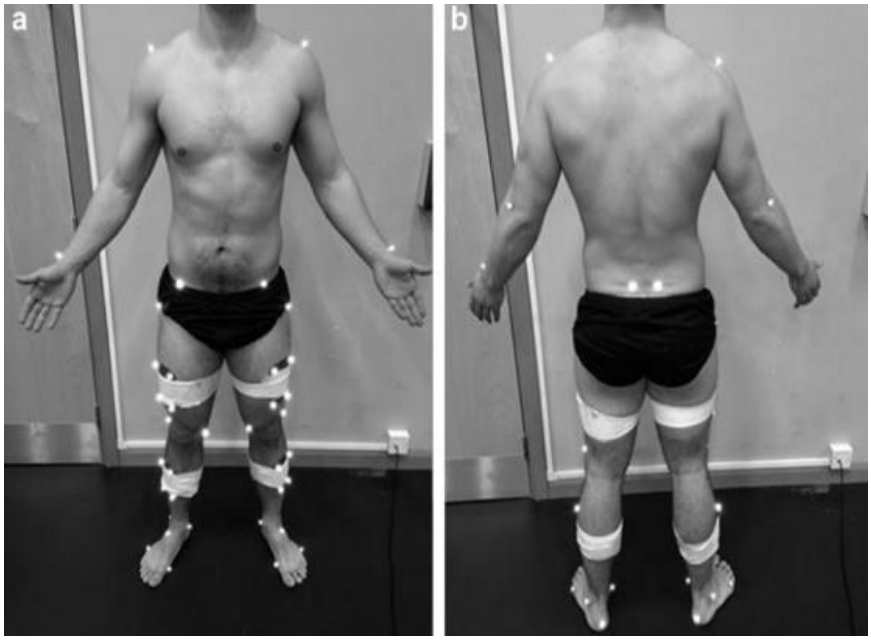


Figure 3.5: The marker set used in Alexander et al. (2016), which was replicated in this study to capture 3-D motion. Image published in Alexander et al. (2016)

Twenty-two markers were placed on the following anatomical landmarks, as per Figure 3.5: posterior superior iliac spine (PSIS), anterior superior iliac spine (ASIS), greater trochanter, medial epicondyle of the femur, lateral epicondyle of the femur, medial malleolus, lateral malleolus, calcaneus, dorsal aspect of first metatarsal heads, dorsal aspect of fifth metatarsal heads, middle cuneiform. Clusters of four markers, attached to a thin sheath of lightweight carbon fibre, were applied to the anterolateral aspect of the tibia and femur. The retroreflective markers used were 12.5mm spheres and on a flat plastic base. The marker base was attached to the participants' skin using double-sized hypo-allergenic tape. This lower-limb marker set has been used in previous clinical research (Sinclair *et al.*, 2013; Alexander *et al.*, 2018).

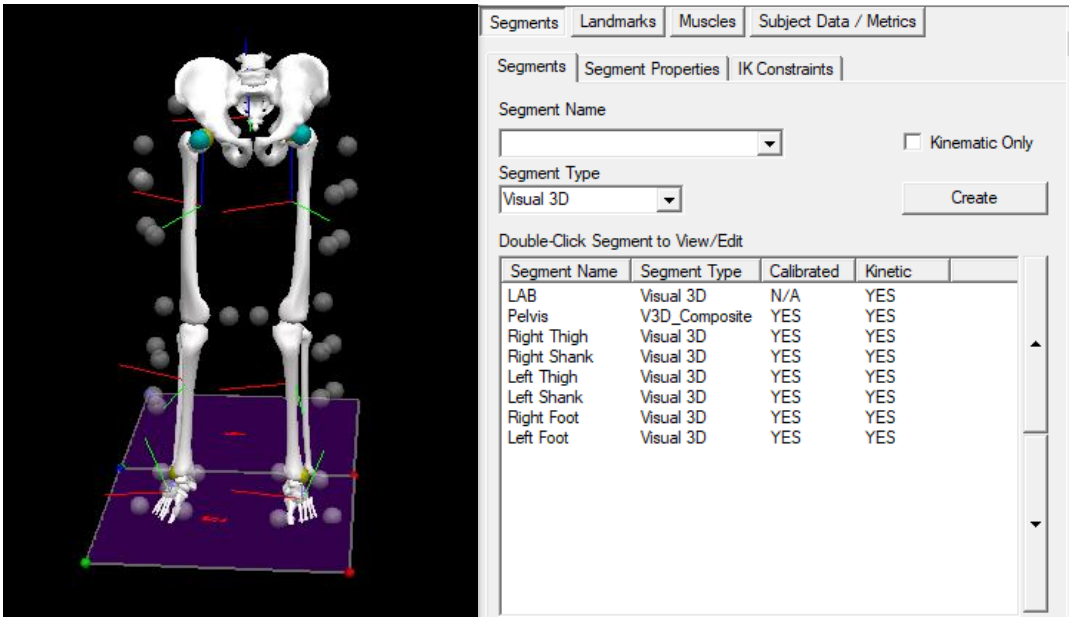


Figure 3.6: Segment modelling in Visual 3D

The pelvis was modelled as a 'V3D Composite' segment type using the markers from ASIS and PSIS. The thigh, shank and foot segments were modelled by using markers to define the proximal and distal ends of each joint. For the thigh, the greater trochanter and hip joint centre were defined as the proximal end and the medial and lateral femoral epicondyles were defined as the distal end. The cluster of markers on the thigh were used for thigh segment tracking. For the shank segment, the medial and lateral femoral epicondyles were defined as the proximal end and the medial and lateral malleoli as the distal end. The cluster of markers on the shank were used for shank segment tracking. For the foot, the medial and lateral malleoli were as the proximal end and the first metatarsal (medial), and fifth metatarsal heads (lateral) were defined as the distal end. Other markers on the foot (calcaneus and middle cuneiform) were used for foot segment tracking.

3.3.3.3 Events

For the small knee bend task, participants were asked to produce a 45° knee bend on their non-dominant knee. The non-dominant leg was used as the weight-bearing limb in the SKB, due to the increased injury rates (Krajnc *et al.*, 2010). The dominant leg was defined as the leg which the participant would spontaneously kick a ball with (Greenberger and Paterno, 1995; van Melick *et al.*, 2017).

Minimum and maximum values of the non-dominant knee joint were labelled using an 'Event Maximum' and 'Event Minimum' pipeline commands in Visual3D. Manual checks

were carried out for each trial to ensure minimum and maximum events labels for each small knee bend. As some participants were right dominant and some were left dominant, right knee values were negated in the X, Y and Z planes and left knee values were negated just in the X plane for analysis purposes in Visual3D to differentiate between the legs.

3.3.4 Pressure pain threshold (Chapters 4 & 5)

Pressure pain threshold (PPT) was defined as the point at which the sensation of 'pressure' changed to 'pain' as signalled by the participant verbally. PPT was measured on the medial aspect of the non-dominant knee (the area being cooled), using a digital algometer (FPX Pain Tester, Wagner, USA). The algometer had a flat circular rubber probe with a surface area of $1cm^2$. The force was applied at a rate of approximately 40 kPa/sec (Keating *et al.*, 2001). The mean of 3 trials was calculated and used for analysis. A 'cluster protocol' was adopted which consists of three measurements being taken successively with a 30 second rest between each measurement, before moving onto the next anatomical location. This method is considered an appropriate protocol for measuring PPT in a clinical research setting (Bisset, Evans and Tuttle, 2015). The minimal detectable change (MDC) in a healthy population at the tibialis anterior was reported as 86.3 kPa (Walton *et al.*, 2011). The reliability of measuring PPT using this method is presented in Table 3.2.

3.3.5 Muscle oxygenation (Chapter 4)

Muscle oxygenation (measured in SmO_2 - Saturation of muscle tissue with oxygen) was measured using a Moxy muscle oxygenation monitor (Swinco, Zurich, Switzerland) located on the tibialis anterior. The PeriPedal software (PeriPedal, Napoleon, USA) was used to record and monitor the data. The tibialis anterior was selected due to the close proximity of the muscle belly to the cooling area. Crum et al., (2017) supports the validity of the Moxy device measuring SmO_2. Reliability of muscle oxygenation is presented in more detail in Table 3.2.

3.3.6 Knee Circumference (Chapter 6)

A standard fabric tape measure was used to record the participant's knee circumference, over the centre of the patella, in order to monitor local knee swelling. Swelling is frequently assessed as an outcome measure when determining the effectiveness of a treatment for an acute soft tissue injury (Bleakley, McDonough and MacAuley, 2006). During the initial assessment, participants were shown how to measure their knee circumference. Participants were asked to record their own knee circumference consistently throughout the intervention period. Differences have been reported between testers when recording knee circumferences so it was important to ensure the same individual performed the measurements (Jakobsen *et al.*, 2010). It is also important to note that Jakobsen et al. (2010) highlighted that the clinical experience of the individual did not seem to affect knee joint circumference reliability. Reliability of knee circumference measurements using a tape measure is presented in Table 3.2.

Rohner-Spengler et al. (2007) reported estimated magnitude of oedema for malleolar fracture post-operative patients by measuring each ankle (using the Figure-of-Eight method) and reporting the difference between the affected and unaffeced ankle. Therefore, the participant's non-injured knee circumference was also recorded. However, it's important to keep in mind that individuals' knee circumference may be asymmetrical.

With no defined MCIC explicitly reported for swelling reduction, a reduction of 0.5cm in knee circumference will be required to deem an intervention a clinically relevant treatment, as Sari et al. (2019) reported this figure following a standard clinical cold-pack treatment on patients with knee osteoarthritis. It is important to note that patients within Sari et al. (2019) were also treated with ultrasound, transcutaneous electrical nerve stimulation, neuromuscular electrical stimulation, and exercise as part of the intervention.

3.3.7 Thermal sensation and comfort (Chapter 4)

Thermal sensation and comfort scores were collected during Study 1A reported in Chapter 4 (section 4.3). Thermal comfort and sensation ratings were collected using thermal comfort & sensation numeric rating scales (Cholewka *et al.*, 2012; Iso, 1995). Participants were asked to rate their thermal comfort on a five-point scale (Iso, 1995) on the scale in Figure 3.7. Participants were asked to rate their thermal sensation on the nine-point standard scale in Figure 3.8 (Cholewka *et al.*, 2012). Participants were instructed to state their sensations at the time of reporting.

0	1	2	3	4
Comfortable	Slightly Uncomfortable	Uncomfortable	Very Uncomfortable	Extremely Uncomfortable

Figure 3.7: Thermal Comfort Scale

+4	+3	+2	+1	0	-1	-2	-3	-4
Very Hot	Hot	Slightly Hot	Slightly Warm	Neutral	Slightly Cool	Cool	Cold	Very Cold

Figure 3.8: Thermal Sensation Scale

The reliability of the thermal sensation and comfort scales have not yet been reported in the literature. However, reliability of five-point and nine-point Likert type scales in general are presented in Table 3.2.

3.3.8 Participant perceived pain (Numeric pain rating scale) (Chapters 5 & 6)

Participant perceived pain scores were measured using a numeric pain rating scale (NPRS) in studies 2 & 3 outlined in this thesis (Chapters 5 & 6). The NPRS consists of an 11-point scale where 0=no pain and 10=worst possible pain (Farrar *et al.*, 2001) (Figure 3.9).

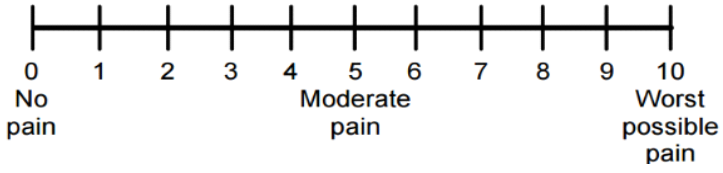


Figure 3.9: The numeric pain rating scale

Reliability of the NPRS is presented in Table 3.2. The minimal clinically important change (MCIC) reported as the following for different patient groups; 1.3-points (acute pain, emergency room) (Bijur, 2003), 1 point (chronic musculoskeletal pain) (Salaffi *et al.*, 2004) and 1 point (patellofemoral pain) (Piva *et al.*, 2009).

Sloman et al. (2006) stressed the importance of considering initial pain levels and suggested presenting NPRS change as a percentage. The authors highlighted that a 2-point change from 2 to 0 may be more meaningful than a 2-point change from 10 to 8. Post-operative clinically meaningful percentage improvements were reported as; minimal relief - 35%, moderate relief - 67%, much relief - 70% and complete relief - 93% (Sloman et al., 2016).

3.3.9 Participant perceived stability (Chapter 6)

Participant perceived knee stability was explored during the single-case experiments reported in Chapter 6. Participants reported their perceived stability using an 11-point scale, which ranged from 'very unstable' to 'very stable' (Figure 3.10).

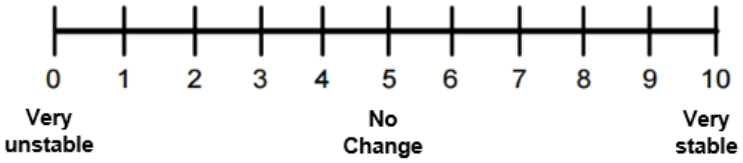


Figure 3.10: Stability 11-point scale

With no defined MCIC explicitly reported for reductions in participant-reported knee instability, the global rate of change for an 11-point numeric rating scale of 2-points was used to assess the participant-reported perceived knee stability scores (Jaeschke, Singer and Guyatt, 1989). A 2-point change is a common value used to assess clinically important changes for 11-point scales (Jaeschke, Singer and Guyatt, 1989; Farrar *et al.*, 2001). Reliability of an 11-point numeric scale is presented in Table 3.2.

3.4 Data analysis (Chapter 4, 5 & 6)

For the kinematic data collected in Chapters 4 & 5, anatomical markers were labelled in Qualisys Track Manager and exported as a C3D file. The C3D files were then imported into Visual 3D (Version 2020 10.3, C-Motion, USA). Knee joint angles were exported, including mean and standard deviation data, as an ASCII file. Data was also normalised to 101 data points. ASCII files were imported into Microsoft Excel for further processing. Average minimum, maximum and knee joint range of motion values were calculated for each time point and used in statistical analyses.

All statistical analyses in Chapters 4 & 5 were carried out in Statistical Package for the Social Sciences (SPSS, IBM Version 27, USA). For most outcome measures, repeated measures ANOVAs (3x2) with post-hoc pairwise comparisons, were used to assess changes between time points and interventions. The significance level was set at $P<0.05$. MCIC and MDC values reported in literature were used in analysis, if appropriate.

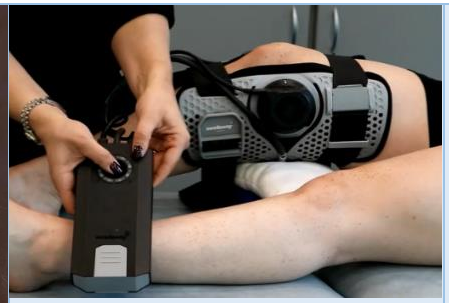
Chapter 6 adopted a single-case experiment design, which assessed individuals temporarily across three consecutive days, in order to understand the effectiveness of interventions. Visual analysis of graphical data was conducted for each individual. Effect sizes were calculated for each outcome measure and compared between interventions. Cohen's d effect sizes were calculated by subtracting the difference between two means and dividing by the data's standard deviation, for each outcome measure and compared between interventions. Visual analysis and effect size calculations are relevant analysis methods for single-case research using an alternating treatment design (Barker *et al.*, 2011). Each outcome measure was assessed for the clinical relevance using the relevant MCIC and global rate of change.

3.5 Cooling, Heating and Compression Device Summary

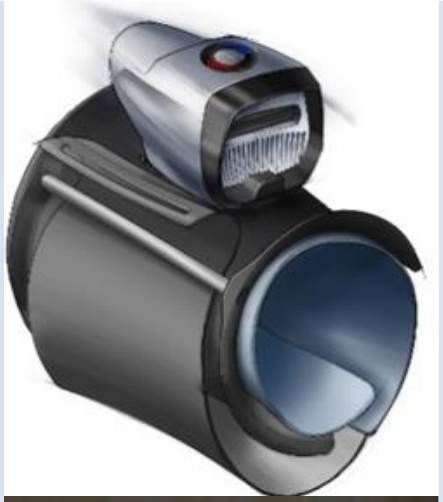
Due to the commercial ties associated with this PhD, the cooling, heating, and compression device (CHCD) evolved through two prototype iterations during the time frame of this PhD research (Table 3.1). The first prototype iteration, Swellaway Knee Unit, was used in the preliminary testing undertaken in Chapter 4. The second prototype, *ProMOTION* V1, was used for the main intervention studies discussed in Chapters 5 and 6. In an ideal world, the same prototype would have been used throughout all the intervention studies. However, the preliminary results reported in Chapter 4 identified areas to develop the first prototype iteration (Swellaway Knee Unit), in order to optimise performance and usability prior to commercially launching the product. In addition to market feedback, these results informed the development and redesign of the first prototype iteration. The device was rebranded and commercial launched in September 2021 as *ProMOTION* EV1.

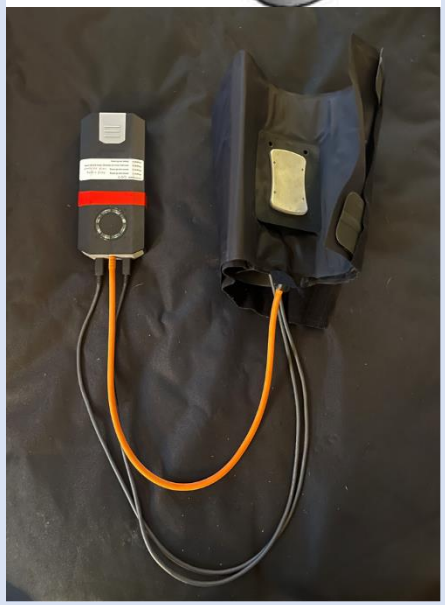
The findings from Chapter 4 informed the development of the compression design, which evolved from a brace design applying pressure through medial and lateral pneumatic bladders, to a circumferential pneumatic knee wrap. Additionally, due to market feedback indicating that the prototype needed to be more anatomically versatile, the medial and lateral cooling plates (7 x 5cm each = 70cm^2) in the first prototype were changed to one larger cooling plate (10 x 7cm = 70cm^2), which could be positioned on either side of the knee joint or other areas of the lower limb. However, it is important to note that despite design changes, the total surface area cooled remained the same and the core technology achieving the cooling and heating remained the same.

Table 3.1: A summary of the CHCD prototypes used in this thesis

Prototype Iteration	**Image of the Prototype**	**Prototype In Use**	**Study**	**Interventions**
Swellaway Knee Unit V1			**Chapter 4:** An exploration of targeted cryotherapy protocols, using the Swellaway Knee Unit, on healthy male participants.	10 °C & 50 mmHg 15 °C & 50 mmHg 10 °C & 32 mmHg 10-40 °C & 25-50 mmHg

ProMOTION V1





Chapter 5: Exploring effects of cryotherapy modalities on pain, muscle strength and joint position sense in healthy participants with experimentally induced knee pain.

Chapter 6: An exploration into the effectiveness of cryotherapy modalities on patients with knee injuries, through a series of single-case experiments

10 °C & 50 mmHg

3.6 Outcome Measure Reliability

Reliability indicates the extent to which a measurement can be replicated (Daly & Bourke, 2000). Test-retest reliability is defined as the variation in measurements, using the same participant, under the same conditions and is critical in research to understand the measurement error of instruments (Koo & Li, 2016; Hopkins, 2000). Intrarater reliability is defined as the variation within data, when measured by 1 rater for 2 trials or more (Koo & Li, 2016). Whereas interrater reliability refers to variation between raters (2 or more), when measuring the same participant group (Koo & Li, 2016). Intraclass correlation coefficient (ICC) is commonly used as a measure of reliability, as it reflects both the degree of correlation, and the agreement between measurements (Koo & Li, 2016). ICC can be graded from excellent to poor based on the 95% conference interval of the ICC value. Excellent reliability would be considered from ICC values greater than 0.90, good reliability between 0.75-0.90, moderate reliability between 0.5-0.75 and poor reliability less than 0.5 (Koo & Li, 2016).

MDC is defined as the smallest detectable change beyond measurement error (de Vet and Terwee, 2010). Therefore, a change less than the MDC could be due to measurement error. Whereas, MCIC is defined as the smallest change that patients perceive as beneficial (Jaeschke, Singer and Guyatt, 1989).

Table 3.2 presents the test-retest reliability, ICC, SEM, MDC and MCIC identified in literature for the outcome measures outlined in Section 3.3.

Table 3.2: Reliability studies presented in literature for the outcome measures outlined in Chapter 3

Outcome Measure	**Equipment**	**SEM**	**ICC (Intra-rater)**	**ICC (Inter-rater)**	**Test-retest**	**MDC**	**MCIC**	**Other**
Skin Surface Temperature	ThermoVision A40M (FLIR Systems, Danderyd, Sweden) Emissivity: 0.97-0.98	Thermal imaging measured on average 1.8 °C (±1.16) higher in comparison to a thermistor (Maley et al., 2020)	Good-Excellent: 0.82-0.97 (Selfe et al., 2006)					Ideal therapeutic range has been reported as 10-15 °C (Rivenburgh, 1992) A systematic review by Selfe et al. (2008) suggested that a temperature asymmetry >0.5ºC at the anterior knee is clinically important.
Muscle Strength	Lafayette manual muscle tester (model 01165) electronic hand dynamometer	9.3% 7.73% (Mentiplay et al., 2015) 1.02Nm/kg (0.6%) (Almeida et al. 2019) <u>Knee extensors</u>	Excellent: 0.91 (Mentiplay et al., 2015). <u>Knee extensors:</u> Excellent: 0.91 (0.82, 0.96) (Right limb) 0.93 (0.84, 0.96) (Left	Good: 0.89 (Mentiplay et al., 2015) Excellent: 0.98 (Almeida et al. 2019)	Excellent: 0.98 (Almeida et al. 2019)	21.42% (Intra) 18.23% (Inter) (Mentiplay et al., 2015). 2.8Nm/kg (1.7%) (Almeida et al. 2019)		Hand-held dynamometer presented moderate to good validity with the IKD (isokinetic dynamometer), evaluating quadriceps peak moment in patients with ACL reconstruction (Almeida et al. 2019). Weng et al. (2015) found a significant correlation for the comparison between the HHD (Lafayette HHD model 01163)

		Right limb: 18.9Nm (12%) Left limb: 18.4Nm (12%) (Martins et al., 2017)	limb) (Martins et al., 2017)			<u>Knee extensors</u> Right limb: 52.4Nm Left limb: 51.1Nm (Martins et al., 2017)		and Cybex dynamometer ($r=0.71$, $r^2=0.504$, $p=0.001$ and concluded that HHD can be used in clinical practice Reductions of 4% in isometric quadriceps strength and 6% in quadriceps strength normalised to body mass were associated with clinically important changes in WOMAC functional disability scores (Ruhdorfer, Wirth and Eckstein, 2015).
Joint Position Sense	Nine camera infra-red Oqus motion analysis system (Qualisys medical AB, Gothenburg, Sweden)	1.29 (Intra) 1.25 (Inter) -0.1-0.2° systematic error (Agustsson et al., 2019)	Excellent: 0.997 (Agustsson et al., 2019)	Excellent: 0.997 (Agustsson et al., 2019)				Five repetitions during an assessment of active knee joint positioning are recommended for stabilisation of the data (Selfe et al., 2006).
Pressure Pain Threshold	Digital algometer (FPX Pain Tester, Wagner, USA)	*Healthy, Intra:* 18.2 kPa (upper fibres of trapezius) 37.4 kPa (tibialis anterior)	Excellent: 0.94-0.97 (Walton et al., 2011) Tibialis Anterior 0.92	Good: 0.79-0.84 (Walton et al., 2011)	*Good: 0.76-0.79* (Walton et al., 2011)	*Healthy, Intra:* 86.3 kPa (Tibialis Anterior) *Inter:* 137 kPa (Tibialis Anterior)		15–25% changes have been recommended as indicative values for a clinically important change (McGregor *et al.*, 2014). Ohrbach and Gale (1989) found no significant difference over 5 trials and therefore

		Inter: 52.5 kPa (UFT) 59.2 kPa (TA) (Walton et al., 2011)	(95% confidence interval: 0.76-0.98) (Bisset, Evans and Tuttle, 2015)			(Walton et al., 2011)		concluded no measurement effect. Digital algometers are considered more reliable than algometers with a manually-operated stop button due to the increased control of rate of pressure and the non-reliance on reaction time of the researcher/clinician (Vaughan, McLaughlin and Gosling, 2007).
Muscle Oxygenation	Moxy muscle oxygenation monitor (Swinco, Zurich, Switzerland)		Good-Excellent: 0.773–0.992 Spearman's Rank-Order correlation: r = 0.842–0.993 (Crum et al., 2017)					Crum et al. (2017) stated that Moxy is a reliable device for the measurement of SmO_2 at low-moderate intensities, but increased intensity leads to increased variation in measurements.
Knee Circumference	Standard Tape Measure	Coefficient of variation 0.14 (Tan et al., 2013)	Good-Excellent: 0.98, 0.97, 0.82 (involved leg)	Excellent: 0.989				Sari et al. (2019) reported an average reduction in knee swelling from pre-to-post treatment of 2cm

		Mean difference between the raters of 0.48 cm (da Silva et al., 2014) Average variation 0.160 cm^2 (Nicholas, et al., 1976)	0.91, 0.85, 0.88 (uninvolved leg)	(CI 95%: Inferior 0.97 Superior 0.99) Good: (involved leg) 0.81 0.72 (uninvolved leg) 0.78 0.80				(intermittent pneumatic compression) and 0.5cm (cold pack). The use of a measuring tape as a resource to measure knee circumference in individuals with osteoarthritis is a reliable and reproducible method (da Silva et al., 2014). Jakobsen et al. (2010) found that within both inexperienced and experience physiotherapists, the ICC was close to 1 (0.98 and 0.99) for measuring knee joint circumference with a standard tape measure, indicating brilliant relative intra-tester and inter-tester reliability.
Thermal Sensation and Comfort	Five-point thermal comfort scale (Iso, 1995) Nine-point thermal sensation scale (Cholewka *et al.*, 2012)		A 5-point likert scale (0.82-0.91) A 9-point likert scale (0.85-0.94) (Preston and Colman, 2000)					

Participant Perceived Pain (using NPRS)	11-point 'Numeric Pain Rating Scale' (0, no pain; 10, worst pain possible) (Farrar *et al.*, 2001)	0.48 (Alghadir et al., 2018)	Excellent: 0.95 (0.93-0.96) (Alghadir et al., 2018)		Moderate-high: ranging from 0.67 to 0.96 (Kahl and Cleland, 2005)	1.33 (Alghadir et al., 2018)	MCIC for acute pain in an emergency room population: 1.3 points (Bijur, 2003). MCIC for a population with patellofemoral pain: 1 point (Piva *et al.*, 2009). MCIC for a population with chronic musculoskeletal pain: 1 point (Salaffi *et al.*, 2004).	Post-operative clinically meaningful percentage improvements: minimal relief - 35%, moderate relief - 67%, much relief - 70%, complete relief - 93% (Sloman et al. 2006)
Participant Perceived Stability	11-point numeric rating scale (0, very unstable; 10 very stable)	0.48 (Alghadir et al., 2018)	Excellent: 0.95 (0.93-0.96) (Alghadir et al., 2018)			*1.33* (Alghadir et al., 2018)		The global rate of change for an 11-point numeric rating scale is 2 points (Jaeschke et al., 1989).

Chapter 4: An exploration of targeted cryotherapy interventions using a cooling, heating, and compression device on healthy male participants

4.1 Abstract

Purpose

With the development of the guidelines for acute injury management evolving from **PRICE** to **POLICE**, the ability to facilitate optimal loading is key to promote early recovery with early activity. A 20-minute ice application has been reported to inhibit muscle strength and joint position sense. Therefore, the purpose of this study was to explore if targeted cryotherapy, over a smaller surface area using the CHCD, could achieve the desired T_{sk}, whilst minimising potential reductions in muscle strength or joint position sense post-intervention; hence facilitating early optimal loading.

Methods

Four 20-minute interventions, with different combinations of temperature and compression, were explored: 1) 10 °C & 50 mmHg, 2) 15 °C & 50 mmHg 3) 10 °C & 32 mmHg 4) 10-40 °C & 25-50 mmHg alternating every 4 minutes. Each intervention required a separate visit, in a randomised crossover design. To minimise any interference between outcome measures, data collection was split into two parts. Part A investigated the effects on T_{sk}, tissue oxygenation, thermal sensation/comfort, on a convenience sample of 13 healthy male participants (21.5 ± 3.0 yrs). Part B explored the effects on muscle strength, pressure pain threshold and joint position sense, on a convenience sample of 13 healthy male participants (25.3 ± 3.4 yrs). Both parts used all three interventions and recorded all outcome measures pre, post and 20 minutes post-intervention.

Results

Interventions set with a target temperature of 10 °C achieved T_{sk} within the therapeutic range. Whereas interventions set at 15 °C, did not achieve T_{sk} within the therapeutic range. No significant differences ($p>0.05$) were found in T_{sk} between 32 mmHg and 50 mmHg compression levels. Most participants described the compressive cryotherapy interventions as thermally ‘comfortable’ (80%) and ‘slightly cool’ (50%). No significant differences ($p>0.05$) were found in pressure pain threshold or tissue oxygenation between timepoints or interventions. No significant differences ($p>0.05$) were found in maximum knee flexion following all interventions. All interventions decreased isometric quadriceps strength post-intervention by approximately 3-7%. Previous literature has presented quadriceps muscle strength deficits of 16% following ice interventions.

The targeted cooling approach, using the CHCD, can achieve the desired cooling and appears to reduce the magnitude of inhibition to muscle strength and joint position sense. Interventions set at 10 °C achieved T_{sk} within the therapeutic range may be considered effective cryotherapy interventions. However, interventions set at 15 °C did not achieve T_{sk} within the therapeutic range so may be considered ineffective in achieving physiological responses to cooling.

4.2 Introduction

With the cooling, heating, and compression device (CHCD) offering full control on temperature (from 6 to 40 °C), compression (from 20 to 75 mmHg) and time (from 1 to 20 minutes), it is possible to explore the effect of a range of set protocols for knee injury management. The technology allows control of the parameters up to 1 °C/1 minute/1 mmHg increments. It has been calculated (Appendix E) using an algorithm in Microsoft Excel, that the number of combinations of time, temperature and pressure within the above parameter ranges totals 39,200.

4.2.1 Defining the Interventions

The studies detailed in this chapter explored possible optimal temperature and pressure combinations through four different interventions using the CHCD. These four interventions were defined using clinically relevant dosages and commonly used values investigated in literature. As a starting point for the temperature parameters, anchor points of the ideal therapeutic range (10 and 15 °C) (Rivenburgh, 1992) were used for the four interventions. As a starting point for compression, high- and low-pressure values were determined. For sports injury management, a high compression level is considered between 50-75 mmHg (Rigby and Dye, 2017; Alexander *et al.*, 2021a). A static pressure of 32 mmHg is reported in the literature as the average capillary occlusion threshold (Landis, 1930). Therefore, the low compression used in this study was set at 32 mmHg. The high compression was set above this threshold at 50 mmHg, as the optimal compression pressure to reduce chronic oedema of the lower extremity has been reported to be between 50–60 mmHg (Partsch, Damstra and Mosti, 2011). The lower end of this range was selected to be conservative for safety reasons in this area where there is a lack of consensus. The duration for all interventions was set at 20 minutes, as this is a clinically

relevant duration, frequently used for local cryotherapy applications (Chesterton, Foster and Ross, 2002; Kennet *et al.*, 2007; Alexander *et al.*, 2018). Interventions 1-3 were compressive cryotherapy interventions using the range of temperature (10-15 °C) and compression (32-50 mmHg).

Intervention 4 was a contrast therapy intervention, which alternated from 10 °C with 50 mmHg to 40 °C with 25 mmHg, every 3 minutes. Contrast therapy is a commonly used therapeutic intervention in sport and post-exercise recovery, yet there is a significant lack of research on the efficacy of contrast therapy for soft tissue injury management (Greenhalgh *et al.*, 2021). The control of the targeted CHCD provides a unique, practical opportunity to explore this therapeutic intervention for knee injury management for the first time. The contrast therapy intervention was defined using temperature ranges reported in literature for contrast therapy applications (Hing *et al.*, 2008). The compression level set for contrast therapy was defined based upon known physiological effects of heat therapy and compression. It is accepted that heat therapy increases blood flow (Malanga, Yan and Stark, 2015) and high levels of compression reduces blood flow (Halperin, Friedland and Wilkins, 1948). Therefore, simultaneously applying high compression with heat may have been counterproductive. For this reason, compression was set at 25 mmHg during the heat cycles, which is below the average capillary occlusion threshold and equally half of the high compression setting used.

As previously discussed in Chapter 2, contrast therapy may offer beneficial effects functionally rather than the physiological outcome measures commonly evaluated in cryotherapy studies. Therefore, a range of outcome measures were investigated in this first study in order to explore both the functional and physiological effects of the interventions.

To avoid outcome measure interference, this first study was split into two parts. Part A explored the effects of four CHCD interventions on the tissue response. Whilst Part B explored the effects of the same interventions on pressure pain threshold, muscle strength and joint position sense.

4.3 Part A: Exploring the Effects of Different CHCD Interventions on Tissue Physiology

4.3.1 Introduction

Physiological parameters such as skin surface temperature (T_{sk}) and muscle oxygenation saturation (SmO_2) are important measures for understanding the tissue response to compressive cryotherapy interventions. The effects of compression and cryotherapy on SmO_2 and T_{sk} differ depending on dosage (Alexander, Greenhalgh and Rhodes, 2020).

Compression and cryotherapy applied separately appear to have opposite responses to SmO_2 as previous studies have reported decreases to SmO_2 following cryotherapy (Yeung *et al.*, 2016) and increases in SmO_2 following compression (Neuschwander *et al.*, 2012). When cryotherapy and compression are applied simultaneously, an initial increase in SmO_2 has been observed immediate post intervention, followed by a continued decline up to 20 minutes post intervention (Alexander, Greenhalgh and Rhodes, 2020). Interestingly, the authors advised that cryotherapy may have a longer lasting effect than compression over a 20-minute rewarming period. Higher compression levels used in compressive cryotherapy devices, reduced SmO_2 more significantly than lower levels of compression (Alexander, Greenhalgh and Rhodes, 2020). It has been suggested that reductions to SmO_2 may be beneficial for injury management to reduce metabolic activity to assist tissue survival during a period of hypoxia in the acute stage of injury (Nadler, Weingand and Kruse, 2004; Knight, 1995).

A greater understanding of tissue response to different combinations of compression and cryotherapy would be beneficial to inform the development of optimal interventions for knee injury management. The aim of this study was to explore the effects of four CHCD interventions, on physiological measures (T_{sk} and SmO_2) and subjective measures (thermal sensation and thermal comfort).

4.3.2 Methods

The study conformed to the Declaration of Helsinki (WMA, 2013) and full ethical approval was obtained from the University of Central Lancashire STEMH Ethics committee (STEMH 953) and Manchester Metropolitan University (EthOS Reference Number: 7880).

4.3.2.1 Participant Recruitment

Figure 4.1 illustrates the participant recruitment process. This initial study investigated male participants only due to the known gender differential response to thermal stress which is a common method used to reduce variability in cryotherapy studies (Selfe *et al.*, 2014).

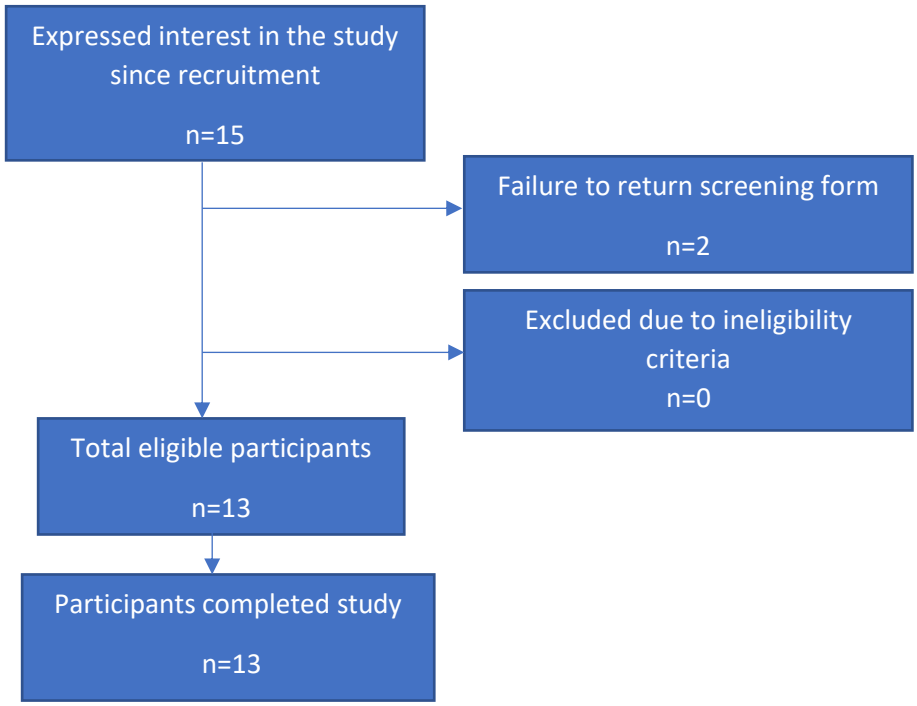


Figure 4.1: A summary of participant recruitment for Part A

Participants were recruited through campus-based advertisements from Manchester Metropolitan University and the University of Central Lancashire, which included staff and students. Volunteers from outside the universities who heard of the study through word of mouth (snowballing effects) were also eligible to be included. Participants had to actively opt into the study by contacting the researchers to express their interest in participating in the study, using the contact information provided. Potential participants were provided with an information sheet, consent form and the opportunity to ask the research team any questions regarding the study (Appendix A). All participants provided written informed consent prior to the study and all information collected was kept strictly confidential and in accordance with GDPR (Commission, 2018). Table 4.1 details the inclusion/exclusion criteria.

Table 4.1: Inclusion Criteria for both Part A and Part B outlined in this chapter

Inclusion	Exclusion
• Healthy male participants • 18-65 years old • No current musculoskeletal injuries to their lower limbs and no known adverse reactions to cold, heat or pressure applications	Participants were screened using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) screening tool (Warburton, Bredin and Gledhill, 2011) (Appendix A) and were excluded from the study if they had: • A current musculoskeletal injury • Any condition that could be made worse through physical activity, cooling, heating, or compression.

An a *priori* power analysis was conducted, using figures presented in Kennet et al. (2007) which explored four different cryotherapy interventions. It was estimated that a minimum of 10 participants were needed for each condition to detect a 2.6 °C difference in T_{sk} with a power of 80% and an alpha level of 0.05 (Table 4.2).

Table 4.2: Sample size calculation based on the work by Kennet et al. (2007)

Mean Difference	Standard Deviation	Power	Significance
2.6	1.8	0.84	0.05

Each intervention required a separate visit. During recruitment, all potential participants were asked to indicate how many sessions they were interested in participating in, to minimise participant drop out. Following consent, participants were then allocated to intervention(s) based upon the number of sessions they were interested in taking part in. For those participating in more than one session, a randomisation plan was created on www.randomisation.com to randomise the order in which the sessions were carried out. Participant's health status was actively monitored throughout the data collection. No adverse effects were reported during or following this study.

4.3.2.2 Data Collection Procedure

The study conformed to the TISEM guidelines (Moreira *et al.*, 2017) as discussed in Chapter 3. As detailed in Table 4.3, 3 outcome measures were recorded at 6 time points.

Table 4.3: Part A data collection protocol

Time Point	**Procedure**	**Duration (mins)**
Pre	Room temperature and humidity, body weight and height recorded	5
	Acclimatisation	20
	T_{sk} Assessment 1	5
	Muscle O_2 Assessment 1	
	Thermal Sensation and Comfort 1	
Intervention	Fit the device	
	Intervention 1, 2, 3 or 4 (randomised)	20
	Removal of the device	
Immediately Post	T_{sk} Assessment 2	5
	Muscle O_2 Assessment 2	
	Thermal Sensation and Comfort 2	
5 Mins Post	T_{sk} Assessment 3	5
	Muscle O_2 Assessment 3	
	Thermal Sensation and Comfort 3	
10 Mins Post	T_{sk} Assessment 4	5
	Muscle O_2 Assessment 4	
	Thermal Sensation and Comfort 4	
15 Mins Post	T_{sk} Assessment 5	5
	Muscle O_2 Assessment 5	
	Thermal Sensation and Comfort 5	
20 Mins Post	T_{sk} Assessment 6	5
	Muscle O_2 Assessment 6	
	Thermal Sensation and Comfort 6	
	END OF SESSION	**75**

The methodology used for recording T_{sk} using thermal imaging (TI), thermal sensation/comfort using the Thermal Sensation and Comfort Questionnaires and muscle oxygenation (SmO_2 - *Saturation of muscle tissue with oxygen* measured at the tibialis anterior), is outlined in Chapter 3 (sections 3.3.1, 3.3.5 and 3.3.7). The site of measurement, tibialis anterior, was selected as it was located in close proximity to the area being cooled but would also not interfere with the thermal imaging region of interest to avoid an interaction between the outcome measures. This location was standardised throughout the study.

4.3.2.3 Interventions

Four different interventions were explored, using the CHCD, within a range of 10-40 °C and 25-50 mmHg (Figure 4.2). As previously mentioned, each intervention required a separate testing session and there was a minimum of 24 hours in between sessions. This is a common method used in other cryotherapy studies using a randomised crossover design (Kennet *et al.*, 2007).

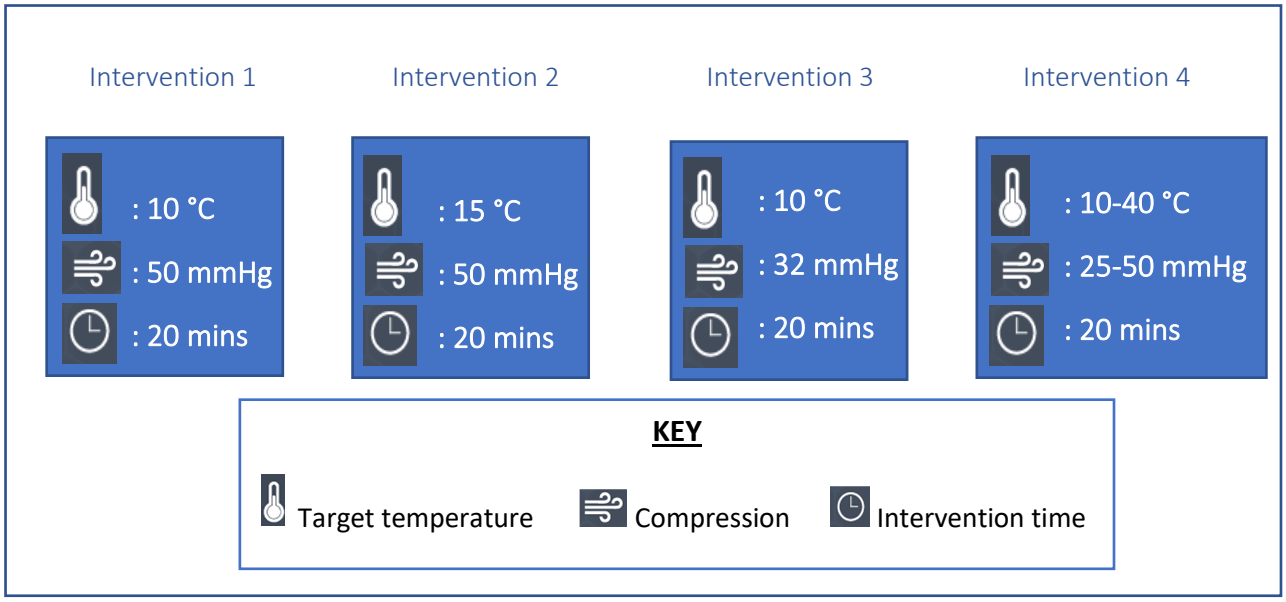


Figure 4.2: All interventions used in the studies outlined in Chapter 4

4.3.2.4 Statistical Analysis

All data was inputted into SPSS Version 26 (SPSS Inc, Chicago, USA). Descriptive statistics, including means and standard deviations, were calculated for each intervention.

Analysis of the distribution of the data for thermal data and oxygenation confirmed suitability for parametric statistical testing. Friedman Tests were used to analyse Thermal Sensation and Comfort questionnaire nominal data, to explore differences between time points and interventions.

A repeated measures ANOVA was used to assess the effect of the interventions on muscle oxygenation over a 20-minute rewarming period (6 x 4 - time points by interventions). Significance was accepted at $p<0.05$. Paired sample T-tests were used to compare the immediate effect of compression (high and low) and temperature (10 and 15 °C) on muscle oxygenation and thermal sensation/comfort. Two factor repeated measures ANOVAs with post-hoc pairwise comparisons were used to assess the following for T_{sk}:

1) Immediate effects of compression on medial and lateral knee $T_{sk.}$ The two factors were low/high compression and medial/lateral knee $T_{sk.}$
2) Immediate effects of temperature settings on medial and lateral knee $T_{sk.}$ The two factors were 10/15 °C temperature settings and medial/lateral knee $T_{sk.}$
3) How the interventions performed over a 20-minute rewarming period. The two factors were time (time points) and interventions (interventions).

If any interactions were found between factors, further post-hoc analyses were carried out on medial and lateral sides of the knee separately. A Bonferroni correction was used to account for Type I error (e.g., a false-positive result) with multiple testing (Armstrong, 2014) . The Bonferroni correction adjusted the *p* value based on the number of combinations assessed, dropping the threshold *p* value to $p<0.0125$ for 2x2, 3x2 and $p<0.008$ for 6x1 repeated measures ANOVAs respectively.

4.3.3 Results

Thirteen healthy male participants were recruited for this part of the study (Part A). Each intervention recruited 10 participants in total. Three participants took part in a single session and 10 participants took part in multiple sessions. The average age of participants was 21.5 ± 3.0 years. The average body mass index (BMI) of the participants was 26.7 ± 2.0.

4.3.3.1 Skin Surface Temperature

Ambient room temperature was 19.3 ± 1.2 °C and was not found to be significantly different ($p \geq 0.05$) inter-session or intra-sessions. Table 4.4 presents minimum T_{sk} for medial and lateral aspects of the knee at each time point.

Table 4.4: Descriptive statistics for mean minimum T_{sk} for each intervention and time point (n=10).

	Mean Minimum T_{sk} ± (SD) °C							
Time Point	**Intervention 1**		**Intervention 2**		**Intervention 3**		**Intervention 4**	
	Medial	*Lateral*	*Medial*	*Lateral*	*Medial*	*Lateral*	*Medial*	*Lateral*
Pre	27.6 (1.4)	27.3 (1.2)	28.0 (1.6)	27.3 (1.9)	27.6 (1.1)	27.5 (1.1)	28.6 (1.3)	28.4 (1.0)
Post	14.2 (1.2)	17.2 (3.5)	17.9 (0.8)	19.2 (1.3)	14.3 (0.6)	16.2 (1.6)	27.5 (5.1)	27.2 (4.9)
5 Mins Post	20.8 (2.1)	22.0 (1.6)	22.2 (2.3)	22.9 (0.7)	20.3 (1.1)	21.4 (1.3)	28.9 (2.3)	28.0 (2.7)
10 Mins Post	22.9 (2.3)	23.6 (2.0)	24.6 (1.3)	24.6 (1.2)	23.0 (0.9)	23.3 (1.4)	28.7 (1.6)	28.4 (1.4)
15 Mins Post	24.4 (1.7)	24.6 (1.4)	25.5 (1.7)	25.1 (1.2)	24.2 (1.1)	24.5 (1.8)	29.0 (1.4)	28.5 (1.3)
20 Mins Post	25.2 (1.3)	25.2 (1.2)	26.3 (1.6)	25.9 (1.3)	25.4 (0.9)	25.2 (1.9)	28.9 (1.4)	28.2 (1.3)

When comparing the immediate effects of low (32 mmHg) and high (50 mmHg) compression on medial and lateral T_{sk}, the results indicate that the level of compression did not significantly affect T_{sk} ($p \geq 0.05$). However, significant main effects were found in T_{sk}

when comparing differences between medial and lateral aspects of the knee (p=0.007). No significant interactions were found between factors (p≥0.05). Post-hoc analyses indicated that the medial aspect of the knee cooled significantly lower than the lateral aspect of the knee (Table 4.5) p<0.0125.

Table 4.5: Pairwise comparison and descriptive statistics of immediate effects of high and low compression on medial and lateral T_{sk} using a repeated measures ANOVA with post-hoc analyses (2 x 2 – interventions by medial/lateral). The adjusted Bonferroni correction dropped the significance level to p<0.0125).

Comparison	Mean Difference	Sig.[b]	95% Confidence Interval (CI) for Difference	
			Lower Bound	Upper Bound
Medial vs Lateral	-2.4*	.007	-4.0	-0.8
High vs Low Compression	0.5	.341	-0.6	1.5

When comparing the immediate effects of temperature settings (10 °C and 15 °C) on medial and lateral T_{sk}, significant main effects were found (p<0.001). Significant main effects were also found in T_{sk} between medial and lateral aspects of the knee (p=0.005). No significant interactions were found between factors (p=0.142). Post-hoc analyses indicated that the 10 °C temperature setting reduced T_{sk} significantly greater than the 15 °C temperature setting, and the medial aspect of the knee cooled significantly more than the lateral aspect of the knee (Table 4.6) (p<0.0125).

*Table 4.6: Pairwise comparison and descriptive statistics of immediate effects of temperature settings (10 °C and 15 °C) on medial and lateral T_{sk} (n=10) (*denotes a significance, using a repeated measures ANOVA with post-hoc analyses (2 x 2 – interventions by medial/lateral). The adjusted Bonferroni correction dropped the significance level to p<0.0125).*

Comparison	Mean Difference	Sig.[b]	95% CI for Difference	
			Lower Bound	Upper Bound
Medial vs Lateral	-2.1*	.005	-3.4	-0.8
10 vs 15 °C Temperature settings	-2.8*	<.001	-4.2	-1.5

4.3.3.1.1 How do the interventions perform over a 20-minute rewarming period?

4.3.3.1.1.1 Intervention 1 (10 °C with 50 mmHg)

When assessing how intervention 1 performed over a 20-minute rewarming period, significant main effects were found in T_{sk} between time points ($p \leq 0.001$). Significant main effects were also found in T_{sk} between medial and lateral aspects of the knee ($p=0.040$). Significant interactions were found between the two factors (medial/lateral and time). As significant interactions were found between factors, further post-hoc analyses were carried out on medial and lateral sides of the knee separately ($p \leq 0.001$).

Medial

Further post-hoc analyses showed significant decreases in T_{sk} on the medial aspect of the knee between pre-intervention T_{sk} and all other time points (Table 4.7). No significant differences were found in medial T_{sk} between 10 minutes and 20 minutes post intervention, which suggests that T_{sk} began to plateau 10 minutes post intervention.

*Table 4.7: Pairwise comparison and descriptive statistics of immediate effects of intervention 1 on lateral minimum T_{sk} (n=10) over a rewarming period of 20 minutes (*denotes a significance, using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention). The adjusted Bonferroni correction dropped the significance level to p<0.008).*

Time Point Comparison		Mean Difference	Sig.[b]	95% CI for Difference	
				Lower Bound	Upper Bound
Pre	Immed. Post	13.4*	.000	11.1	15.7
Pre	5 Mins Post	6.9*	.000	5.1	8.7
Pre	10 Mins Post	4.7*	.000	2.6	6.8
Pre	15 Mins Post	3.2*	.000	2.3	4.2
Pre	20 Mins Post	2.5*	.000	1.5	3.5
Immed. Post	5 Mins Post	-6.5*	.000	-9.4	-3.6
Immed. Post	10 Mins Post	-8.7*	.000	-11.8	-5.6
Immed. Post	15 Mins Post	-10.2*	.000	-12.8	-7.6
Immed. Post	20 Mins Post	-10.9*	.000	-12.8	-9.0
5 Mins Post	10 Mins Post	-2.2*	.004	-3.6	-0.7
5 Mins Post	15 Mins Post	-3.6*	.000	-5.0	-2.2
5 Mins Post	20 Mins Post	-4.4*	.000	-6.0	-2.7
10 Mins Post	15 Mins Post	-1.5	.068	-3.0	0.1
10 Mins Post	20 Mins Post	-2.2	.014	-4.0	-0.4
15 Mins Post	20 Mins Post	-0.7	.065	-1.5	0.0

Lateral

Post-hoc analyses indicated that significant decreases in T_{sk} were found on the lateral aspect of the knee from pre-intervention T_{sk} to all other time points (Table 4.8). Similar to the medial side, no significant differences were found in lateral T_{sk} between 10 minutes post to 20 minutes post, which suggests that T_{sk} also began to plateau 10 minutes post intervention.

*Table 4.8: Pairwise comparison and descriptive statistics of immediate effects of intervention 1 on lateral minimum T_{sk} (n=10) over a rewarming period of 20 minutes (*denotes a significance, using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention). The adjusted Bonferroni correction dropped the significance level to p<0.008).*

Time Point Comparison		Mean Difference	Sig.[b]	95% CI for Difference	
				Lower Bound	Upper Bound
Pre	Immed. Post	10.1*	.000	6.0	14.1
Pre	5 Mins Post	5.3*	.000	3.8	6.9
Pre	10 Mins Post	3.7*	.000	2.4	5.1
Pre	15 Mins Post	2.7*	.000	1.8	3.5
Pre	20 Mins Post	2.1*	.000	1.1	3.1
Immed. Post	5 Mins Post	-4.7	.010	-8.4	-1.0
Immed. Post	10 Mins Post	-6.3*	.000	-9.6	-3.1
Immed. Post	15 Mins Post	-7.4*	.000	-10.9	-3.9
Immed. Post	20 Mins Post	-7.9*	.000	-11.4	-4.4
5 Mins Post	10 Mins Post	-1.6	.097	-3.4	0.2
5 Mins Post	15 Mins Post	-2.7*	.001	-4.1	-1.3
5 Mins Post	20 Mins Post	-3.2*	.000	-4.8	-1.7
10 Mins Post	15 Mins Post	-1.1	.018	-2.0	-0.2
10 Mins Post	20 Mins Post	-1.6	.016	-2.9	-0.3
15 Mins Post	20 Mins Post	-0.5	.054	-1.1	0.0

4.3.3.1.1.2 Intervention 2 (15 °C with 50 mmHg)

For intervention 2, significant main effects were found in T_{sk} between time points ($p \leq .001$) over the 20-minute rewarming period. No significant differences were found in T_{sk} between medial and lateral aspects of the knee ($p=0.783$). Significant interactions were found between the two factors (medial/lateral and time). As significant interactions were found between factors, further post-hoc analyses were carried out on medial and lateral sides of the knee separately ($p \leq .001$).

Medial

Post-hoc analyses showed significant decreases in T_{sk} on the medial aspect of the knee from pre-intervention T_{sk} to all other time points (Table 4.9). No significant differences were found in medial T_{sk} between 15 minutes and 20 minutes post, indicating that T_{sk} had begun to plateau at the end of the 20-minute rewarming period.

*Table 4.9: Pairwise comparison and descriptive statistics of immediate effects of intervention 2 on medial minimum T_{sk} (n=10) over a rewarming period of 20 minutes (*denotes a significance, using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention). The adjusted Bonferroni correction dropped the significance level to p<0.008).*

Time Point Comparison		Mean Difference	Sig. [b]	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
Pre	Immed. Post	10.1*	.000	8.7	11.4
Pre	5 Mins Post	5.9*	.000	4.2	7.5
Pre	10 Mins Post	3.5*	.000	2.7	4.3
Pre	15 Mins Post	2.6*	.000	1.7	3.5
Pre	20 Mins Post	1.8*	.001	0.8	2.7
Immed. Post	5 Mins Post	-4.2*	.001	-6.5	-1.9
Immed. Post	10 Mins Post	-6.6*	.000	-7.9	-5.4
Immed. Post	15 Mins Post	-7.5*	.000	-9.2	-5.8
Immed. Post	20 Mins Post	-8.3*	.000	-9.8	-6.8
5 Mins Post	10 Mins Post	-2.4	.010	-4.3	-0.5
5 Mins Post	15 Mins Post	-3.3*	.001	-5.0	-1.6
5 Mins Post	20 Mins Post	-4.1*	.000	-5.9	-2.3
10 Mins Post	15 Mins Post	-0.9*	.003	-1.5	-0.3
10 Mins Post	20 Mins Post	-1.7*	.000	-2.3	-1.1
15 Mins Post	20 Mins Post	-0.8	.009	-1.4	-0.2

Lateral

Post-hoc analyses indicated that significant decreases in T_{sk} were found on the lateral aspect of the knee from pre-intervention T_{sk} up to 10 minutes post intervention (Table 4.10). No significant differences were found in lateral T_{sk} from pre-intervention to 15 minutes and 20 minutes post intervention, which suggests that T_{sk} had returned close to baseline approximately 15 minutes after the removal of the device.

*Table 4.10: Pairwise comparison and descriptive statistics of immediate effects of intervention 2 on lateral minimum T_{sk} (n=10) over a rewarming period of 20 minutes (*denotes a significance, using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention). The adjusted Bonferroni correction dropped the significance level to p<0.008).*

Time Point Comparison		Mean Difference	Sig. [b]	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
Pre	Immed. Post	8.1*	.000	5.6	10.6
Pre	5 Mins Post	4.3*	.001	1.8	6.9
Pre	10 Mins Post	2.7*	.008	0.7	4.8
Pre	15 Mins Post	2.1	.027	0.2	4.1
Pre	20 Mins Post	1.4	.163	-0.3	3.2
Immed. Post	5 Mins Post	-3.8*	.000	-5.3	-2.2
Immed. Post	10 Mins Post	-5.4*	.000	-7.5	-3.3
Immed. Post	15 Mins Post	-6.0*	.000	-8.2	-3.7
Immed. Post	20 Mins Post	-6.7*	.000	-8.9	-4.4
5 Mins Post	10 Mins Post	-1.6	.051	-3.2	0.0
5 Mins Post	15 Mins Post	-2.2*	.008	-3.9	-0.5
5 Mins Post	20 Mins Post	-2.9*	.001	-4.6	-1.2
10 Mins Post	15 Mins Post	-0.6	.162	-1.3	0.1
10 Mins Post	20 Mins Post	-1.3*	.000	-1.9	-0.7
15 Mins Post	20 Mins Post	-0.7*	.004	-1.2	-0.2

4.3.3.1.1.3 Intervention 3 (10 °C with 32 mmHg)

For intervention 3, significant main effects were found in T_{sk} between time points (p≤.001) over the 20-minute rewarming period. No significant differences were found in T_{sk} between medial and lateral aspects of the knee (p=0.198). Significant interactions were found between the two factors (medial/lateral and time). As significant interactions were found between factors, further post-hoc analyses were carried out on medial and lateral sides of the knee separately (p≤.001).

Medial

Post-hoc analyses indicated that significant decreases in T_{sk} were found on the medial aspect of the knee from pre-intervention T_{sk} to all other time points (Table 4.11). Significant differences were found in medial T_{sk} 20 minutes post, which indicates that T_{sk} still had not returned to baseline at the end of the 20-minute rewarming period.

*Table 4.11: Pairwise comparison and descriptive statistics of immediate effects of intervention 3 on medial minimum T_{sk} (n=10) over a rewarming period of 20 minutes (*denotes a significance, using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention). The adjusted Bonferroni correction dropped the significance level to p<0.008).*

Time Point Comparison		Mean Difference	Sig. [b]	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
Pre	Immed. Post	13.3*	.000	11.5	15.1
Pre	5 Mins Post	7.3*	.000	6.2	8.4
Pre	10 Mins Post	5.0*	.000	3.5	6.4
Pre	15 Mins Post	3.5*	.000	2.4	4.6
Pre	20 Mins Post	2.3*	.000	1.7	2.9
Immed. Post	5 Mins Post	-6.0*	.000	-7.8	-4.2
Immed. Post	10 Mins Post	-8.3*	.000	-10.2	-6.5
Immed. Post	15 Mins Post	-9.8*	.000	-11.6	-8.0
Immed. Post	20 Mins Post	-11.0*	.000	-12.5	-9.4
5 Mins Post	10 Mins Post	-2.4*	.000	-3.6	-1.1
5 Mins Post	15 Mins Post	-3.8*	.000	-4.6	-3.0
5 Mins Post	20 Mins Post	-5.0*	.000	-5.7	-4.2
10 Mins Post	15 Mins Post	-1.5*	.001	-2.3	-0.6
10 Mins Post	20 Mins Post	-2.6*	.000	-3.6	-1.7
15 Mins Post	20 Mins Post	-1.2*	.002	-1.9	-0.4

Lateral

Post-hoc analyses indicated that significant decreases in T_{sk} were found on the lateral aspect of the knee from pre-intervention T_{sk} up to 15 minutes post intervention (Table 4.12). No significant differences were found in T_{sk} between baseline and 20 minutes post or 15 minutes post to 20 minutes post, which indicates that T_{sk} began to plateau after 15 minutes post intervention.

*Table 4.12: Pairwise comparison and descriptive statistics of immediate effects of intervention 3 on lateral minimum T_{sk} (n=10) over a rewarming period of 20 minutes (*denotes a significance, using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention). The adjusted Bonferroni correction dropped the significance level to p<0.008).*

Time Point Comparison		Mean Difference	Sig.[b]	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
Pre	Immed. Post	11.1*	.000	8.8	13.5
Pre	5 Mins Post	6.2*	.000	4.4	7.9
Pre	10 Mins Post	4.2*	.000	2.6	5.8
Pre	15 Mins Post	3.0*	.002	1.1	4.9
Pre	20 Mins Post	2.3	.027	0.2	4.4
Immed. Post	5 Mins Post	-5.0*	.000	-7.1	-2.9
Immed. Post	10 Mins Post	-6.9*	.000	-8.6	-5.2
Immed. Post	15 Mins Post	-8.1*	.000	-10.6	-5.6
Immed. Post	20 Mins Post	-8.8*	.000	-11.7	-5.9
5 Mins Post	10 Mins Post	-2.0*	.002	-3.2	-0.8
5 Mins Post	15 Mins Post	-3.1*	.001	-4.8	-1.5
5 Mins Post	20 Mins Post	-3.8*	.000	-5.6	-2.0
10 Mins Post	15 Mins Post	-1.2	.012	-2.1	-0.2
10 Mins Post	20 Mins Post	-1.9*	.004	-3.1	-0.6
15 Mins Post	20 Mins Post	-0.7	.023	-1.3	-0.1

4.3.3.1.1.4 Intervention 4 (Contrast Therapy – 10-40 °C with 25-50 mmHg alternating)

For intervention 4, no significant differences were found in T_{sk} between time points ($p \geq 0.05$) over the 20-minute rewarming period. Significant main effects were found in T_{sk} between medial and lateral aspects of the knee ($p=0.009$). No significant interactions were found between the two factors (medial/lateral and time). As no significant interactions were found between factors, no further post-hoc analyses were carried out.

4.3.3.1.2 Rewarming Curves

Figures 4.3 and 4.4 present the medial and lateral rewarming curves for the T_{sk} over a 20-minute rewarming period post intervention for Interventions 1, 2 and 3. Interventions 1 and 3 (10 °C) demonstrate very similar cooling and rewarming curves despite having different levels of compression (32 mmHg and 50 mmHg).

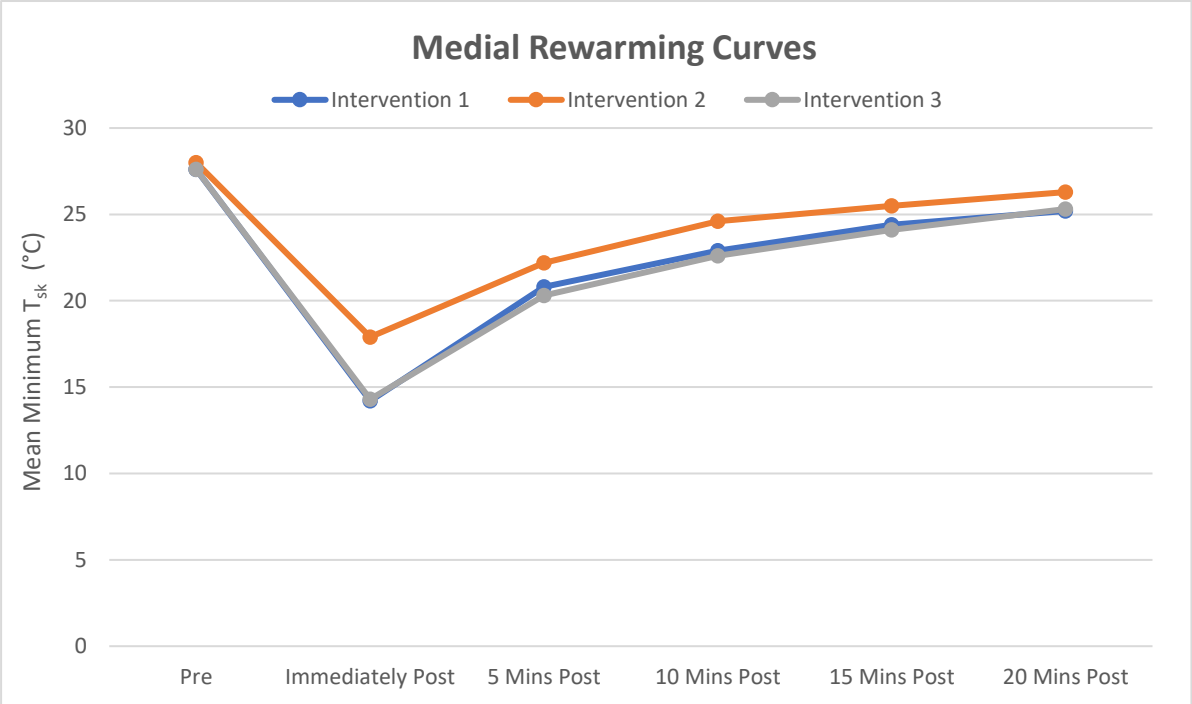


Figure 4.3: A line graph to demonstrate the rewarming curve of mean minimum T_{sk} (n=10) on the medial aspect of the knee over a 20-minute period post intervention. Significant differences between time points were assessed using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention).

Figure 4.4 demonstrates the lateral T_{sk} rewarming curves over a 20-minute rewarming period post intervention for interventions 1, 2 and 3. When compared to Figure 4.5, it is apparent that T_{sk} on the lateral aspect of the knee is warmer than the medial aspect up until approximately 15 minutes post intervention.

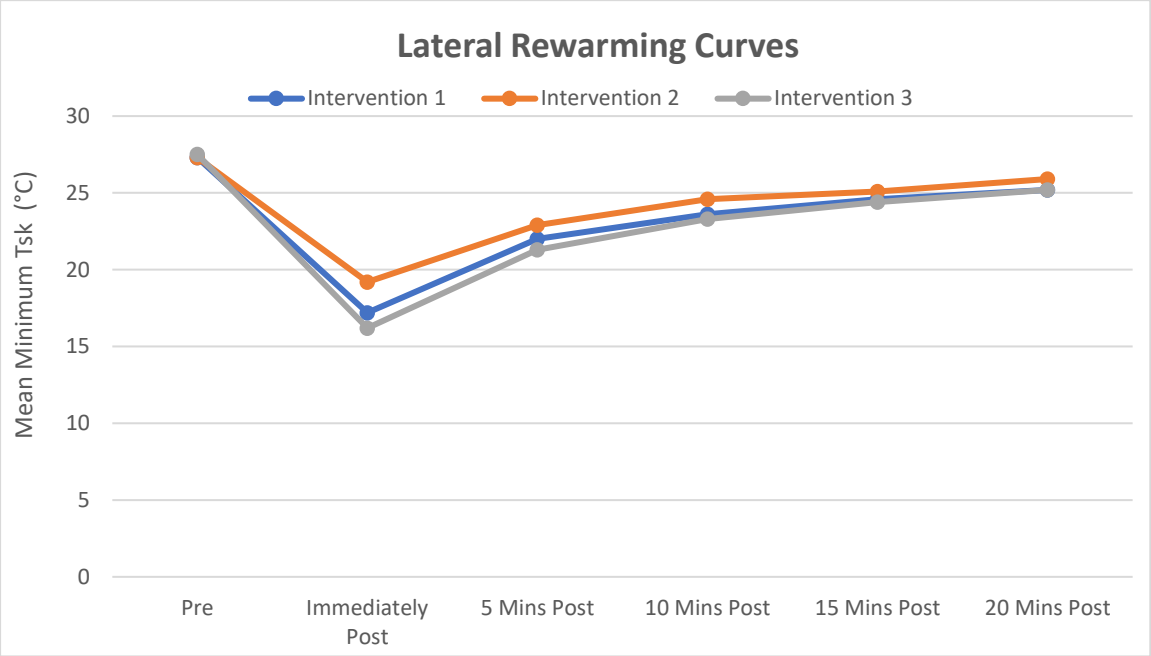


Figure 4.4: A line graph to demonstrate the rewarming curve of mean minimum T_{sk} (n=10) on the lateral aspect of the knee over a 20-minute period post intervention. Significant differences between time points were assessed using a repeated measures ANOVA with post-hoc analyses (6 x 1 – timepoints by intervention).

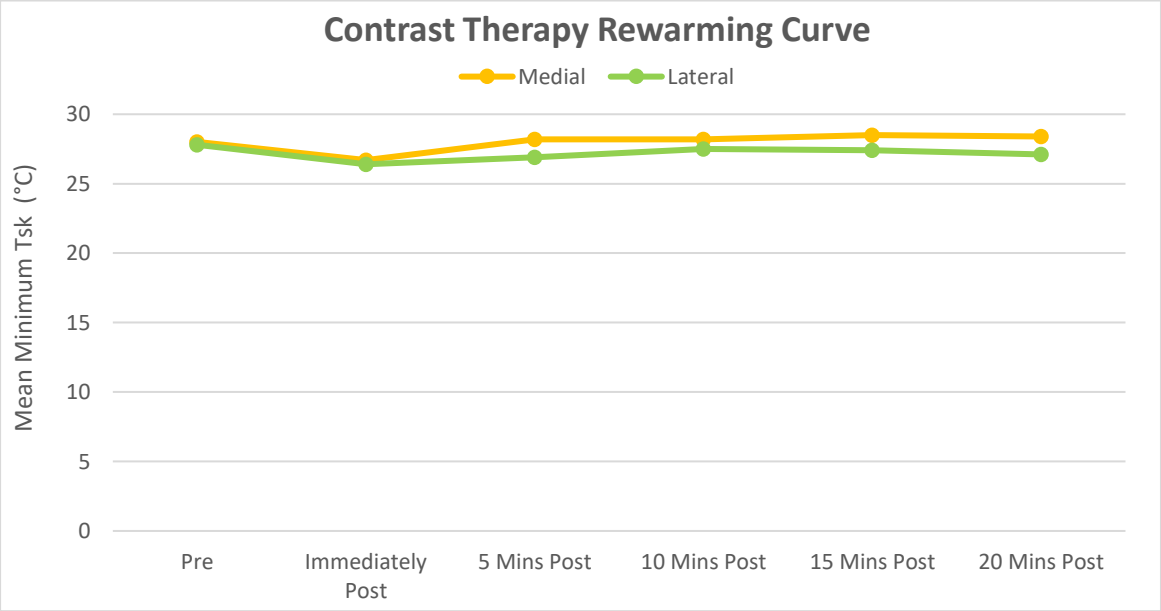


Figure 4.5: A line graph to demonstrate the rewarming curve of mean minimum T_{sk} (n=10) on the medial and lateral aspects of the knee over a 20-minute period post intervention 4. Significant differences between time points were assessed using a repeated measures ANOVA.

Figure 4.5 illustrates the fluctuated response recorded throughout the 20-minute rewarming period following the fluctuated stimulus, intervention 4, which consisted of contrast therapy alternating between 10-40 °C and 25-50 mmHg every 3 minutes. The rewarming period following a 20-minute contrast therapy intervention is yet to be recorded in literature and it is evident that contrast therapy produced a different response to T_{sk} than the other three interventions and published cryotherapy rewarming curves, as expected.

4.3.3.2 Thermal Sensation and Comfort

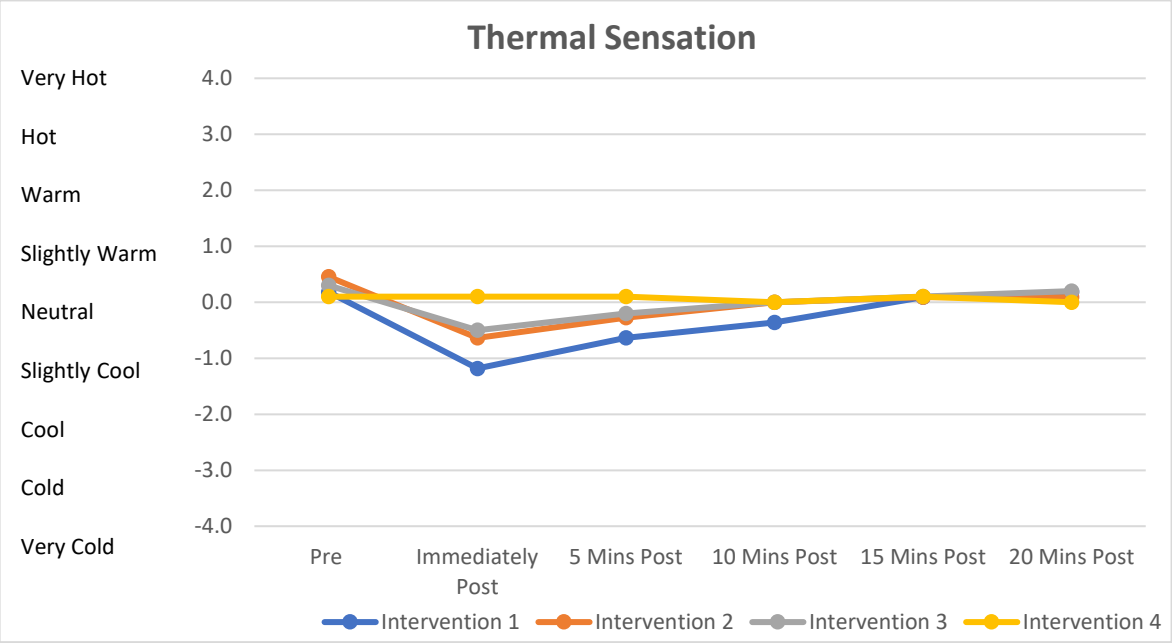


Figure 4.6: Mean thermal sensation scores (n=10) for all interventions across the six time points (-4 to 4. 4= very hot, 3 =hot, 2= warm, 1= slightly warm, 0= neutral, -1 =slightly cool, -2 = cool, -3= cold, -4 = very cold). Significant differences assessed using Friedman tests, with a significance level set at p<0.05.

Significant differences were found in thermal sensation scores pre and immediately post T_{sk} for interventions 1 (p=0.014) & 2 (p=0.005). No significant differences were found in thermal sensation scores pre and immediately post T_{sk} for interventions 3 & 4 (p>0.05). On average, participants described their thermal sensation as 'slightly cool' immediately post intervention for interventions 1, 2 and 3. Intervention 1 was still described as 'slightly cool' 5 minutes post intervention (Figure 4.6). All other time points were described as neutral. No significant differences were found between the immediate effects of high and low compression on thermal sensation (p=0.068). No significant differences were found between the immediate effects of temperature settings on thermal comfort (p=0.081).

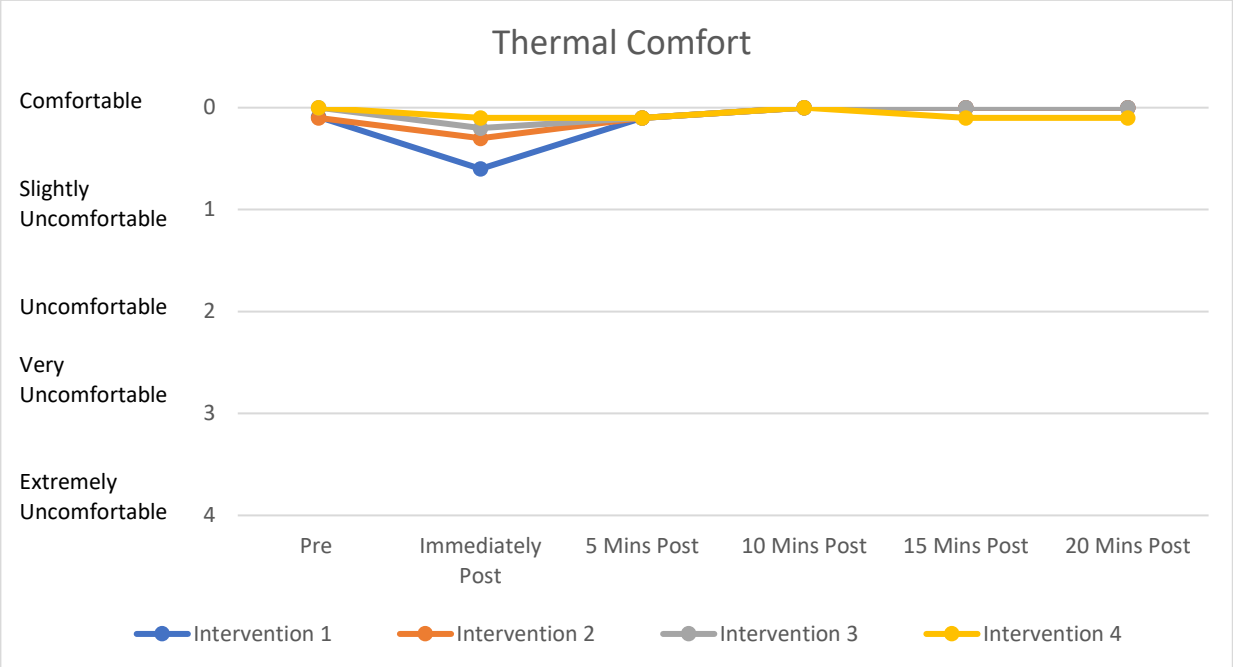


Figure 4.7: Mean thermal comfort scores (n=10) for all interventions across the six time points (0 =comfortable, 1 = slightly uncomfortable, 2 = uncomfortable, 3= very uncomfortable, 4 =extremely uncomfortable) Significant differences assessed using Friedman tests, with a significance level set at $p<0.05$.

No significant differences were found in thermal comfort scores when comparing pre and immediately post T_{sk} for all interventions ($p>0.05$). On average, participants would describe their thermal comfort as 'comfortable' across all time points and interventions apart from immediately post intervention 1 which is described as 'slightly uncomfortable' (Figure 4.7). No significant differences were found between the immediate effects of high and low compression on thermal comfort ($p=0.223$). No significant differences were found between the immediate effects of temperature settings on thermal comfort ($p=0.279$).

4.3.3.3 Muscle Oxygenation

Table 4.13: Mean muscle oxygenation (SmO_2, %) for all four interventions and time points (n=10). Significant differences assessed using repeated measure ANOVAs (6 x 4 – time points by interventions), with a significance level set at p<0.05.

Intervention	Mean SmO_2 ± (SD) %					
	Pre	Immediately post	5 mins post	10 mins post	15 mins post	20 mins post
1	60.1 (14.1)	57.5 (12.9)	56.0 (14.6)	55.3 (15.5)	58.1 (13.1)	59.3 (13.9)
2	59.9 (14.5)	57.9 (10.3)	56.2 (11.1)	53.4 (13.3)	52.7 (13.9)	49.1 (17.0)
3	58.7 (12.8)	61.3 (14.0)	59.0 (18.9)	60.7 (17.1)	58.5 (18.9)	59.9 (15.0)
4	58.2 (10.9)	56.8 (12.8)	53.7 (16.3)	56.0 (16.8)	53.5 (15.7)	53.6 (15.6)

No significant differences were found between muscle oxygenation (SmO_2) pre and post intervention at the tibialis anterior for any of the four interventions. Interventions 1, 2 and 4 demonstrated a reduction in SmO_2 from pre to immediately post intervention (Table 4.13), whereas intervention 3 demonstrates an increase post intervention. However, these differences were not statistically significant ($p>0.05$). No significant differences were found between the immediate effects of high and low compression on muscle oxygenation ($p=0.303$), using paired sample T-tests with a significance set at $p<0.05$. Similarly, no significant differences were found between the immediate effects of temperature settings on muscle oxygenation ($p=0.882$).

4.3.4 Discussion

The purpose of this study was to explore investigate the effect of four CHCD interventions on $T_{sk,}$ muscle oxygenation, thermal sensation, and comfort.

4.3.4.1 Skin Surface Temperature

T_{sk} was significantly reduced on the medial aspect of the knee up to 20 minutes post intervention, following all the compressive cryotherapy interventions (interventions 1, 2 and 3). Intervention 1 (10 °C, 50 mmHg) also significantly reduced T_{sk} on the lateral aspect of the knee up to 20 minutes post intervention. When comparing the immediate effects of the two temperature settings (10 °C and 15 °C), 10 °C significantly reduced T_{sk} greater than the 15 °C temperature setting. Findings indicate that CHCD interventions set at 10 °C (1 and 3) demonstrated a potential therapeutic effect throughout the 20-minute rewarming period.

T_{sk} rewarming has been demonstrated to be a possible indication of deeper tissue cooling as superficial tissues draw heat from the deeper tissues in order to rewarm (Hardy and Woodall, 1998; Kennet *et al.*, 2007; Hardaker *et al.*, 2007). The rewarming curves reported in this study did not return to baseline 20 minutes post intervention (see section 4.3.3.1.2). This reflects published cryotherapy rewarming curves (Kennet *et al.*, 2007). There were no significant differences in T_{sk} at any time point following contrast therapy (Intervention 4). It is important to note that the rewarming curve for the contrast therapy intervention followed a different pattern to the compressive cryotherapy interventions (see section 4.3.3.1). Interestingly, the contrast therapy T_{sk} rewarming curve appeared to fluctuate over the entire rewarming period. There are no published rewarming curves following contrast therapy currently in literature, to the authors knowledge.

No significant differences in T_{sk} were found between 32 mmHg and 50 mmHg when the CHCD was set at 10 °C. Interestingly, it was noted that the lower compression achieved the lowest minimum T_{sk} immediately post treatment recorded within the study (12.2 °C). This highlights that the compression design within the device did not enhance the therapeutic cooling rate, which refutes previous studies reporting an increased magnitude of cooling with the addition of compression (Song *et al.*, 2016; Alexander, Greenhalgh and Rhodes, 2020). This could be due to the design of compression within the CHCD version used in this study (Swellaway Knee Unit), which consisted of two air

bladders applying pressure to either side of the knee, as opposed to circumferential coverage.

It was observed during the study that the inflation of the air bladders hindered the contact of the cooling plate on the skin, particularly the lateral aspect of the knee and ultimately impeded the rate of energy transfer. Additionally, due to the design of the air bladders and the anatomy of the knee, contact between the cooling plate and the skin appeared to be greater on the medial aspect of the knee than the lateral side. This was supported by the findings of the study as the medial aspect of the knee cooled significantly greater than the lateral aspect of the knee for all interventions, except contrast therapy (intervention 4). This finding helped to inform product design changes and led to the creation of a new prototype, ProMOTION V1, with circumferential compression (Table 3.1). Interestingly, studies which have demonstrated an increased magnitude of cooling with the addition of compression, have used a circumferential compression design (Song *et al.*, 2016; Alexander, Greenhalgh and Rhodes, 2020).

4.3.4.2 Thermal Sensation and Comfort

On average, participants described their thermal comfort as 'comfortable' across all timepoints and phases except for intervention 1 post intervention, which was described as 'slightly uncomfortable'. No significant differences ($p>0.05$) however, were found from pre- to post intervention for thermal comfort scores following all interventions. These findings differ to previous literature which has reported significant reductions to thermal comfort following compressive cryotherapy interventions (Alexander, Greenhalgh and Rhodes, 2020). However, Alexander, Greenhalgh and Rhodes (2020) used different compressive cryotherapy devices (Squid® and Game Ready®) set at a lower target T_{sk} (2 °C), and a higher compression (intermittent: 5-75 mmHg) and therefore may not be an accurate comparison. This suggests that the modalities set with a lower application temperature may decrease the participants perceived thermal comfort.

Participants described their thermal sensation as 'slightly cool' post interventions 1-3. Intervention 1 was still described as 'slightly cool' 5 minutes post intervention. All other time points were described as 'neutral'. No significant differences were found in thermal sensation scores pre and post interventions 3 & 4. Participants reported being significantly cooler immediately post interventions 1 & 2 ($p\leq0.05$). This reflects previous

studies which reported significant reductions to thermal sensation during and immediately post a local cryotherapy application using a compressive cryotherapy device, Game Ready® (Alexander, Greenhalgh and Rhodes, 2020).

Despite interventions 1 & 2 being set at different temperatures (10 °C and 15 °C), both interventions were set at the higher compression level, so it is possible to suggest that the higher compression led to a greater perception of cooling. However, no statistically significant differences were found between the immediate effects of high and low compression on thermal sensation (p=0.068). In addition, despite achieving a similar T_{sk}, participants perceived intervention 1 as 'slightly cool' and intervention 3 as 'neutral'. This also suggests that the higher compression enhanced the perception of cooling, despite average T_{sk} being almost identical in both conditions. These findings echo previous literature demonstrating enhanced therapeutic benefits to cryotherapy with the addition of compression (Song *et al.*, 2016).

All the measurements were recorded pre and post intervention at standardised intervals. However, it was noted that participants appeared to become habituated to the constant thermal sensation by the end of the 20-minute intervention and throughout the 20-minute rewarming period.

4.3.4.3 Muscle Oxygenation

It is generally accepted that tissue oxygenation reduces when cold is applied as vasoconstriction occurs which reduces local blood flow and tissue metabolism (Knight, 1995; Nadler, Weingand and Kruse, 2004; Alexander, Greenhalgh and Rhodes, 2020; Yeung *et al.*, 2016). No significant main effects were found in tissue oxygenation (SmO_2) recorded at the tibialis anterior from pre- to post intervention across any interventions (p=0.414). Interventions 1, 2 and 4 demonstrated a reduction in SmO_2 from pre to immediately post intervention (Table 4.13), which is comparable to previous findings that cryotherapy reduces SmO_2 (Yeung *et al.*, 2016; Alexander, Greenhalgh and Rhodes, 2020). This also highlights that the compression applied in this intervention may not have been effective, as compression is known to increase SmO_2 during and immediately post intervention (Neuschwander *et al.*, 2012). Intervention 2 continued to decline in SmO2 throughout the 20-minute rewarming period, which echoes findings reported in Alexander, Greenhalgh and Rhodes (2020). The continued decline may be because the

cooling continues to penetrate deeper tissues after the intervention has been removed. This assumption is based on previous findings that intramuscular tissues continue to cool approximately 14 minutes following a local cryotherapy application (Zemke *et al.*, 1998; Hardaker *et al.*, 2007). However, it is important to consider that the research stated above is based on cooling a muscle, which will react differently to cooling a synovial joint such as the knee, with bony anatomical structures.

Intervention 3 demonstrated an increase immediately post intervention, followed by a slight fluctuation in SmO_2. Interestingly, this intervention had a lower compression and produced the lowest minimum T_{sk} recorded in the study. Based on previous findings, higher compression would be expected to increase SmO_2 more than lower compression (Alexander, Greenhalgh and Rhodes, 2020) so this conflicts with previous research. When comparing the immediate effects of compression (high and low) on muscle oxygenation, no significant differences were found (p=0.303). When comparing the immediate effects of temperature settings (10 °C and 15 °C) on muscle oxygenation, no significant differences were found (p=0.882).

A possible suggestion for no significant differences being found following the compressive cryotherapy interventions would be the location of the oxygenation sensor. It is also possible that the effects of compression and cryotherapy counteracted each other as the literature presents opposite responses to SmO_2. Future work should explore the different measurement sites for the MOXY sensor such as directly over the cooling site. This wasn't possible during this study as it would have interfered with the thermal imaging measurements, as the MOXY sensor would have warmed the area being cooled.

4.3.4.4 Limitations

With the device offering over 30,000 possible temperature and compression combinations, ideally the study would have explored a wider range of interventions. Four visits were selected to ensure the recruitment would be manageable and to minimise participant drop out. All interventions within the study incorporated some form of compression adjunct (Figure 4.2). It has been noted that the air bladders providing the pressure within the CHCD (Section 4.3.3.1) could have hindered the contact between the plate and the skin when inflated. An intervention with no compression may have

provided a greater understanding of the role of the pressure within the effects of the intervention and the CHCD prototype design.

A limitation of the study outlined in this chapter was that the product used was a 'production quality prototype' of the CHCD, which may have affected the performance of the device. Due to the nature of the product being in prototype stage, there were usability issues encountered such as straps slipping during compression and possible small leaks in the air bladder; this may be a factor influencing the lack of significance across the different pressure levels. Also, another limitation of this study is the lack of a control group that did not receive a CHCD intervention within the randomised crossover design.

A further limitation of the study is surrounding the convenience sample within the university staff and student populations within a sport and health science cohort. Despite never using this particular CHCD previously, most of the participants were familiar with cryotherapy applications and had experience with previous cryotherapy modalities. Convenience sampling of this nature can limit external validity, which limits the ability to generalise the findings to a wider population outside of the sport and health science cohort (Andrade, 2020). In addition, only healthy male participants were recruited which limits the transferability of these findings to injured populations or females.

4.3.5 Conclusions

Interventions 1 & 3, set with a target temperature of 10 °C, achieved T_{sk} within the therapeutic range and could therefore be considered the most effective cryotherapy treatments for the knee when compared to interventions set with a target temperature of 15 °C. Intervention 2, set at 15 °C, did not achieve a T_{sk} within the therapeutic range and can be considered ineffective in achieving the desired physiological effects of knee joint cooling. It is clear that 10 °C was the optimal target temperature used in this study. It is difficult to conclude a single optimal intervention from the results of this study alone as there were no significant differences found between the two pressure levels used in interventions 1 & 3 using the CHCD. It is difficult to conclude a single optimal intervention from the results of this study alone as there were no significant differences found

between the two pressure levels used in interventions 1 & 3 using the CHCD. Further product development is required to improve the contact of the cooling plate on the lateral aspect of the knee, as this may have significantly affected the cooling efficiency achieved. As this work was carried out on healthy male participants, further research is required across a wider population in order to define an optimal intervention for knee injury management.

4.4 Part B: Exploring the Effects of Targeted Cryotherapy on Pressure Pain, Strength, and Joint Position Sense

4.4.1 Introduction

With the development of the guidelines for acute injury management evolving from PRICE (Protection, Rest, Ice, Compression and Elevation) to POLICE (Protection, Optimal Loading, Ice, Compression, Elevation), the ability to facilitate optimal loading is key to promote early recovery with early activity. Clinical guidelines for cryotherapy are supported by moderate evidence of the effectiveness to reduce short-term pain for soft tissue contusions in acute ankle injuries (Bleakley *et al.*, 2011). There is also high quality evidence of cryotherapy offering a short-term analgesic effect post-surgery (Bleakley *et al.*, 2011). However, some studies have identified potential adverse effects to muscle performance and knee joint repositioning following ice interventions and have expressed caution to players returning to play immediately after cryotherapy (Uchio *et al.*, 2003; Costello and Donnelly, 2010; Alexander *et al.*, 2016; Alexander *et al.*, 2018; Rhodes and Alexander, 2018). These authors have advised that shorter applications of cryotherapy, as well as a warm-up prior to returning to weight bearing activity, could minimise the increased risk of injury post-cryotherapy. It is not yet known if reducing the surface area being cooled, utilising a targeted cryotherapy approach, may also be a means of minimising the reported increased risk of injury post cryotherapy. Therefore, cryotherapy interventions which can provide short-term pain relief, yet minimise adverse effects, would allow early activity with a lower risk of injury. This study utilised a targeted compressive cryotherapy approach on healthy participants and explored the effects on muscle strength, pressure pain threshold and joint position sense.

4.4.2 Methods

4.4.2.1 Participant Recruitment

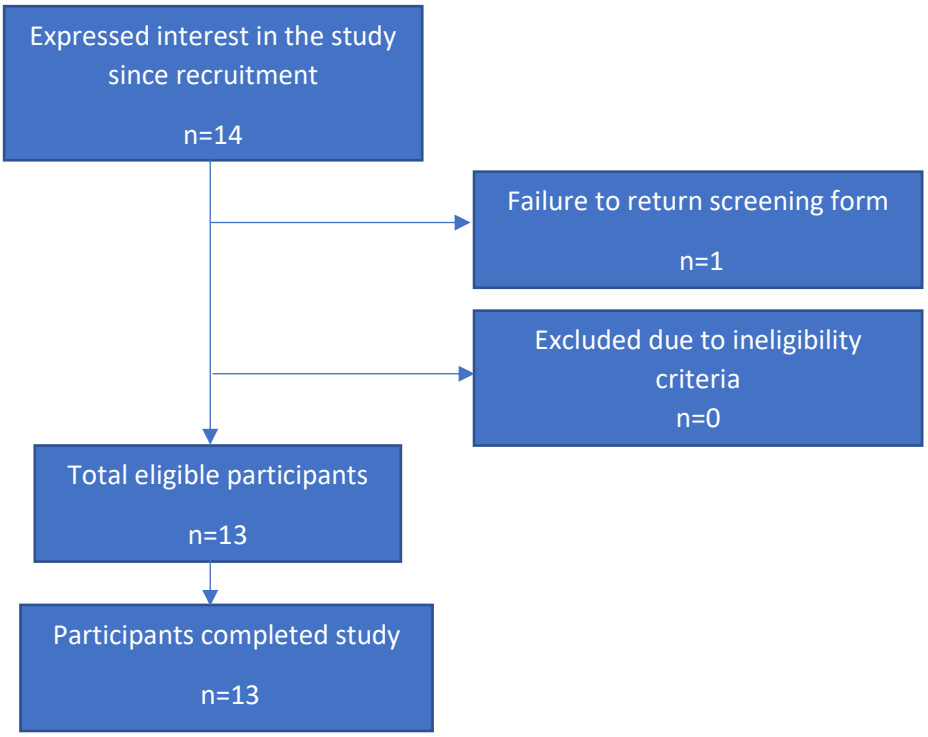


Figure 4.8: A summary of participant recruitment for Part B

Figure 4.8 illustrates the recruitment process for Study 2. Participants were recruited through the process outlined in Part A (see section 4.3.2.1).

4.4.2.2 Data Collection Procedure

Table 4.14: Part B data collection protocol

Time Point	**Procedure**	**Duration (mins)**
Pre	Body weight and height recorded	5
	Application of anatomical markers	20
	JPS Assessment 1	5
	PPT Assessment 1	
	Muscle Strength 1	
Intervention	Fit the device	
	Intervention 1, 2, 3 or 4 (randomised)	20
	Removal of the device	
Immediately Post	JPS Assessment 2	5
	PPT Assessment 2	
	Muscle Strength 2	
20 Minutes Post	JPS Assessment 3	5
	PPT Assessment 3	
	Muscle Strength 3	
	END OF SESSION	**60**

4.4.2.3 Outcome Measures

4.4.2.3.1 Pressure Pain Threshold

PPT was defined as the point at which the sensation of 'pressure' changed to 'pain' as signalled by the participant verbally. PPT was measured using a digital algometer (Wagner FPX, USA). The reliability of the device is reported in Chapter 3 (see section 3.3.4). PPT was measured at three sites on both the medial and lateral aspects of the non-dominant knee (see Figure 4.9):

1. 7cm **above** the centre of the area cooled.
2. The **centre** of the area cooled.
3. 7cm **below** the centre of the area cooled.

7cm was selected as the distance as it is the length of the cooling plate on the CHCD. The mean of three trials was used, which is a common approach used for PPT measurements (Walton *et al.*, 2011). The minimal detectable change (MDC) in a healthy population at the tibialis anterior was reported as 86.3 kPa, which was used in analyses for this study (Walton *et al.*, 2011). To put this into context, 86.3 kPa is equivalent to 0.88 kg/cm^2, which is less than a 1 litre bottle of water per cm^2.

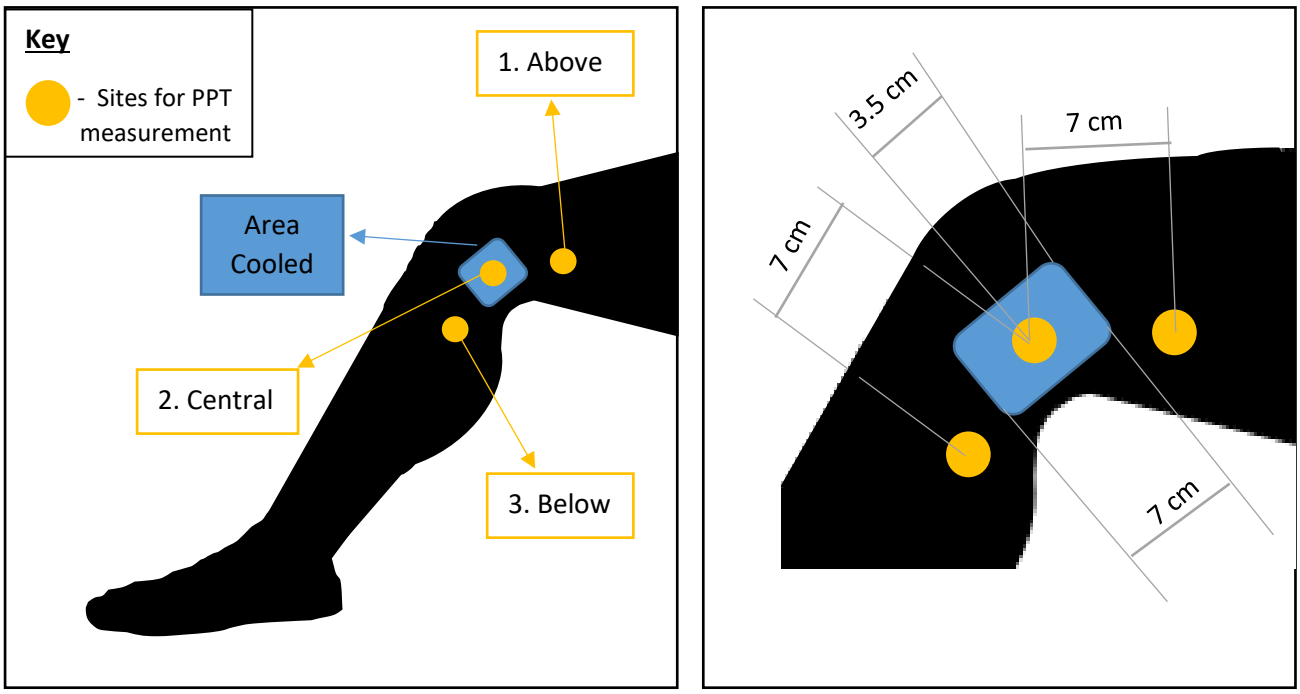


Figure 4.9: The sites for PPT measurement (above the cooled area, within the cooled area and below the cooled area)

4.4.2.3.2 Quadriceps Strength

Quadriceps strength was measured at three time points, using the protocol detailed in Chapter 3 (see section 3.3.7). The reliability of the handheld dynamometer (HHD) (Model 01165, Lafayette Instrument Co, Lafayette, IN) used is discussed in Chapter 3 (see section 3.3.2).

4.4.2.3.3 Joint Position Sense

The Qualisys Motion capture system (Qualisys medical AB, Gothenburg, Sweden) in the Movement Laboratory at Manchester Metropolitan University was used for data collection of 3D kinematic motion. JPS was measured using the protocol outlined in Chapter 3 (see section 3.3.8). Participants were given three attempts to replicate 45° knee flexion, to familiarise with the small knee bend (SKB) protocol. Following the 'practice' attempts participants then completed 5 SKB's on their non-dominant knee. Table 4.15 summaries the direction of the movement corresponding to the maximum and minimum values for each cardinal plane, to assist with the interpretation of the results.

Table 4.15: A summary of the direction of movement corresponding to the minimum and maximum values

Sagittal (X)		**Coronal (Y)**		**Transverse (Z)**	
Minimum	**Maximum**	**Minimum**	**Maximum**	**Minimum**	**Maximum**
Knee Extension	Knee Flexion	Knee Adduction	Knee Abduction	Knee Internal Rotation	Knee External Rotation

4.4.2.4 Statistical Analysis

Descriptive statistics, including means and standard deviations, were calculated for each intervention. Analysis of the distribution of the data for thermal data and oxygenation confirmed suitability for parametric statistical testing. Interventions were assessed over a 20-minute rewarming period, using repeated measures ANOVAs, with post-hoc pairwise comparisons and significance accepted at $p \leq 0.05$.

4.4.3 Results

A total of 13 healthy male participants were recruited overall for Part B. Ten participants took part in multiple sessions and 3 participants took part in a single session. The average age of participants was 25.3 ± 3.4 yrs. The average BMI of the participants was 25.6 ± 2.9.

4.4.3.1 Pressure Pain Threshold

Table 4.16: Descriptive statistics for mean PPT (±SD) on the medial aspect of the knee for all interventions and time points (n=10). Significant differences were assessed using a repeated measures ANOVA (3 x 4 – time points by interventions) with a significance level set at p<0.05.

Mean PPT Medial ± (SD) - kPa

Intervention	Pre			Immediately post			20 minutes post		
	Above Area Cooled	*Area Cooled*	*Below Area Cooled*	*Above Area Cooled*	*Area Cooled*	*Below Area Cooled*	*Above Area Cooled*	*Area Cooled*	*Below Area Cooled*
1	342.3 (132.3)	374.0 (126.5)	338.0 (117.2)	360.6 (158.7)	398.5 (148.7)	355.7 (148.7)	395.9 (157.2)	428.2 (150.1)	385.7 (142.4)
2	381.8 (192.4)	387.7 (144.1)	327.5 (135.2)	389.3 (172.1)	411.9 (185.3)	363.5 (145.1)	430.5 (221.8)	436.7 (233.4)	390.6 (161.6)
3	399.1 (183.7)	435.4 (166.6)	348.8 (128.8)	417.1 (221.1)	464.2 (196.6)	369.7 (139.4)	457.0 (241.2)	496.5 (214.7)	412.9 (164.4)
4	386.7 (123.7)	445.9 (109.1)	370.7 (84.6)	412.2 (156.0)	447.5 (137.4)	371.7 (97.2)	426.3 (174.1)	437.4 (132.6)	408.0 (110.3)

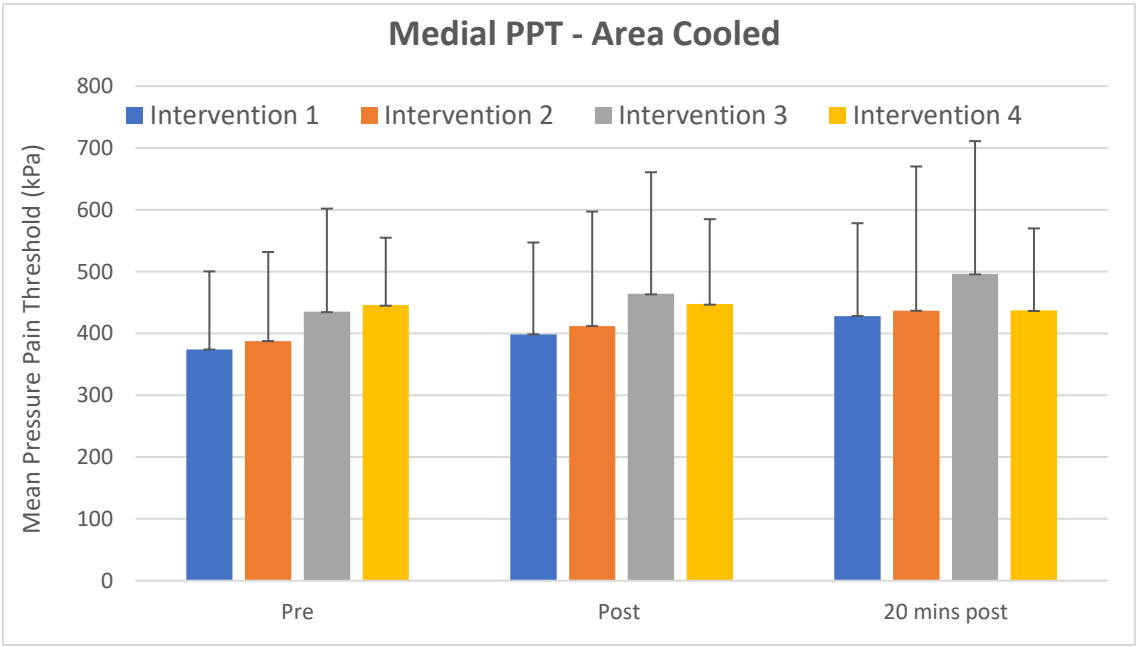


Figure 4.10: Grouped data for mean PPT (kPa) ±SD on the medial aspect of the knee for all interventions and time points (n=10).

Table 4.17: Descriptive statistics for mean PPT (±SD) on the lateral aspect of the knee for all interventions and time points (n=10). Significant differences were assessed using a repeated measures ANOVA (3 x 4 – time points by interventions) with a significance level set at p<0.05.

Mean PPT Lateral ± (SD) - kPa

Intervention	Pre			Immediately post			20 minutes post		
	Above Area Cooled	*Area Cooled*	*Below Area Cooled*	*Above Area Cooled*	*Area Cooled*	*Below Area Cooled*	*Above Area Cooled*	*Area Cooled*	*Below Area Cooled*
1	407.0 (192.4)	397.2 (144.1)	391.3 (135.2)	404.4 (172.1)	425.6 (185.3)	407.3 (145.1)	446.2 (221.8)	467.8 (233.4)	418.4 (161.6)
2	438.0 (260.4)	451.1 (296.7)	466.8 (221.6)	462.9 (329.2)	479.5 (308.8)	466.5 (266.3)	504.1 (316.4)	510.3 (334.3)	486.4 (298.6)
3	439.0 (174.1)	383.8 (156.3)	416.8 (161.2)	459.3 (212.8)	446.9 (193.8)	451.1 (206.4)	487.4 (239.1)	467.1 (223.3)	471.4 (248.5)
4	440.3 (142.0)	413.8 (109.7)	466.8 (207.6)	443.6 (147.5)	413.8 (188.8)	466.8 (213.6)	486.7 (198.5)	468.1 (203.8)	524.7 (261.3)

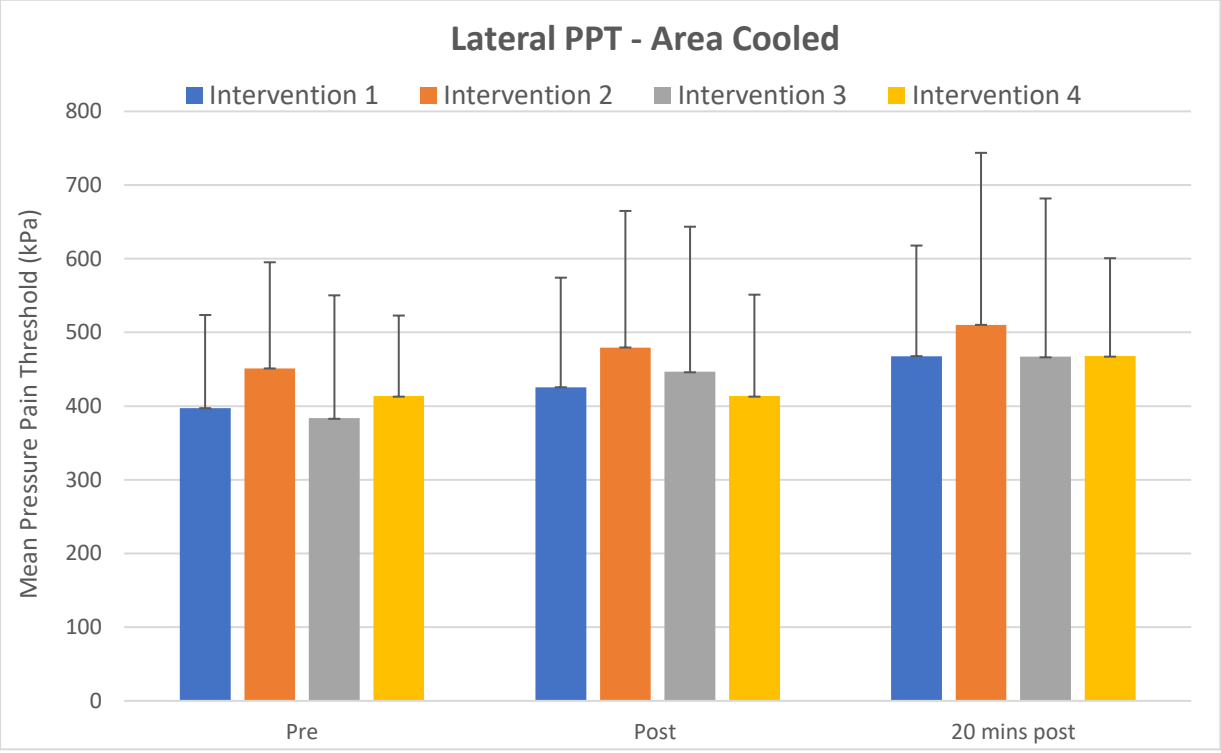


Figure 4.11: Grouped data for mean PPT (kPa) ±SD on the lateral aspect of the knee for all interventions and time points (n=10).

Above vs Central vs Below

In grouped analysis, significant differences were found between PPT measurement sites on the medial aspect of the knee. Table 4.18 presents the pairwise comparison, which demonstrate significant increases for PPT at the cooled area compared to all other locations on the medial aspect of the knee. Significant differences were also seen on the medial aspect between above the cooled area and below the cooled area. On the lateral aspect of the knee, no significant differences were found between PPT measurement sites and thus post-hoc comparisons were not carried out.

*Table 4.18: Pairwise comparison and descriptive statistics of measurement sites for PPT on the medial aspect of the knee (n=10). *****Denotes a statistically significant difference assessed using a repeated measures ANOVA (3 x 3 – time points by locations) with a significance level set at p<0.05.*

Pairwise Comparisons of Medial PPT locations

Comparison		**Mean Difference**	**Significance Value**	**95% Confidence Interval for Difference**
Above	Central	-30.4	.010*	- 51.8 to -9.1
	Below	29.7	.025*	4.7 to 54.7
Cooled Area	Above	30.4	.010*	9.1 to 51.8
	Below	60.1	<.001*	39.6 to 80.6
Below	Above	-29.7	.025*	-54.7 to -4.7
	Central	-60.1	<.001*	-80.6 To -39.6

Medial vs Lateral

Significant increases were found in PPT from medial to lateral aspects of the knee (p=0.002). The medial side had a mean difference 50.2 kPa greater than the lateral aspect of the knee.

Interventions

In grouped analysis, no significant differences between interventions were found. Therefore, post-hoc analyses were not carried out to compare interventions. Significant differences were found between time points on both the medial and lateral aspects of the knee. Tables 4.19 & 4.20 present the post-hoc pairwise comparisons, which demonstrate significant increases in PPT from pre to 20 minutes post intervention and post

intervention to 20 minutes post intervention. No significant differences were found between the immediate effects of high and low compression on medial and lateral PPT ($p>0.05$). No significant differences were found between the immediate effects of temperature settings on medial and lateral PPT ($p>0.05$).

*Table 4.19: Pairwise comparison and descriptive statistics of time points for mean PPT on the medial aspect of the knee (n=10). *****Denotes a statistically significant difference assessed using a repeated measures ANOVA (3 x 4 – time points by interventions) with a significance level set at p<0.05.*

Pairwise Comparisons of Time Points (Media Meanl PPT)

Comparison		**Mean Difference**	**Significance Value**	**95% Confidence Interval for Difference**
Pre	Post	-19.8	.086	-43.0 to 3.4
	20 Mins Post	-39.0*	.024*	-71.4 to -6.5
Post	Pre	19.8	.086	-3.4 to 43.0
	20 Mins Post	-19.2*	.013*	-33.3 to -5.1
20 Mins Post	Pre	39.0*	.024*	6.5 to 71.4
	Post	19.2*	.013*	5.1 to 33.3

*Table 4.20: Pairwise comparison of time points for mean PPT on the lateral aspect of the knee (n=10).*****Denotes a statistically significant difference assessed using a repeated measures ANOVA (3 x 4 – time points by locations) with a significance level set at p<0.05.*

Pairwise Comparisons of Time Points (Lateral Mean PPT)

Comparison		**Mean Difference**	**Significance Value**	**95% Confidence Interval for Difference**
Pre	Post	-35.9	.078	-76.7 to 4.9
	20 Mins Post	-66.9	.019*	-120.1 to -13.7
Post	Pre	35.9	.078	-4.9 to 76.7
	20 Mins Post	-31.0	.008*	-51.4 to -10.5
20 Mins Post	Pre	66.9	.019*	13.7 to 120.1
	Post	31.0	.008*	10.5 to 51.4

4.4.3.2 Quadriceps Strength

Mean peak quadriceps moment (Nm) was calculated using the mean muscle force (N) multiplied by the lever arm length (m). This was then normalised to obtain an index of quadriceps strength independent to body size (Almeida, Albano and Melo, 2019). Table 4.21 presents the mean peak moment for each participant, each intervention, and each time point.

Table 4.21: Mean peak moment (Nm/kg) for each participant (n=10), (normalised to body mass) for all interventions, with 95% confidence intervals presented. Significant differences were assessed using a repeated measures ANOVA (3 x 4 – time points by interventions) with a significance level set at p<0.05.

Mean Peak Moment (Nm/kg)													
Intervention	**Time point**	**Participant**										**Mean (±SD)**	**95% CI**
		1	2	3	4	5	6	7	8	9	10		
1	*Pre*	0.9	0.6	0.8	1.2	1.4	1.5	0.9	1.3	1.4	1.3	**1.1 (0.3)**	0.9, 1.3
	Post	0.7	0.7	1.1	1.3	1.5	1.1	0.9	1.0	1.2	1.2	**1.1 (0.3)**	0.9, 1.3
	20 Mins Post	0.8	0.6	1.1	1.3	1.3	1.5	0.9	1.0	1.1	1.1	**1.1 (0.3)**	0.9, 1.3
2	*Pre*	0.6	0.6	1.1	1.1	1.1	1.1	1.2	1.3	1.1	1.1	**1.0 (0.2)**	1.0, 1.2
	Post	0.6	0.7	0.9	1.1	1.2	1.1	1.0	1.2	1.0	1.2	**1.0 (0.2)**	0.8, 1.2
	20 Mins Post	0.6	0.6	1.0	1.1	1.2	1.1	1.1	1.2	1.1	1.3	**1.0 (0.2)**	0.9, 1.2
3	*Pre*	0.8	0.8	1.3	1.6	0.6	1.2	0.9	1.2	1.3	1.0	**1.1 (0.3)**	0.9, 1.3
	Post	0.9	0.7	1.3	1.6	0.6	0.9	1.0	1.2	1.0	1.0	**1.0 (0.3)**	0.8, 1.2
	20 Mins Post	0.9	0.8	1.1	1.7	0.6	0.9	0.9	1.2	1.1	1.3	**1.1 (0.3)**	0.8, 1.3
4	*Pre*	0.9	0.8	1.1	1.1	1.1	1.0	1.3	1.2	1.3	1.3	**1.1 (0.2)**	1.0, 1.2
	Post	0.9	0.8	1.2	1.1	1.1	1.3	1.1	1.2	1.3	1.3	**1.1 (0.2)**	1.0, 1.3
	20 Mins Post	0.9	0.9	1.2	1.1	1.1	1.1	1.2	1.1	1.3	1.3	**1.1 (0.1)**	1.0, 1.2

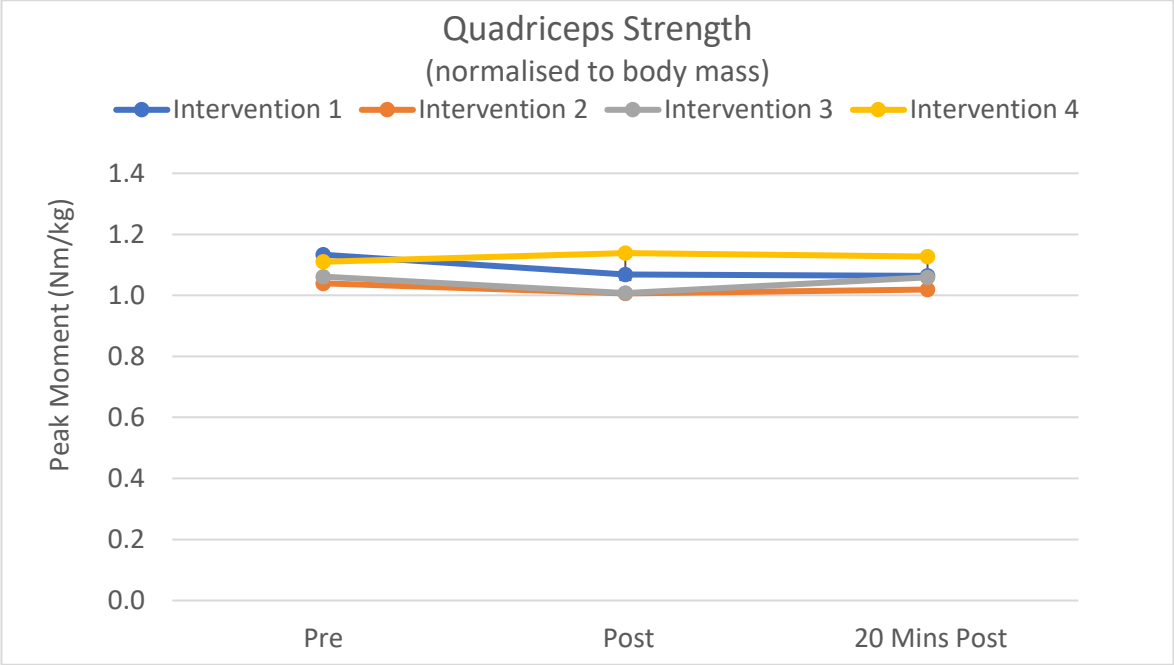


Figure 4.12: Mean peak moment (Nm/kg) for each participant (n=10), (normalised to body mass) for all interventions, ±SD.

No significant differences between time points or interventions were found. Therefore, post-hoc comparisons were not carried out. Despite no statistically significant differences between interventions, Table 4.22 highlights that the decrease in peak moment from pre to post intervention was most apparent following intervention 1 (6% decrease). Although Table 4.21 suggests no change in average peak moment from pre to post intervention 1, the differences are more apparent when the averages are reported to three decimal places (pre: 1.13 and post 1.07 Nm/kg).

Figure 4.12 illustrates the trend for the compressive cryotherapy interventions (1-3), which showed quadriceps strength decreases from pre- to post intervention of approximately 2-6%. This decrease was then followed by an increase of approximately 1-3% from immediately post to 20 minutes post for interventions 2 & 3. Intervention 1 remained plateaued from post to 20 minutes post intervention. On the other hand, contrast therapy (Intervention 4) had the opposite response, with an initial 2% increase in quadriceps strength post intervention, followed by a 1% decrease 20 minutes post intervention.

Table 4.22: Percentage reductions in normalised mean peak moment (n=10) between time points for each intervention.

Intervention	Time points	Mean Peak Moment Deficit (%)
1	*Pre – Immediately Post Cooling*	**5.3**
	Pre – 20 Minutes Post Cooling	**5.6**
2	*Pre – Immediately Post Cooling*	**3.2**
	Pre – 20 Minutes Post Cooling	**2.0**
3	*Pre – Immediately Post Cooling*	**4.7**
	Pre – 20 Minutes Post Cooling	**2.0**
4	*Pre – Immediately Post Cooling*	**-1.8**
	Pre – 20 Minutes Post Cooling	**-0.9**

No significant differences were found between the immediate effects of high and low compression on quadriceps strength ($p>0.05$). No significant differences were found between the immediate effects of temperature settings on quadriceps strength ($p>0.05$).

4.4.3.3 Joint Position Sense

Table 4.23: Mean ROM (°) Knee Flexion (±SD) during a small knee bend with a target angle of 45°, pre, post and 20 minutes post intervention (n=10). Significant difference assessed using a repeated measures ANOVA (3 x 4 – time points by interventions) with a significance level set at p<0.05.

***Knee Range of Motion (±SD)** - Angle°*

Intervention	**Pre**			**Post**			**20 Minutes Post**		
	X	*Y*	*Z*	*X*	*Y*	*Z*	*X*	*Y*	*Z*
1	43.6 (7.3)	8.0 (3.0)	8.0 (1.2)	41.6 (7.9)	5.8 (3.5)	7.9 (1.1)	42.4 (7.0)	6.4 (3.0)	7.5 (1.6)
2	46.0 (8.5)	7.3 (2.4)	9.4 (3.3)	42.6 (6.3)	6.7 (2.7)	7.9 (3.0)	41.5 (6.5)	6.9 (1.8)	7.6 (2.6)
3	42.9 (6.0)	8.1 (2.7)	8.1 (2.1)	43.2 (8.1)	6.0 (1.4)	9.0 (2.9)	44.1 (6.1)	6.4 (1.2)	8.3 (3.9)
4	49.2 (6.1)	13.3 (15.3)	11.5 (6.9)	43.8 (5.5)	11.5 (15.6)	10.9 (6.2)	43.0 (6.0)	12.6 (14.3)	11.0 (6.7)

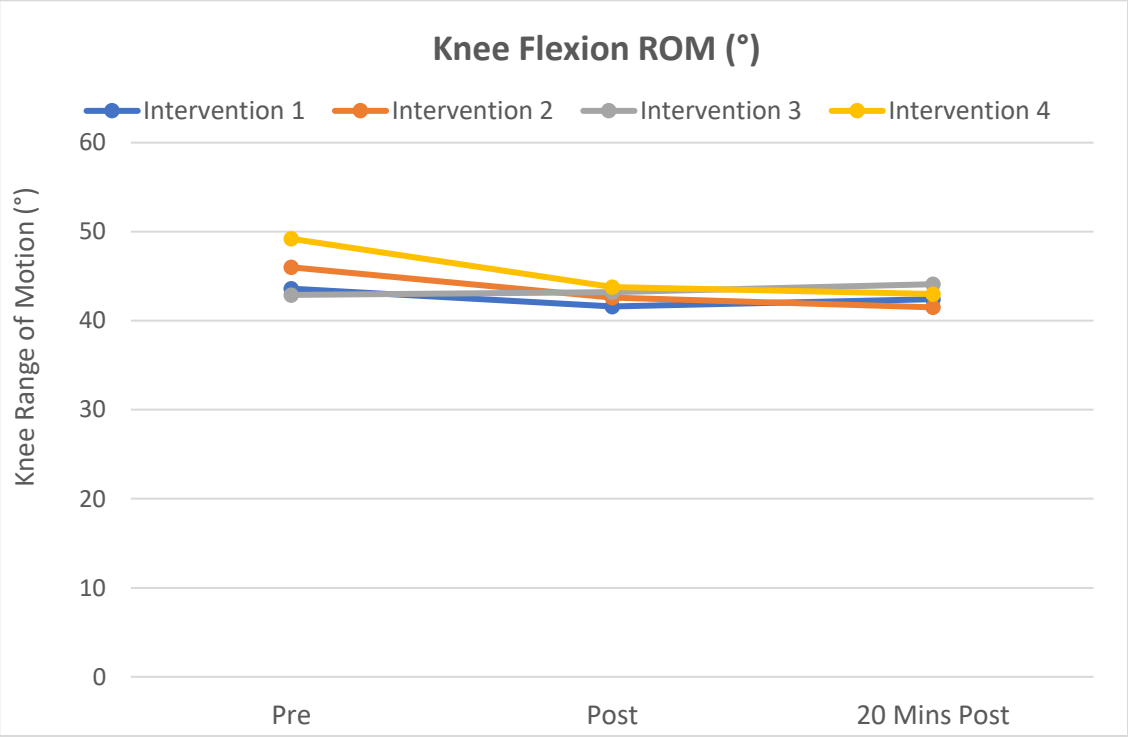


Figure 4.13: Mean ROM Knee Flexion (°) during a small knee bend with a target angle of 45°, pre, post and 20 minutes post intervention for all interventions (n=10).

Table 4.23 presents knee joint range of motion (ROM) in the sagittal plane (X), coronal plane (Y) and the transverse plane (Z) during the small knee bend task (45°). No significant differences (P>0.05) in maximum, minimum or ROM in the sagittal plane (knee flexion) between time points or interventions. Significant decreases were found in knee joint ROM in the coronal plane (knee abduction/adduction) from pre-intervention to post intervention (Table 4.24). No significant differences (P>0.05) in maximum and minimum angles or ROM in the transverse plane (knee internal/external rotation) between time points or interventions.

*Table 4.24: Pairwise comparison and descriptive statistics of time points for knee joint ROM (n=10) in the coronal plane (Y) on the lateral aspect of the knee (*denotes a significance assessed using a repeated measures ANOVA (3 x 4 – time points by interventions) with a significance level set at p<0.05.*

Pairwise Comparisons of Time Points

Comparison		**Mean Difference**	**Significance Value**	**95% Confidence Interval for Difference**
Pre	Post	1.7	.012*	0.6 to 2.8
	20 Mins Post	1.1	.096	--0.3 to 2.5
Post	Pre	-1.7	.012*	-2.8 to -0.6
	20 Mins Post	-0.6	.357	-2.2 to 1.0
20 Mins Post	Pre	-1.1	.096	-2.5 to 0.3
	Post	0.6	.357	-1.0 to 2.2

No significant differences were found between the immediate effects of high and low compression on knee ROM in any of the cardinal planes (p>0.05). No significant differences were found between the immediate effects of temperature settings on knee ROM in all of the cardinal planes (p>0.05).

4.4.4 Discussion

Study 1 Part B explored the effects of four CHCD interventions on pressure pain threshold (PPT), quadriceps strength and joint position sense (JPS).

4.4.4.1 Pressure Pain Threshold

Significant differences were found between PPT measurement sites on the medial aspect of the knee ($p<0.05$). PPT within the cooled area was significantly higher than the other measurement sites recorded. This indicates that the cooling produced an analgesic effect, which led to a higher pain threshold. However, it is important to consider that no average changes were found above the suggested MDC of 86.3 kPa reported by Walton et al. (2011), which may suggest that the changes were due to measurement error. With that being said, the location of the measurements taken from this study varied slightly to the study by Walton et al. (2011), who measured PPT at the tibialis anterior, which could respond differently. Additionally, from these results alone it is difficult to determine the optimal intervention for increasing pain threshold as no significant differences between interventions were found.

Statistically significant differences were found in PPT between the medial to lateral aspects of the knee, with the lateral PPT being higher, on average ($p=0.002$). Interestingly on the medial aspect of the knee, the cooled area recorded the highest mean PPT, with the lowest PPT recorded below the cooled area. Yet, on the lateral aspect of the knee, the cooled area recorded the lowest PPT, with the highest mean PPT being recorded below the cooled area. On the other hand, no significant differences were found between PPT measurement sites on the lateral aspect of the knee. These findings echo Alexander et al. (2019), which reported that the medial aspect of the knee is significantly more sensitive to external stimuli than the lateral aspect of the knee. These findings also reinforce Part A (see section 4.3.4), which identified that the desired cooling may have not been achieved on the lateral aspect of the knee and the contact of the cooling plate on the lateral side of the CHCD may need further improvement, in order to achieve the desired physiological effects.

Significant differences were found between time points on both the medial and lateral aspects of the knee ($p<0.05$). Significant increases in PPT from pre-intervention to 20 minutes post intervention and post intervention to 20 minutes post intervention. Zemke

et al. (1998) reported that intramuscular temperatures (at 1cm) achieved their lowest temperatures at 17.9 ± 2.4 minutes with a 15-minute ice massage and 28.2 ± 12.5 minutes with a 15-minute application of an ice bag. Hardaker et al. (2007) reinforce this continuation of deep tissue cooling post removal of cryotherapy and demonstrated that intramuscular cooling (at 3cm) continues up to 30-40 minutes after removal. Costello et al. (2012a) found that intramuscular temperature (at 3cm) continued to decline up to 60 minutes after both whole-body cryotherapy and cold-water immersion and did not return to baseline temperature within the 60 minutes observed post intervention. Although this is not directly comparable to the local cryotherapy applications investigated in this thesis, this finding highlights the importance of considering the delayed effects associated with cryotherapy applications. With this in mind, it is possible to suggest that the effect of the cooling intervention was initially only superficial immediately post intervention and by 20 minutes post intervention, the deeper tissues may have decreased in temperature.

4.4.4.2 Quadriceps Strength

In grouped analysis, no significant differences between time points or interventions were found ($p>0.05$). Despite no statistically significant changes, there was a general trend for the compressive cryotherapy interventions (1-3) which showed quadriceps strength decreases from pre- to post intervention of approximately 2-6%. This decrease was then followed by a small increase of approximately 1-3% at 20 minutes post compressive cryotherapy interventions. This reflects findings in literature, which present decreases in muscle strength following exposure to cryotherapy (Bleakley, Costello and Glasgow, 2012). Decreases in quadriceps functional performance can lead to an increased risk of knee injury due to the loss of control to prevent excessive or abnormal movements (Shultz *et al.*, 2015; Rhodes and Alexander, 2018).

Although this study focussed on a healthy male population, it is still worth considering possible clinical implications of the interventions investigated. Reductions of 6% in quadriceps strength normalised to body mass have been reported as clinically important, which suggests that the average percentage change reported in Table 4.24 between pre and 20 minutes post Intervention 1, could have been considered clinically important. With that being said, in a healthy population significant decreases of approximately 16% in quadriceps concentric peak and average moment have been reported following a 20-minute application of ice to the knee, in a healthy cohort (Rhodes and Alexander, 2018).

Therefore, it is important to understand the magnitude of inhibition of different cryotherapy intervention in order to ensure a safe return to weight-bearing activity. The findings from this study suggest that targeted cryotherapy may decrease the inhibition to quadriceps function in comparison to ice, which may facilitate an earlier return to weight-bearing activity and optimal loading.

On the other hand, contrast therapy (Intervention 4) had the opposite response, with an initial 5% increase in quadriceps strength post intervention, followed by a 3% decrease 20 minutes post intervention. Contrast therapy initially produced a slight increase in muscle strength from pre- to post intervention (by approximately 5%). This echoes the findings presented by Axman et al. (2013) which also found no significant difference statistically between groups, but the general trend showed an increase in strength during knee extension following the application of a hot-pack. This also echoes the findings that contrast therapy interventions may be more beneficial for functional outcome measures, opposed to physiological responses (Hing *et al.*, 2008).

4.4.4.3 Joint Position Sense

No significant differences in maximum, minimum or ROM in the sagittal plane (knee flexion) between time points or interventions ($p>0.05$). However, significant decreases were found in knee joint ROM in the coronal plane (knee abduction/adduction) from pre-intervention to post intervention. It is difficult to conclude the reasons for the reduction in coronal plane ROM, however it could possibly indicate an increase in stability or stiffness following the cooling intervention. No significant differences ($p>0.05$) in maximum and minimum angles or ROM in the transverse plane (knee internal/external rotation) between time points or interventions. These findings conflict with previous research which has presented significant increases in the ROM in the transverse plane; causing significant reductions in the ability to replicate knee joint angle positioning accurately, 20 minutes following an ice application (Alexander *et al.*, 2016; Alexander *et al.*, 2018). Decreased dynamic stability and knee joint repositioning may cause a potential increased risk of injury when returning to weight-bearing activity (Arnason *et al.*, 2004; Costello and Donnelly, 2010; Alexander *et al.*, 2016; Alexander *et al.*, 2018).

4.4.4.4 Limitations

In addition to the limitations reported in Section 4.3.4, it is also important to consider the possible training effect of continuous PPT measurements, which may lead to an increase as the participant familiarises with the stimulus and cluster testing protocol (Bisset, Evans and Tuttle, 2015). Additionally, despite Weng et al. (2015) reporting good correlation for the comparison between the HHD (Lafayette HHD model 01163) and Cybex dynamometer (Chapter 3, section 3.6), an isokinetic dynamometer (IKD) is still considered to be the gold standard equipment for muscle strength measurements (Weng *et al.*, 2015).

In addition, a limitation of this study is the lack of a control group that did not receive a CHCD intervention within the randomised crossover design.

4.4.5 Conclusions

Inhibition to quadriceps strength and joint position sense may discourage early activity or optimal loading post intervention. The findings from this study suggest that targeted cryotherapy, using the CHCD, may decrease the inhibition to quadriceps function compared to ice by approximately 10%, which may facilitate an earlier return to weight-bearing activity, at a lower risk of injury or re-injury. However, it is important to note that this study was carried out on a healthy male population.

Chapter 5: Exploring the effects of cryotherapy modalities on pain, muscle strength and joint position sense in healthy participants with experimentally induced knee pain

This chapter outlines a randomised crossover pilot trial exploring the effects of two interventions; 1) wetted ice and 2) optimal cooling, heating, and compression device (CHCD) intervention, exploring muscle strength, joint position sense and pain in a population induced with experimentally induced knee pain. The optimal intervention identified in Chapter 4 (10 °C target T_{sk} and 50 mmHg) was compared to ice, which is the cryotherapy modality currently advised within the clinical guidelines.

5.1 Abstract

Purpose

The evidence surrounding the effects of local cryotherapy on inflammation has recently been questioned in the literature. However, the use of cryotherapy for short-term pain relief is well accepted and is supported by high-quality evidence. Studies have identified potential adverse effects to functional measures such as muscle strength and knee joint repositioning following ice interventions. Therefore, cryotherapy interventions which can provide the same analgesic effect achieved through ice, whilst minimising these reported adverse effects to function, may minimise the risk of injury post-intervention. The purpose of this study was to explore if a targeted compressive cryotherapy approach can reduce experimentally induced knee pain in healthy participants, and to explore the effects on muscle strength and joint position sense.

Methods

Healthy participants were recruited and induced with experimental knee pain using topical capsaicin cream. A crossover design was adopted, exploring two 20-minute cryotherapy interventions, *(1)* wetted ice and *(2)* CHCD (10 °C with 50 mmHg), during separate testing sessions. Four outcome measures were explored: i) participant perceived pain, ii) pressure pain threshold (PPT), iii) quadriceps muscle strength and iv) joint position sense (JPS). These outcomes were recorded at four time points: pre-capsaicin cream application (T1), post-capsaicin (T2), post-cooling intervention (T3) and 20 minutes post-cooling (T4). Repeated measures ANOVAs (3x2) with post-hoc pairwise comparisons, were used to assess changes in outcomes between time points.

Results

Ten healthy participants (32.9 ± 11.6 years) were induced with experimental knee pain. Participant-reported pain was reduced by 100% (CHCD) and 91% (ice) 20 minutes post-cooling. Complete pain relief (≥93% pain reduction) was achieved immediately post-cooling in 7 participants for the CHCD and in 4 participants for ice. However, no statistically significant differences were found between interventions ($p>0.05$). Significant increases in PPT were found between post-capsaicin and post-cooling and between post-capsaicin and 20-minute post-cooling time points following the CHCD interventions. Whereas no significant differences were found in PPT between any time points following ice. Ice reduced quadriceps strength by 13% immediately post-cooling and the CHCD had a negligible effect on muscle strength immediately post intervention (+0.3%). However, no statistically significant differences in muscle strength were found between interventions. Significant increases were found in ROM in the coronal plane following the ice intervention, which indicates increased instability (adduction/abduction) following ice. No significant differences in maximum, minimum or ROM in the sagittal or transverse planes between time points or interventions were seen. However, there was a trend towards an increase in instability in the transverse plane from post-capsaicin to 20 mins post-cooling which was most apparent following ice ($p=0.053$).

Conclusion

Targeted compressive cryotherapy has the potential to achieve the same desired analgesic effect as ice on healthy participants with experimentally induced knee pain, whilst minimising the negative effects on muscle strength and dynamic stability. Therefore, a targeted compressive cryotherapy approach may be able to facilitate early optimal loading, with a lower risk of re-injury post-intervention.

5.2 Introduction

5.2.1 Cryotherapy

Ice is a cheap form of cryotherapy, which can be widely used in a number of forms (e.g., cubed, crushed and wetted) and is currently the standard clinical cryotherapy treatment (Bleakley *et al.*, 2011). Clinical guidelines for cryotherapy are supported by moderate evidence of the effectiveness to reduce short-term pain for soft tissue contusions in acute ankle injuries (Bleakley *et al.*, 2011). There is also high quality evidence of cryotherapy offering a short-term analgesic effect post-surgery (Bleakley *et al.*, 2011), but there is a lack of high-quality evidence on the efficacy of using ice to treat soft tissue injuries (Bleakley, McDonough and MacAuley, 2006; Dubois and Esculier, 2019). This indicates that ice, as a therapeutic modality, could be most beneficial in the management of acute injury and post-surgical recovery for short-term pain-relief, through an induced analgesic effect.

The physiological basis of cryotherapy achieving pain relief is not fully understood (Saeki, 2002; Algafly and George, 2007; Bleakley *et al.*, 2011). Authors have suggested that alterations to NCV could be the mechanism by which cryotherapy achieves pain relief (Algafly and George, 2007). Other mechanisms such as pain gate theory (Melzack and Wall, 1965) and diffuse noxious inhibitory controls (Willer, Roby and Le Bars, 1984) have also been suggested. Algafly & George (2007) reported a significant increase in perceived pain threshold and tolerance, with a decrease in skin surface temperature. Reducing T_{sk} to 10 °C at the ankle resulted in a pain threshold increase of 71% (Algafly and George, 2007). The authors also reported rates of NCV reduction of 0.4m/s decrease for every 1 °C reduction in T_{sk} (Algafly and George, 2007). Based on this evidence, it is plausible to suggest that a reduction in T_{sk} could lead to an increase in pain threshold, through alterations to NCV.

Some studies have identified potential adverse effects to muscle performance and knee joint repositioning following ice interventions. Authors have expressed caution about players returning to play immediately after cryotherapy (Costello and Donnelly, 2010; Dewhurst *et al.*, 2010; Bleakley, Costello and Glasgow, 2012; Alexander *et al.*, 2016; Alexander *et al.*, 2018). Bleakley, Costello and Glasgow (2012) advised that shorter applications of cryotherapy, as well as a warm up prior to returning to weight bearing activity, could minimise the increased risk of injury post cryotherapy.

In 2012, the guidelines for acute injury management evolved from **PRICE** (**P**rotection, **R**est, **I**ce, **C**ompression and **E**levation) to **POLICE** (**P**rotection, **O**ptimal **L**oading, **I**ce, **C**ompression, **E**levation) (Bleakley, Glasgow and MacAuley, 2012). 'Optimal loading' was introduced into the clinical guidelines to promote early activity (Bleakley, Glasgow and MacAuley, 2012). Any intervention which facilitates early activity whilst achieving other elements of the POLICE guidelines can therefore be considered beneficial. It is not yet known if reducing the surface area being cooled, (i.e., a targeted cryotherapy approach) may also be a means of minimising the reported increased risk of injury post cryotherapy.

5.2.2 Experimental Knee Pain

Pain is the primary symptom of a number of knee conditions (Henriksen, 2011). The efficacy of a treatment or intervention is often evaluated by the ability to reduce pain (Zhang *et al.*, 2010; Sørensen *et al.*, 2012). Experimental knee pain models provide the opportunity to investigate the isolated effects of knee pain on motor functions in healthy participants, without the addition of disease-related factors (D'Agostino, 2005; Sørensen *et al.*, 2012). Common experimental pain methods include hypertonic saline injections and topical capsaicin cream (Modir and Wallace, 2010; Sørensen *et al.*, 2012).

Pain in the form of a heat or burning sensation has been reported following an application of topical capsaicin cream as between 2-6 on a NPRS (0-10; 0, no pain; 10, worst pain possible) (Chrubasik, Weiser and Beime, 2010). Capsaicin cream (Axsain®, 0.075%) is commonly used to induce experimental pain (Petersen and Rowbotham, 1999; Modir and Wallace, 2010) and was used in this study as it was considered the most ethical and is the least invasive experimental method of inducing pain. Capsaicin is the primary active ingredient of hot chilli peppers. When applied to the skin, capsaicin binds to receptors called TRPV1, which leads to nerve depolarisation and a stimulation of substance-P, which causes an intense burning sensation that can be perceived as painful or itchy for the majority of people (Papoiu and Yosipovitch, 2010). Capsaicin initially induces a hypersensitisation but with prolonged use creates a long-lasting nerve desensitisation, which is why it is often used as pain relief for chronic conditions (Papoiu and Yosipovitch, 2010).

Experimental knee pain can have a significant inhibitory impact on muscle function, reducing knee extension and flexion muscle strength, and is positively correlated with

pain intensity (Henriksen, 2011). It is important to note however, that Henriksen (2011) used hypertonic saline (5.8% solution) into the infrapatellar fat pad. Interestingly, experimental knee pain (using hypertonic saline injection into the infrapatellar fat pad) was not found to affect knee joint position sense in healthy participants (Bennell *et al.*, 2005).

To date, there is currently no research exploring effects of cryotherapy interventions on healthy participants with experimentally induced knee pain. Furthermore, no current studies are available that explore the effects of a targeted compressive cryotherapy approach, for example cooling a relatively small surface area, on knee pain or experimentally induced pain.

5.3 Methods

5.3.1 Participants

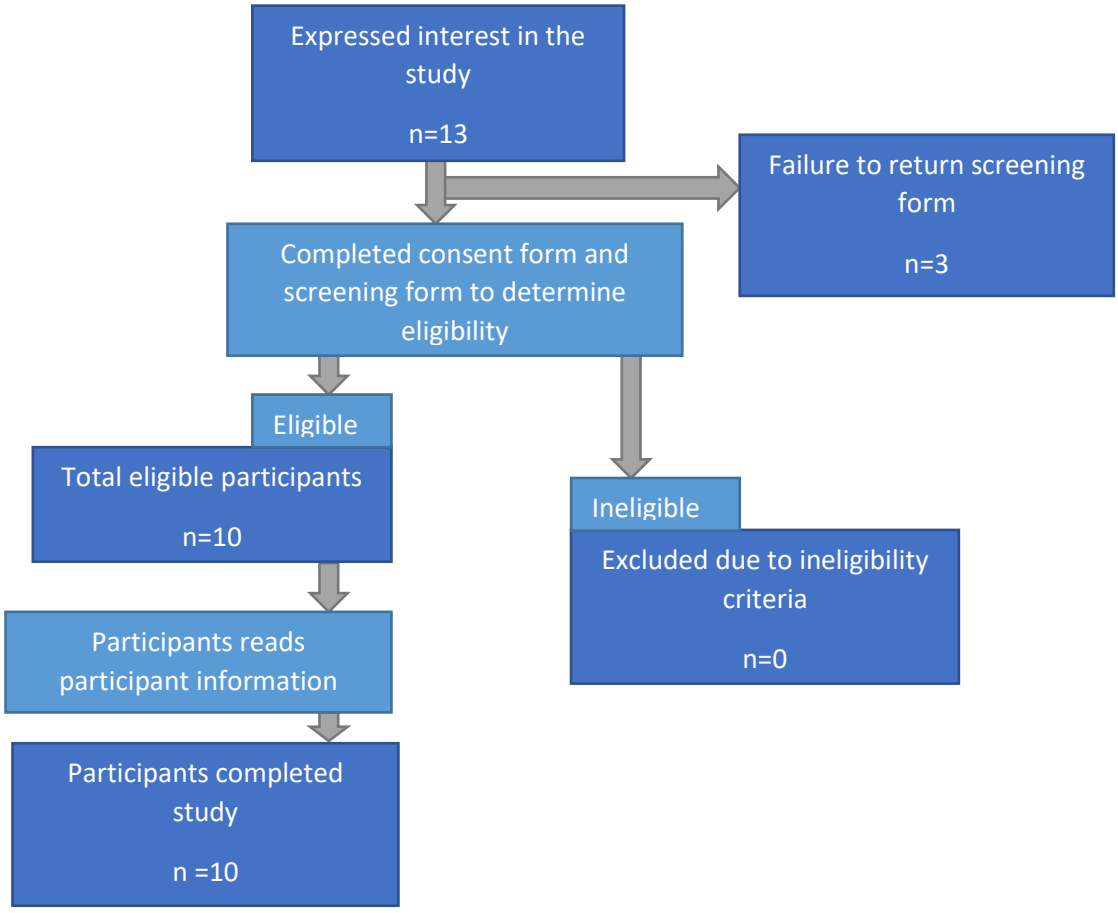


Figure 5.1: The recruitment process used in this study

Figure 5.1 illustrates the recruitment process for this study. Participants were recruited from Manchester Metropolitan University and University of Central Lancashire, including staff and students, through campus-based advertisements. Volunteers from outside the universities who heard of the study through word of mouth (snowballing effects) were also eligible to be included. Participants had to actively opt into the study by contacting the researchers to express their interest in participating in the study, using the contact information provided. Participants who actively opted into the study were provided with an information sheet, consent form and the opportunity to ask the research team any questions regarding the study. Table 5.1 details the inclusion/exclusion criteria.

Table 5.1: Inclusion/Exclusion Criteria

Inclusion	Exclusion
• Healthy participants • 18-65 years old • No current musculoskeletal injuries to their lower limbs and no known adverse reactions to cold, heat or pressure applications • No known adverse reactions to capsaicin cream (0.075%) • Able to shave the region of interest on the knee (as detailed below)	Participants were screened using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) screening tool (Warburton, Bredin and Gledhill, 2011) (Appendix A) and were excluded from the study if they had: • A current musculoskeletal injury • Any condition that could be made worse through physical activity, cooling, or the application of capsaicin cream. • Broken or irritated skin in the region of interest Participants were also excluded from the study if they were or could have been pregnant as advised in the capsaicin cream manufacturer's guidelines (Appendix E)

An a *priori* power analysis was conducted, using the muscle strength data presented in Chapter 4 (Section 4.3.3.2) due to the preliminary findings indicating possible clinical implications of targeted cryotherapy and contrast therapy interventions on functional outcome measures. It was estimated that a minimum of 9 participants were needed for each condition to detect a 0.4 Nm/kg difference in peak moment with a power of 80% and an alpha level of 0.05. A peak moment of 0.4 Nm/kg was the greatest reduction reported in Chapter 4 from pre to post for Intervention 1.

Table 5.2: Sample size calculation based on the findings from Chapter 4

Mean Difference	Standard Deviation	Power	Significance
0.4	0.3	0.84	0.05

5.3.2 Ethical Considerations

The study conformed to the Declaration of Helsinki and ethical approval was obtained from the Faculty of Health, Psychology and Social Care Ethics committee of Manchester Metropolitan University (EthOS no. 10731) and University of Central Lancashire (HEALTH 0039) (Appendix B). All participants provided written informed consent prior to the study and all information collected was kept strictly confidential and in accordance with GDPR (Commission, 2018). No adverse effects were reported during or following this study.

This study was registered on the ISRCTN registry for clinical trials as a pilot study titled 'A pilot study exploring the efficacy of cryotherapy modalities, on pain, joint position sense and muscle strength in healthy subjects with experimentally induced pain' (ISRCTN17516106). Capsaicin cream (Axsain®, 0.075%) was used in this study to induce experimental knee pain. The cream was obtained via a private prescription for research purposes and was used in accordance with the manufacturer's guidance (Appendix E). Participants were required to shave an area approximately $2cm^2$ on the medial aspect of their non-dominant knee 24 hours prior to the study. The non-dominant leg was used as the weight-bearing limb in the SKB, due to the increased injury rates (Krajnc *et al.*, 2010).

5.3.3 Data Collection

Participants attended two separate testing sessions, exploring two different cryotherapy interventions (Figure 5.2) in a crossover design. The data collection procedure is detailed in Figure 5.3. Each intervention was applied for 20-minutes, which is a clinically relevant dosage time commonly used in both sporting and clinical settings (Kennet *et al.*, 2007; Alexander *et al.*, 2016). A randomisation plan was created on www.randomisation.com to randomise the order in which the interventions were carried out. Wetted ice was selected as the form of ice as it has been reported to be the most effective form of ice for reducing T_{sk} and intramuscular temperatures (Dykstra *et al.*, 2009). There was a minimum of 24 hours recovery in between each session. The sessions took place at the Movement

Laboratory, Manchester Metropolitan University and the Movement Analysis Laboratory, University of Central Lancashire.

Experimental Intervention:

CHCD (*ProMOTION* V1 device)

Target T_{sk} 10°C & 50mmHg

Control Intervention:

Ice (wetted)

400 ml cubed ice, 400 ml water

Figure 5.2: The two cryotherapy interventions used in this study

As detailed in Figure 5.3, 4 outcome measures were recorded at four time points (T1-4):

Outcome measures:

- Participant-reported pain using NPRS
- Pressure pain threshold (PPT)
- Muscle strength
- Joint position sense (JPS)

Time points:

T1 – Pre-capsaicin cream application

T2 - Post-capsaicin cream application

T3 – Immediately post intervention

T4 – 20-minutes post intervention

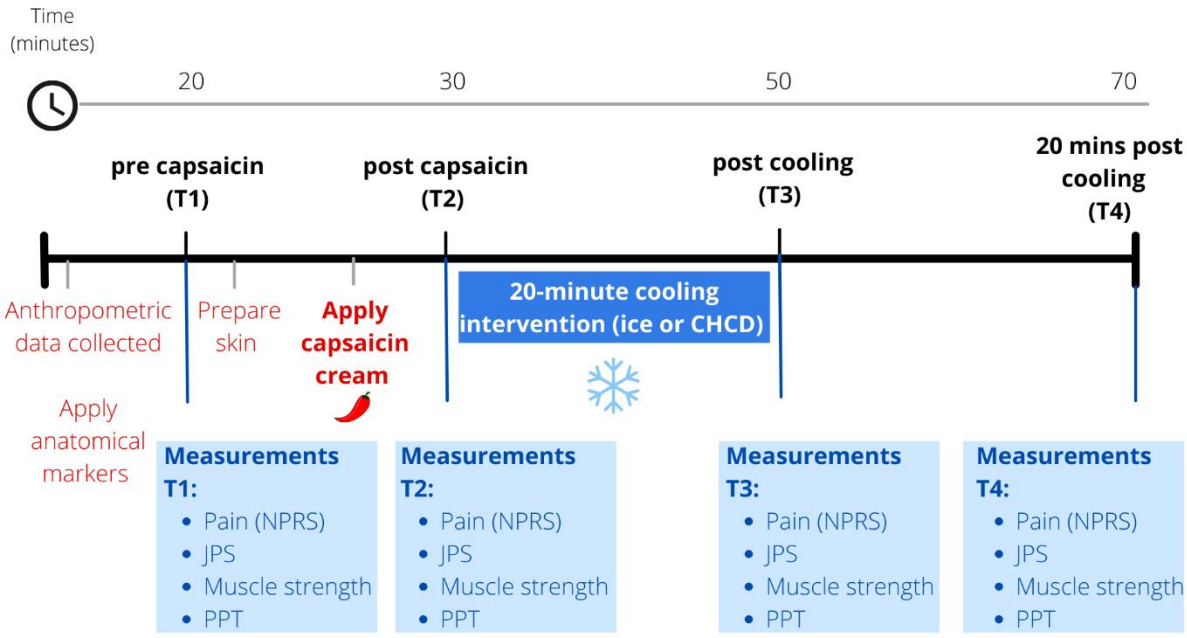


Figure 5.3: Overview of the data collection procedure

5.2.3.1 Participant-Reported Pain

Participant-reported pain scores were measured using a numeric pain rating scale (NPRS) (Figure 5.4), which consists of an 11-point scale where 0=no pain and 10=worst possible pain (Farrar *et al.*, 2001).

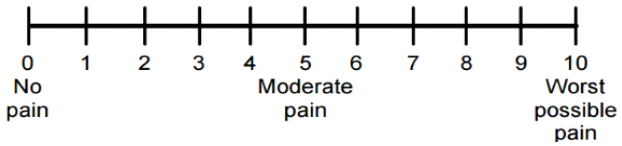


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Figure 5.4: The numeric pain rating scale

The MCIC for acute, sub-acute and chronic pain used for this analysis is outlined in Chapter 3 (section 3.3.2).

5.2.3.2 Pressure Pain Threshold (PPT)

The protocol for measuring and analysing PPT is outlined in Chapter 3 (section 3.3.6).

5.2.3.3 Muscle Strength

The protocol for measuring and analysing isometric quadriceps extension strength is outlined in Chapter 3 (section 3.3.7).

5.2.3.4 Joint Position Sense

The protocol for measuring and analysing joint position sense is outlined in Chapter 3 (section 3.3.7) and Chapter 4 (4.3.2.3.3)

5.3.4 Data Analysis

All statistical analyses were carried out in Statistical Package for the Social Sciences (SPSS, IBM Version 27, USA). Descriptive statistics, including mean and standard deviations, were calculated for each intervention at each time point. Averaged data was used for statistical analyses. In order to assess the potential clinical relevance, changes were assessed against the minimal clinically important changes for each outcome measure.

JPS data was tracked and exported from Qualisys Track Manager (Qualisys Medical AB, Gothenburg, Sweden) and analysed in Visual3D (C- Motion, Inc., Kingston, ON, Canada) to produce non-dominant knee joint angles in the three cardinal planes.

For each outcome measure, interventions were assessed over a 20-minute rewarming period, using repeated measures ANOVAs (3 x 2 - time points by interventions), with post-hoc pairwise comparisons. The significance level was set at $p<0.05$. 'Post-capsaicin cream' (T2) was used as the baseline value in analyses for muscle strength and JPS, to determine the effect of the cooling interventions once the participant had been induced with experimental knee pain. However, it was also important to establish the level of pain induced by the topical capsaicin cream. Therefore, repeated measures ANOVA (2x2 – time points by interventions) were used to assess changes from pre-capsaicin cream (T1) to post-capsaicin cream (T2), to determine the effects of the experimentally induced pain.

5.4 Results

Ten healthy participants (7 females, 3 males) were recruited (Figure 5.1). The average age was 32.9 ± 11.6 years. The average BMI was 24.7 ± 3.0.

5.4.1 Participant-Reported Pain

Experimental knee pain, via capsaicin cream, caused an average participant-reported pain of approximately 2 out of 10 (0- no pain, 10-worst pain possible) (Figure 5.5). Eight participants experienced a burning sensation on application of the capsaicin cream during both intervention sessions (Table 5.2).

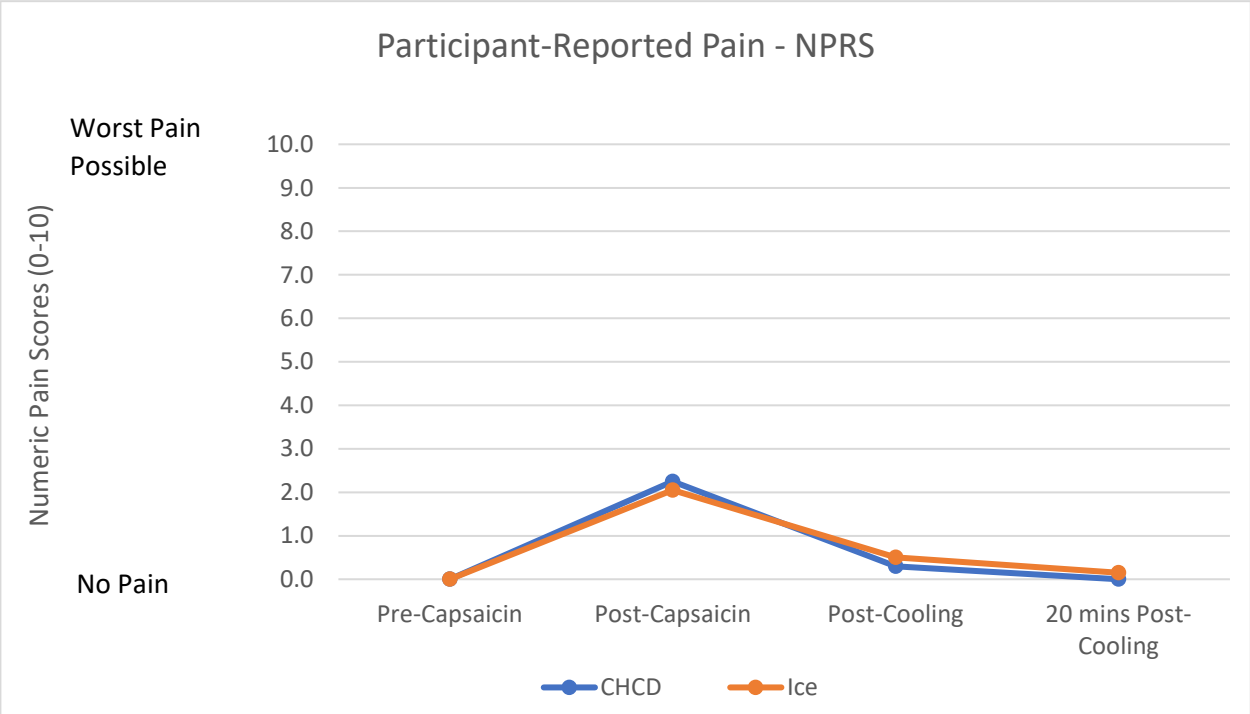

Figure 5.5: Mean participant-reported pain (NPRS 0-10) at four time points for each intervention (n=10).

Table 5.3: Mean participant-reported pain (NPRS) for each participant (n=10) for both ice and CHCD intervention, with 95% confidence interval (CI) ranges. Significant differences were assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.

Mean Participant-Reported Pain – NPRS (MCIC = 1.3)														
Intervention	**Time point**	**Participant**										**Mean**	**95% CI**
		1	2	3	4	5	6	7	8	9	10		
CHCD	*Pre-capsaicin*	0	0	0	0	0	0	0	0	0	0	**0.0**	0, 0
	Post-Capsaicin	3	4	4	2	2	3.5	2	1	0	1	**2.3**	1.28, 3.22
	Post-Cooling	0	2	0	0	0	1	0	0	0	0	**0.3**	-0.18, 0.78
	20-Mins Post-Cooling	0	0	0	0	0	0	0	0	0	0	**0.0**	0, 0
Ice	*Pre-capsaicin*	0	0	0	0	0	0	0	0	0	0	**0.0**	0, 0
	Post-Capsaicin	2.5	3	3	2	3	2	4	1	0	0	**2.1**	1.10, 3.01
	Post-Cooling	0	1	1	0	1	0	2	0	0	0	**0.5**	-0.01, 1.01
	20-Mins Post-Cooling	0	1	0	0	0	0	0.5	0	0	0	**0.2**	-0.10, 0.39

Significant main effects were found in pain scores between time points (p<0.001). No statistically significant differences were found between interventions (p=0.809). Post-hoc analyses (Table 5.4) indicated significant differences in participant-reported pain between time points T2, T3 and T4.

Table 5.4: Pairwise comparison and descriptive statistics of participant-reported pain from post-capsaicin to 20-minutes post cooling (n-=10). Significant differences were assessed using a repeated measures ANOVA (2 x 2 – time points by interventions) with a significance level set at p<0.05.

Pairwise Comparisons of Time Points (Participant-Reported Pain - NPRS)

Comparison		**Mean Difference**	**Significance Value**	**95% Confidence Interval for Difference**
Post-Capsaicin	Post	1.8	<.001*	1.1 to 2.4
	20 Mins Post	2.1	<.001*	1.2 to 2.9
Post-Cooling	Pre	-1.8	<.001*	-2.4 to -1.1
	20 Mins Post	0.3	.022*	0.1 to 0.6
20 Mins Post	Pre	-2.1	<.001*	-2.9 to -1.2
	Post	-0.3	.022*	-0.6 to -0.1

When comparing participant-reported pain scores before and after the application of capsaicin cream, significant main effects were found between time points (p<0.001). As capsaicin cream was applied to induce experimental knee pain, this significant increase in participant-reported pain was anticipated. No statistically significant differences were found between interventions for participant-reported pain from pre- to post-capsaicin cream (p=0.565).

*Table 5.5: Changes in mean participant-reported pain - NPRS between time points for each intervention (n=10). *****denotes a statistically significant difference assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.*

Intervention	Time point	Mean Pain Relief (%)
CHCD	*Post-Capsaicin – Post-Cooling*	**87***
	Post-Capsaicin - 20-Mins Post-Cooling	**100***
Ice	*Post-Capsaicin – Post-Cooling*	**76***
	Post-Capsaicin - 20-Mins Post-Cooling	**91***

Table 5.5 highlights percentage reductions to participant-reported pain found between time points compared to the 'post-capsaicin' time point for each intervention. A colour coding system has been used (see key below) to illustrate the level of pain relief observed between time points.

With the MCIC for acute pain being reported as 1.3-points (Bijur, 2003), both interventions achieved reductions in pain immediately following cooling which could be considered clinically important. Complete pain relief is considered when pain is reduced by 93% (Sloman *et al.*, 2006), at 20-minutes post-cooling, participant perceived NPRS was reduced by 100% (CHCD) and 91% (ice). Seven participants demonstrated complete pain relief immediately post-cooling following the CHCD interventions. In comparison, 4 participants demonstrated complete pain relief immediately post-cooling following ice interventions. Only 2 participants reported pain 20 minutes post-cooling, both of these were found following ice interventions.

5.4.2 Pressure Pain Threshold

Table 5.6 details the mean PPT for each participant, time point and intervention.

Table 5.6: Mean Pressure Pain Threshold for each participant for both ice and CHCD interventions (n=10). Significant differences were *assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.*

Mean Pressure Pain Threshold (kPa) *(MDC: 86.3 kPa)*														
Intervention	**Time point**	**Participant**										Mean (±SD)	**95% CI**
		1	2	3	4	5	6	7	8	9	10		
CHCD	*T1*	304.0	441.3	330.2	843.4	608.0	179.8	444.6	581.9	349.8	350.1	443.3 (190.2)	307, 579
	T2	313.8	382.5	101.3	764.9	375.9	124.2	255.0	434.8	326.9	399.5	347.8 (184.7)	215, 480
	T3	392.3	349.8	297.5	985.2	434.8	117.7	431.5	509.9	545.9	358.3	442.3 (224.8)	282, 603
	T4	379.2	320.4	258.2	983.6	457.6	173.3	392.3	460.9	385.7	350.4	416.2 (217.6)	261, 572
Ice	*T1*	346.5	398.8	317.1	874.8	565.5	196.1	356.3	519.8	416.8	282.8	427.5 (190.6)	291, 564
	T2	320.4	362.8	147.1	957.5	313.8	101.3	277.9	389.0	381.2	313.8	356.5 (231.7)	191, 522
	T3	320.4	474.0	199.6	1013.0	418.4	170.0	313.8	438.0	368.7	242.2	394.8 (240.0)	223, 567
	T4	349.8	385.7	183.1	911.4	588.4	179.8	336.7	428.2	363.5	339.0	406.6 (212.1)	255, 558

Key
PPT changes in comparison to MDC:
No change
Decrease >86.3 kPa
Decrease <86.3 kPa
Increase <86.3 kPa
Increase >86.3 kPa

*Table 5.7: Changes in % pressure pain threshold between time points for each intervention (n=10). *Denotes a statistically significant difference* assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.

Intervention	Time point	Change in Pain Threshold (%)
CHCD	*Pre-capsaicin T1 – Post-Capsaicin T2*	**-21***
	Post-Capsaicin T2 – Post Cooling T3	**+27***
	Post-Cooling T3 – 20-Mins Post-Cooling T4	**-6**
Ice	*Pre-capsaicin T1 – Post-Capsaicin T2*	**-17**
	Post-Capsaicin T2 – Post-Cooling T3	**+11**
	Post-Cooling T3 – 20-Mins Post-Cooling T4	**+3**

Table 5.7 highlights the percentage changes in pain threshold between each time point for each intervention. PPT changes between time points were colour coded based on the relevance to the reported MDC, 86.3 kPa (Walton *et al.*, 2011). As expected from the literature, significant decreases occurred in PPT from pre- to post- capsaicin cream application.

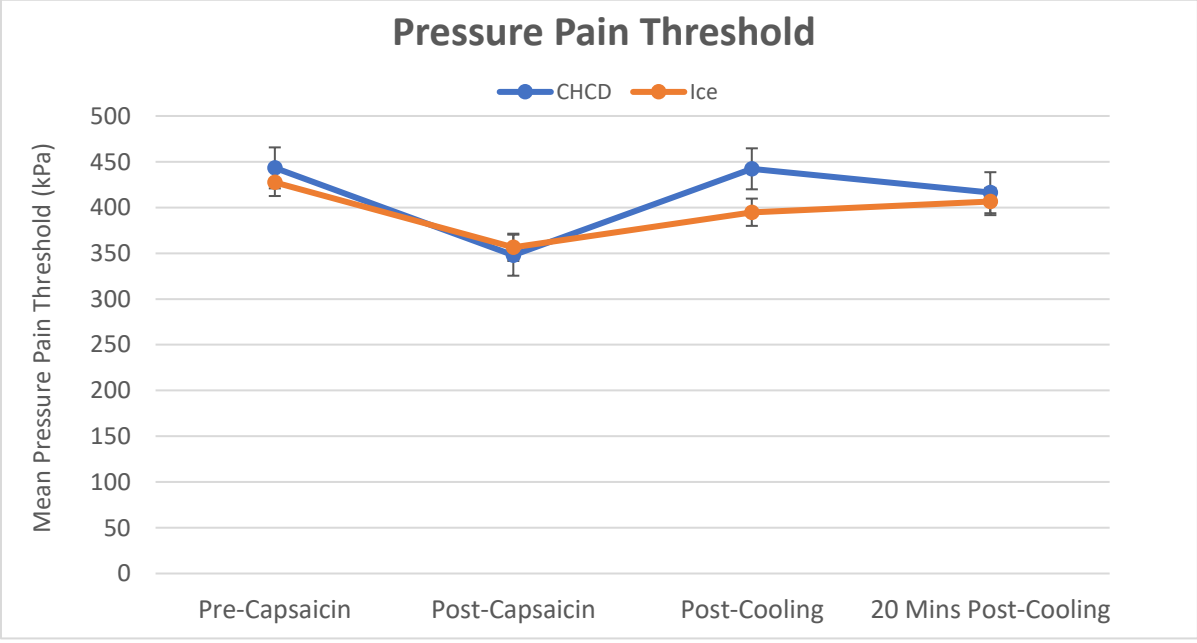

Figure 5.6: Mean pressure pain threshold (kPa) ±SD at four time points for each intervention (n=10).

Significant main effects were found in PPT between time points (p=0.041). No statistically significant differences were found between interventions (p=0.118). Post-hoc analyses (Table 5.8) showed significant differences in PPT between time points T2 and T4.

*Table 5.8: Pairwise comparison and descriptive statistics of PPT from post-capsaicin to 20-minutes post cooling (n=10). *****Denotes a statistically significant difference assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.*

Pairwise Comparisons of Time Points (PPT)

Comparison		**Mean Difference**	**Significance Value**	**95% Confidence Interval for Difference**
Post-Capsaicin	post-cooling	-1.6	.946	-53.2 to 50.1
	20 mins post	-53.6	.022*	-97.4 to -9.8
Post-Cooling	Pre-capsaicin	1.6	.946	-50.1 to 53.2
	20 mins post	-52.0	.056	-105.6 to 1.6

Significant interactions were found between the two factors (time and interventions) and therefore, further post-hoc analyses were carried out on the interventions separately (p=0.020).

*Table 5.9: Pairwise comparison and descriptive statistics of PPT for each intervention separately (n=10).**Denotes a statistically significant difference assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.*

Pairwise Comparisons of Time Points for Each Intervention (PPT)

Intervention	Time Point Comparison		Mean Difference	Significance Value	95% Confidence Interval for Difference
ICE	post-capsaicin	post-cooling	-38.3	.055	-77.7 to .992
		20 mins post	-50.1	.100	-111.9 to 11.8
	post-cooling	pre-capsaicin	38.3	.055	-.992 to 77.7
		20 mins post	-11.8	.651	-68.5 to 45.0
CHCD	post-capsaicin	post-cooling	-94.4	.017*	-167.9 to -20.9
		20 mins post	-68.3	.035*	-130.7 to -5.9
	post-cooling	pre-capsaicin	94.4	.017*	20.9 to 167.9
		20 mins post	26.1	.180	-14.5 to 66.8

Significant main effects were found in PPT between time points for the CHCD interventions (p=0.007). No significant main effects were found in PPT for ice interventions (p=0.114). Post-hoc analyses (Table 5.9) indicated significant differences in PPT exist between time points for CHCD interventions. Significant increases in PPT were found post-capsaicin to post-cooling (p=0.017) and post-capsaicin to 20-minute post-cooling time points (p=0.035) following the CHCD interventions. However, no significant differences were found between post-capsaicin (T3) and 20 minutes post-capsaicin (T4), Despite a trend of an increase from post-capsaicin to post-cooling (p=0.055) (Figure 5.7), no significant differences were found between time points following ice interventions.

When comparing PPT before and after the application of capsaicin cream, significant main effects were found between time points (p=0.19). The findings indicate that PPT was significantly reduced by the induced experimental knee pain, using capsaicin cream (0.075%).

5.4.3 Quadriceps Strength

Peak quadriceps moment (Nm) was calculated using the average muscle force (N) multiplied by the lever arm length (m). This was then normalised to obtain an index of quadriceps strength independent to body size (Almeida, Albano and Melo, 2019). Table 5.10 presents the mean peak moment for each participant, across each time point and intervention.

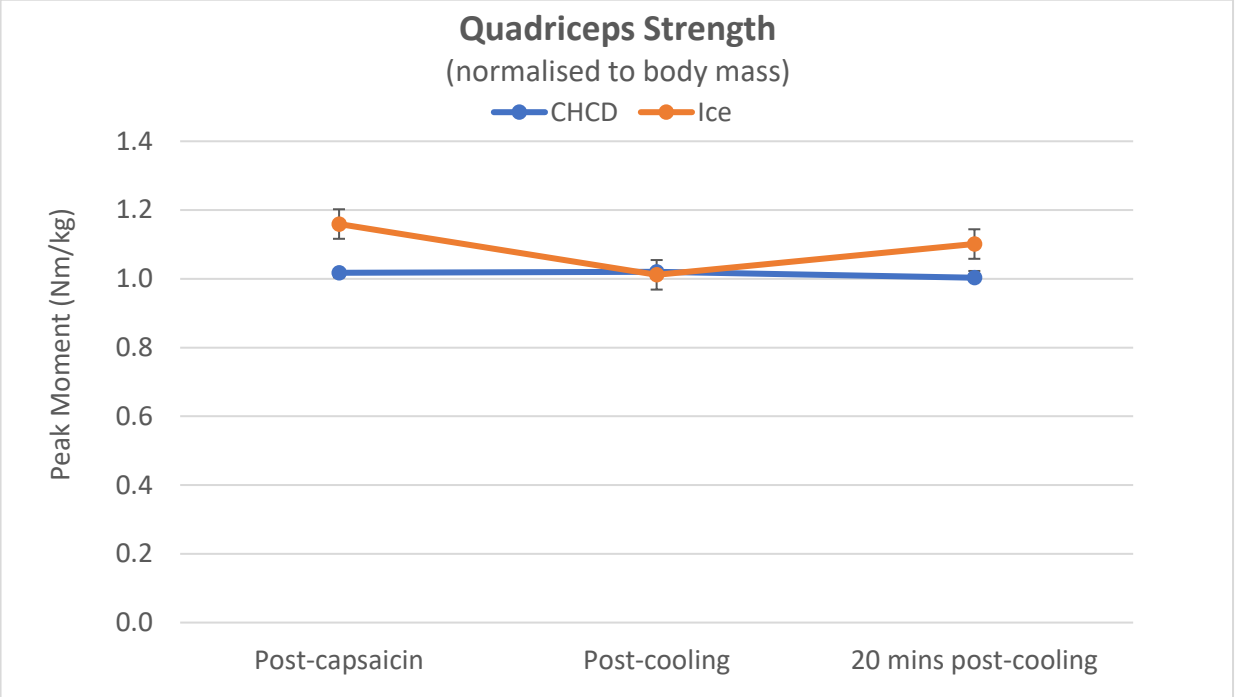

Figure 5.7: Mean peak moment (normalised to body mass) (Nm/kg) ±SD at four time points for both interventions (n=10).

Table 5.10: Mean peak moment (Nm/kg) for each participant (normalised to body mass) for both ice and CHCD interventions. *(n=10). Significant differences* were *assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.*

Mean Peak Moment (Nm/kg)														
Intervention	**Time point**	**Participant**										**Mean (±SD)**	**95% CI**
		1	2	3	4	5	6	7	8	9	10		
CHCD	*Pre-capsaicin*	0.8	1.2	1.0	1.7	1.2	0.7	0.8	1.0	0.9	0.9	**1.0 (0.3)**	0.88, 1.22
	Post-Capsaicin	0.8	1.0	1.0	1.5	1.2	0.8	0.8	1.1	0.9	0.9	**1.0 (0.2)**	0.97, 1.35
	Post-Cooling	0.9	0.9	1.1	1.5	1.2	0.8	0.8	1.0	0.9	1.0	**1.0 (0.2)**	0.85, 1.17
	20-Mins Post-Cooling	0.8	0.7	1.2	1.6	1.1	0.8	0.8	1.2	0.9	1.1	**1.0 (0.3)**	0.89, 1.32
Ice	*Pre-capsaicin*	1.0	0.7	1.4	1.4	1.2	0.9	0.9	0.9	1.1	1.0	**1.1 (0.2)**	0.88, 1.22
	Post-Capsaicin	1.2	0.9	1.5	1.4	1.3	0.8	0.9	1.0	1.0	1.5	**1.2 (0.3)**	0.87, 1.17
	Post-Cooling	0.9	0.8	1.0	1.3	1.3	0.8	0.9	0.8	1.0	1.3	**1.0 (0.2)**	0.87, 1.18
	20-Mins Post-Cooling	1.0	0.7	1.2	1.5	1.3	0.9	0.9	0.9	1.1	1.4	**1.1 (0.3)**	0.81, 1.21

Muscle Strength Deficit

Key
Muscle strength changes compared to the MCIC

No change
Decrease >6%
Decrease<6%
Increase< 6%
Increase>6%

Table 5.11: Percentage reductions in normalised mean peak moment between time points for each intervention (n=10), which can be compared to the MCIC values reported in the key.

Intervention	Time points	Mean Peak Moment Deficit (%)
CHCD	*Post-Capsaicin T2 – Post-Cooling T3*	**-0.3**
	Post-Capsaicin T2 – 20-Mins Post-Cooling T4	**1.4**
Ice	*Post-Capsaicin T2 – Post-Cooling T3*	**12.7**
	Post-Capsaicin T2 - 20-Mins Post-Cooling T4	**5.0**

Table 5.11 presents the mean normalised muscle strength deficit (as a percentage) between time points compared to 'post-capsaicin' for each intervention. No statistically significant main effects were found in strength between time points (p=0.079) or interventions (p=0.225). Although, Figure 5.7 illustrates that there was a trend demonstrating a greater deficit to mean peak moment following ice interventions (p=0.057).

The strength deficit post ice was greater than 6%, and therefore would be considered clinically important in a population with knee osteoarthritis (Ruhdorfer, Wirth and Eckstein, 2015). In fact, a 12.7% deficit was more than double the clinically important percentage change for quadriceps strength normalised to body mass (Table 5.11). Interestingly, the CHCD had a negligible effect on muscle strength immediately post intervention and actually saw a very small increase (0.3%). Contrary to previous findings in the literature (Henriksen, 2011), no significant differences were found in peak moment between pre- and post-capsaicin application (p=0.307).

5.4.4 Joint Position Sense

*Table 5.12: Mean minimum knee angles, maximum knee angles and knee joint range of motion (ROM) for all cardinal planes and interventions (n=10). *Denotes a statistically significant difference assessed using a repeated measures ANOVA (3 x 2 – time points by interventions) with a significance level set at p<0.05.*

Intervention		Sagittal Plane (Knee Flexion°)			Coronal Plane (Knee Abduction/Adduction°)			Transverse Plane (Knee Internal/External Rotation°)		
		Post-Capsaicin	Post-Cooling	20 mins Post-Cooling	Post-Capsaicin	Post-Cooling	20 mins Post-Cooling	Post-Capsaicin	Post-Cooling	20 mins Post-Cooling
CHCD	ROM	43.1	42.8	42.8	6.9	6.9	7.3	1.6	5.7	6.2
	MIN	7.8	8.7	7.1	-1.6	-1.7	-1.1	-7.0	-3.7	-2.7
	MAX	50.9	51.5	49.9	5.3	5.2	6.2	8.6	9.3	8.9
ICE	ROM	42.9	45.0	44.5	9.4*	11.4*	13.9*	8.2	9.4	10.3
	MIN	7.3	6.4	5.8	-1.7	-2.7	-4.2	-7.8	-5.6	-6.3
	MAX	50.2	51.4	50.3	7.7	8.7	9.7	0.4	3.7	4.0

Table 5.12 presents the minimum and maximum knee angles and knee joint range of motion (ROM) in the sagittal plane (X), coronal plane (Y) and the transverse plane (Z) during the small knee bend task (45°). No statistically significant main effects were found in knee flexion ROM in the sagittal plane between time points (p=0.368) or interventions (p=0.090). Similarly, no significant main effects were found in knee abduction/adduction ROM in the coronal plane between time points (p=0.376) or interventions (p=0.499) or for knee internal/external rotation ROM in the transverse plane between time points (p=0.201) or interventions (p=0.428).

Mean knee flexion was greater than 5° from the target angle at two time points following the CHCD and three time points following ice and therefore would be considered 'poor' proprioceptive status (Callaghan *et al.*, 2008) (Table 5.12). Mean knee flexion was less than 5° from the target angle at one time point, which was following the CHCD intervention, 20-minutes post-cooling. Significant increases were found in ROM following the ice interventions compared to the CHCD interventions (p=0.013) which indicates increased instability (adduction or abduction) following ice interventions. There were no significant differences (p>0.05) in maximum and minimum angles or ROM in the

transverse plane (knee internal/external rotation) between time points or interventions. However, there was a trend towards increased instability in the transverse plane from pre-20 mins post cooling which was most apparent following the ice interventions ($p=0.053$).

When comparing knee flexion ROM before and after the application of capsaicin cream, significant main effects were found between interventions ($p=0.016$) (Table 5.15). No significant differences were found in knee joint ROM between the interventions or time points in the other cardinal planes.

5.5 Discussion

The purpose of this investigation was to explore the effects of two cryotherapy interventions (1. wetted ice and 2. 10 °C and 50 mmHg using a novel cooling, heating, and compression device) on strength, pain (NPRS and PPT) and joint position sense in healthy participants with experimentally induced knee pain. The findings of this study provide an insight into the effects of the optimal intervention identified in Chapter 4 and the current standard clinical treatment (ice), in a population with experimentally induced pain. This is the first study to date which explores the use of the novel CHCD on a symptomatic population, providing key information to inform the development of optimal cryotherapy interventions for knee injury management.

5.5.1 Participant-Reported Pain

Experimental knee pain, using capsaicin cream, induced an average participant-reported pain of approximately 2 out of 10 (0- no pain, 10-worst pain possible). The majority (80%) of participants experienced a burning sensation on application of the capsaicin cream during intervention sessions, which is comparable to previous studies (Chrubasik, Weiser and Beime, 2010). This increase in pain induced by the capsaicin cream was found to be statistically significant. This is also comparable to other experimental pain studies (Sørensen *et al.*, 2012). Ice and the CHCD interventions were both effective in reducing participant-reported pain immediately post-cooling (76% and 87%) and 20-minute post-cooling (91% and 100%). Both interventions achieved reductions in pain post-cooling which would be considered clinically important in an acute injury population. Complete pain relief was achieved by 20-minutes post-cooling for the CHCD intervention. Ice achieved 'much relief' (70%) by 20-minutes post-cooling. However, no statistically significant differences in participant-reported pain were found between interventions. Significant increases in were found pre- and post-capsaicin cream application. Significant increases in were found in participant-reported pain post-capsaicin to post-cooling, post-cooling to 20 minutes post-cooling and post-capsaicin to 20 minutes post-cooling. Thus, both interventions were effective at reducing short-term experimental knee pain. The induced analgesic effect and clinical evidence for ice reducing short term pain for soft tissue contusions and acute ankle injuries is discussed in the literature (Bleakley *et al.*, 2011). However, there is a lack of research investigating the effect of targeted cryotherapy approaches (cooling a smaller surface area) on short-term pain. This study

provides the first findings of the effect on pain reduction following a targeted cryotherapy intervention, using the CHCD on the knee. The magnitude of pain relief would be considered clinically important in the management of acute injuries.

5.5.2 Pressure Pain Threshold (PPT)

The application of capsaicin cream significantly decreased PPT (p=0.019), which indicates that the capsaicin cream may have caused an increase in superficial tissue sensitivity (Chrubasik, Weiser and Beime, 2010). Significant increases in PPT were found from post-capsaicin (T2) to post-cooling (T3) and from post-capsaicin (T2) to 20-minute post-cooling (T4) following the CHCD interventions. This is in agreement with previous findings reporting significant increases in perceived pain threshold and tolerance, with a decrease in T_{sk} (Algafly and George, 2007). This suggests that a local analgesic effect occurred, and thus the targeted compressive cryotherapy approach may have the potential to provide short-term pain relief. Despite a trend of increase from post-capsaicin to post-cooling, no significant differences found between time points following ice interventions. The average relative increases in PPT were 27% (CHCD) and 11% (ice). These relative increases are lower than values reported in the literature at the ankle (71%) (Algafly and George, 2007). However, as PPT varies significantly depending on anatomical location and with increases in PPT at the knee yet to be reported, it is difficult to make a comparison. The MDC for PPT at the tibialias anterior has been reported as 86.2 kPa. The decrease in PPT observed pre- and post-capsaicin application and the increase in PPT from post-capsaicin to post-CHCD intervention were both slightly higher than this (at 95 kPa and 94 kPa respectively). This indicates a potentially meaningful increase in PPT following the CHCD intervention.

5.5.3 Muscle Strength

No significant differences were found in peak moment between pre and post capsaicin application, which conflicts with previous research that reported a positive correlation between experimentally induced pain intensity and a reduction of knee extension and flexion muscle strength (Henriksen, 2011). Statistically significant decreases were found from post-capsaicin to post-cooling which is in agreement with previous literature reporting decreased muscle strength following cryotherapy (Rhodes and Alexander, 2018). No statistically significant differences were found between interventions, however there was a trend that peak moment deficit was greater following ice intervention

(p=0.057). Reductions of 6% in quadriceps strength normalised to body mass relate to MCIC WOMAC functional deficit in people with osteoarthritis. The strength deficit post ice was greater than 6%, therefore could be considered clinically important in individuals with knee osteoarthritis. In fact, a 13% deficit was more than double the clinically important percentage change for quadriceps strength normalised to body mass (Table 5.10). Decreases in quadriceps functional performance can lead to an increased risk of knee injury due to the loss of control to prevent excessive or abnormal movements (Shultz *et al.*, 2015; Rhodes and Alexander, 2018). Therefore, it is important to understand the magnitude of inhibition of different cryotherapy protocols in order to ensure a safe return to weight-bearing activities.

Interestingly, the CHCD had a negligible effect on muscle strength immediately post intervention and actually saw a very small increase (0.3%). This suggests that targeted cryotherapy may minimise the inhibition to quadriceps function in comparison to ice, which may facilitate an earlier return to weight-bearing activity and optimal loading.

5.5.4 Joint Position Sense

Previous studies have also demonstrated inhibition to knee joint repositioning following cryotherapy (Uchio *et al.*, 2003; Surenkok *et al.*, 2008; Costello and Donnelly, 2010; Alexander *et al.*, 2016; Alexander *et al.*, 2018). No significant differences in maximum, minimum values, or knee joint ROM in the sagittal plane (knee flexion) between time points or interventions were observed. Significant increases were found in ROM in the coronal plane following the ice interventions, which indicates increased instability (adduction or abduction). Despite no significant differences in maximum, minimum or knee joint ROM in the transverse plane, there was a trend of increased instability in the transverse plane from post-capsaicin to 20 mins post-cooling, which was most apparent following the ice interventions (p=0.053). Increased instability 20-minutes post-cooling reflects previous literature, which has demonstrated that deeper intramuscular tissues continue to cool after the cryotherapy intervention has been removed and achieve their coolest temperatures approximately 14 minutes post removal (Zemke *et al.*, 1998; Hardaker *et al.*, 2007). Decreased dynamic stability and knee joint repositioning may cause a potential increased risk of injury when returning to weight-bearing activity (Arnason *et al.*, 2004; Bahr and Krosshaug, 2005; Alexander *et al.*, 2016; Alexander *et al.*,

2018), and any inhibition to joint position sense may discourage early activity or optimal loading post intervention.

5.5.5 Limitations

One of the main limitations of this study was the small magnitude of pain caused by the capsaicin cream. As some participants experienced no pain (0/10) or minimal pain (1/10), the magnitude of effect provided by the cooling was difficult to measure. Thus, a 'floor effect' may have been present for these participants. A floor effect refers to very low measurements of the dependent variable near/at the possible lower limit (the floor), which reduces the magnitude of the variation and can hide potential effects of the independent variable (Vogt and Johnson, 2011). Future work could explore the effects of cryotherapy on an experimental pain method with a greater average pain score to determine the extent of pain relief provided by the cryotherapy modalities.
Another limitation of this study is the lack of a control group that did not receive a cryotherapy intervention within the randomised crossover design. However, it was considered less ethical to have a control group within an experimental pain study.

5.6 Conclusion

This study provides the first findings of potentially important and statistically significant pain relief following a targeted compressive cryotherapy intervention, using the CHCD. Experimental knee pain, using topical capsaicin cream, induced an average participant-reported pain of approximately 2 out of 10 in this study. Both interventions were effective in reducing participant-reported pain immediately post-cooling (ice - 76% and CHCD - 87%) and 20-minute post-cooling (ice - 91% and CHCD - 100%). Despite both interventions increasing PPT post-cooling, the CHCD was found to be more effective at increasing PPT post-cooling. The findings of this study were comparable to previous findings which reported significant reductions to joint position sense and quadriceps muscle strength following 20-minute ice interventions. Despite an average 13% peak moment reduction following ice interventions, no significant differences in peak moment were found between time points or interventions. No significant differences were found in maximum, minimum knee angles or range of motion in any of the cardinal planes, following the CHCD interventions. This highlights that adopting a targeted cooling approach may minimise this inhibition to knee joint repositioning and dynamic stability observed following other cryotherapy approaches.

Chapter 6: An exploration into the effectiveness of cryotherapy modalities on participants with knee injuries, through a series of single-case experiments

Due to restrictions within the regulatory framework, a randomised control trial with injured participants was not possible without medical device approval. Therefore, a variety of research methods were explored to identify an appropriate design for intervention comparison. A single-case experiment design was suggested by the supervisory team to explore further as it would allow detailed individual analysis of interventions and individuals. I sought expertise and training from academics internally (Professor Marc Jones, MMU) and externally (Dr Matt Parkes, The University of Manchester) who were more familiar with single-case designs and n-of-1 trials. Through this additional training and academic support, an Alternating Treatment Design was selected as the most effective and practical study design, which was the strongest level of evidence available given the regulatory framework.

6.1 Abstract

Purpose

Knee injuries are a significant health burden to people of all ages. Cryotherapy is one method commonly used for knee injury management in both sport and clinical settings. It has previously been suggested that a single 'panacea' clinical cooling protocol is unlikely to exist. This highlights the need for further exploration into the effectiveness of different cooling protocols on a range of injuries. The purpose of this study was to explore the effectiveness of two cryotherapy modalities at reducing pain, swelling and instability in people with a range of knee injuries, through a series of single-case experiments.

Methods

Individuals with a range of knee injuries were recruited in an alternating treatment design. Two 20-minute interventions, (A) wetted ice (400g cubed ice, 400ml water) and (B) CHCD (10°C with 50mmHg compression), were applied once a day for three consecutive days. The order of intervention was randomised (ABABAB or BABABA), with a minimum of two hours between interventions. Three outcome measures were recorded pre- and post-interventions: i) Swelling using a tape measure, ii) Pain using the 11-point numeric pain rating scale (NPRS), iii) Stability on an 11-point scale (very unstable-very stable). The data was analysed using visual analysis of graphical data individually and collectively.

Results

Across the series of eleven single-case experiments (38.7 ± 19.2 years), a clinically important reduction in patient-reported pain was reported in 48% of the CHCD interventions and 39% of ice interventions. A clinically important swelling reduction was recorded in 48% of the CHCD interventions and in 27% of the ice interventions. Only 3% of ice interventions and 6% of CHCD interventions observed clinically important increases in patient-reported stability. In regard to the sum of clinically important changes in patient-reported pain, stability and swelling, CHCD was the most effective intervention for 9 of the 11 individuals with knee injuries.

Conclusions

The compressive cryotherapy CHCD intervention appeared more beneficial for the majority (82%) of individuals with knee injuries, reducing swelling and pain, compared to the current standard clinical treatment of ice.

6.2 Introduction

Knee injuries are one of the most common types of injuries in sport and affect people of all ages (Majewski, Susanne and Klaus, 2006; Lundblad *et al.*, 2013; Owoeye *et al.*, 2020). Cryotherapy is one method commonly used for knee injury management in both sport and clinical settings (Bleakley, McDonough and MacAuley, 2004). Cooling and compression are both regularly used in conjunction during the first week of rehabilitation programmes for grade I and II knee ligament injuries (Holden, Eggert and Butler, 1983; van den Bekerom *et al.*, 2013) and to control knee effusion and pain control for meniscus injuries (Kelly, 2013). However, cryotherapy protocols used in sport and clinical practice vary significantly in regards to modality used, temperature applied, compression levels, application time and frequency of application (Alexander *et al.*, 2021a).

Technical evaluations by Selfe et al. (2017) and the investigations outlined in Chapter 4, determined that the CHCD can achieve the therapeutic skin temperature range in healthy participants. This indicates that the device could provide the desired therapeutic effects for injury management, once T_{sk} is cooled and maintained within the therapeutic range (Rivenburgh, 1992; Bugai, 1975; Kennet *et al.*, 2007). Being able to compare the effects of a novel approach to the current standard clinical practice is important in order to establish and define optimal protocols for injury management. In addition, Alexander,

Allan and Rhodes (2021) highlighted that real-world implementation of knowledge into applied practice is lacking, despite many robust studies available investigating cryotherapy applications in sport. Exploring the effectiveness of interventions, in a pragmatic manner, provides an insight into the performance under real-life conditions (Revicki and Frank, 1999).

As personalised cryotherapy protocols have been advocated to consider the injury and individual characteristics (Bleakley, Glasgow and Webb, 2012; Fu *et al.*, 2016), further exploration into the effectiveness of different cooling protocols on a range of knee injuries and individuals is warranted. A single-case experimental design was utilised for this study to assess the effectiveness of two cryotherapy interventions as applied to each individual knee injury.

Single-case experimental designs are rigorous experimental designs, particularly useful to assess individuals in order to understand the effectiveness of treatments as applied to them, on an individual basis (Polgar and Thomas, 1988; Krasny-Pacini and Evans, 2018). Single-case designs are also well-suited to provide preliminary evidence of the effectiveness or efficacy of an intervention (Freeman *et al.*, 2010; Krasny-Pacini and Evans, 2018). Krasny-Pacini & Evans (2018) described the following (Figure 6.1) as study characteristics that may be suited to a single-case experiment design.

Dallery et al. (2013) discussed the advantages of utilising the single-case designs to assess the preliminary efficacy of novel technology-based health interventions, most commonly referring to studies assessing interventions in regards to psychological behavioural change (Silverman *et al.*, 1996). The authors acknowledge logistical issues associated with group designs when conducting initial efficacy testing for new technology-based interventions such as the significant time and money to produce prototypes which may require further troubleshooting and product development, causing long delays within large sample group designs and consequently becoming unaffordable (Dallery, Cassidy and Raiff, 2013). However, despite a reduction to possible resource or time burdens accompanying group designs, single-case designs do require significant volume of data for each participant and contrary to common misconception, often require more than one single-case experiment to reliably demonstrate any experimental effects (usually between 6-20 cases) (Silverman *et al.*, 1996; Dallery, Cassidy and Raiff, 2013).

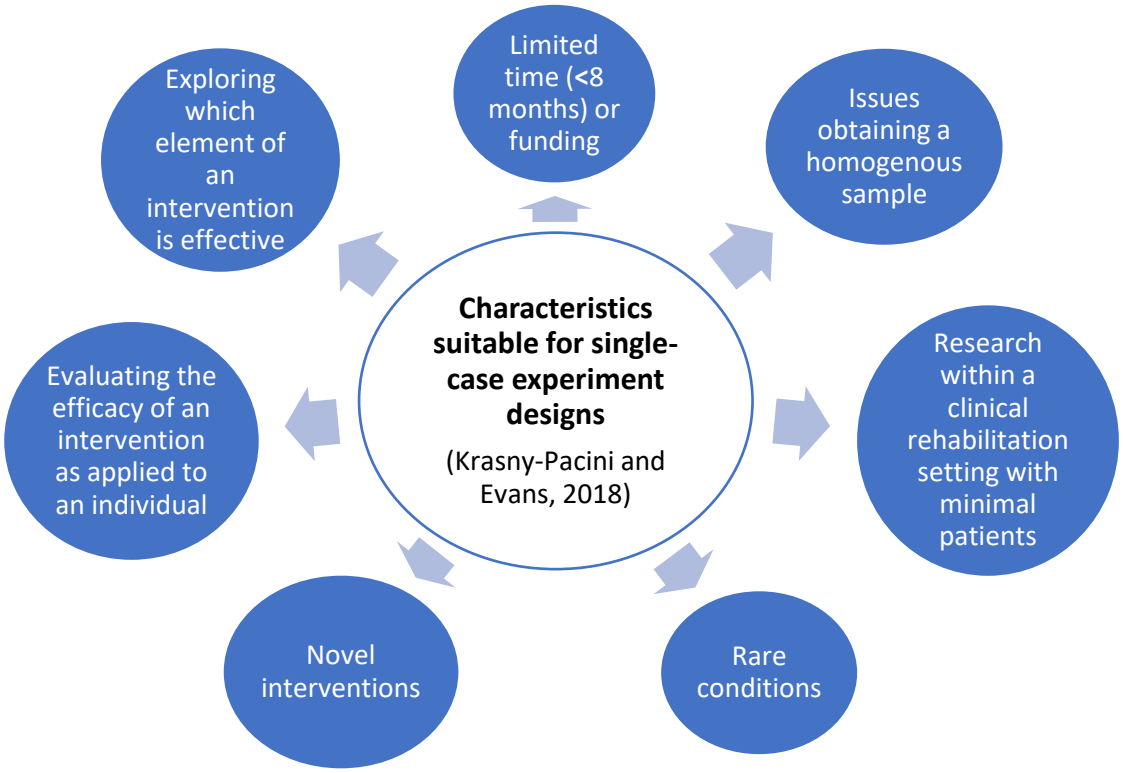

Figure 6.1: Study characteristics suited to a single-case experimental design as discussed in Krasny-Pacini & Evans (2018)

Alternating treatments designs are the most prevalent single-case method for comparing interventions (Barker *et al.*, 2011) and involve a rapid alternation of treatments (two or more) in order to compare intervention effectiveness. This design removes the ethical dilemma of treatment withdrawal associated with other designs (Barker *et al.*, 2011). An alternating treatment design (Section 6.3.2) adopted to explore the optimal CHCD intervention from Chapters 4 & 5 (10 °C and 50 mmHg) and wetted ice, on a population with knee injuries.

6.3 Methods

6.3.1 Participants

Participants with knee injuries were recruited within the series of single-case experiments under 3 injury states:

- **Acute** = injury in the last 24 hours (single-case experiment 8)
- **Subacute** = between 25 hours and 1-week post injury (single-case experiment 2)
- **Chronic** = an injury older than 1-week (single-case experiment 1,3-7 & 9-11)

The study conformed to the Declaration of Helsinki, except registration in a database, and ethical approval was granted from Manchester Metropolitan University (EthOS 11729) and University of Central Lancashire (STEMH 1010). A number of sports clubs were informed of the study, including Rylands FC, Burnley FC Women and Warrington Wolves RFC. When an injury occurred, the healthcare professional at the respective clubs provided an information sheet to the injured player. Participants who were interested then had to actively opt into the study. All participants provided written informed consent prior to the study and all information collected was kept strictly confidential and in accordance with GDPR (Commission, 2018). No adverse effects were reported during or following this study.

Table 6.1. Inclusion/Exclusion Criteria

Inclusion	**Exclusion**
1) Lower limb injury suitable for device 2) Over the age of 18	1) A pain score of 9 or over on the NPRS scale 2) An open wound 3) Peripheral vascular disease 4) Any known adverse reactions to cold or pressure applications

Prior to data collection, a qualified healthcare professional with significant experience in management of knee injuries, determined the eligibility of the participants by carrying out an initial injury assessment and using the inclusion/exclusion criteria (Table 6.1).

6.3.2 Data Collection

The patient-reported outcome measures pain, swelling (knee circumference) and stability were recorded pre- and immediately post-each intervention. A standard tape measure was used to record the knee circumference. The numerical pain rating scale (NPRS) was used to measure patient-reported pain levels, using an 11-point scale, where 0=no pain and 10=worst possible pain (Farrar *et al.*, 2001). Patient-reported stability was measured using an 11-point numeric rating scale, ranging from ‘very unstable’ to ‘very stable’. The same measurements were taken for all participants.

There were two interventions: (A) wetted ice (400 ml water, 400 ml ice) and (B) CHCD (*ProMOTION* V1, Swellaway Ltd, UK). These were both applied once a day, for 3 days, in a randomised alternating treatment design order (either ABABAB or BABABA), with at least a 2-hour washout period in between each intervention (Figure 6.2). This is a common

intervention plan for AB alternating treatment design studies (Barker *et al.*, 2011). A randomisation plan for participants was created on www.randomisation.com. Wetted ice was the selected form of ice as it has been determined the most effective for reducing T_{sk} (Dykstra *et al.*, 2009). It has been reported in previous studies that T_{sk} recovery plateaus below baseline by 30 minutes post-cryotherapy treatments (Kennet *et al.*, 2007). Participants were asked to avoid remaining stationary for the 2-hour period or perform strenuous exercise, a 10-minute light walk was encouraged to assist tissue rewarming (Myrer, Measom and Fellingham, 2000).

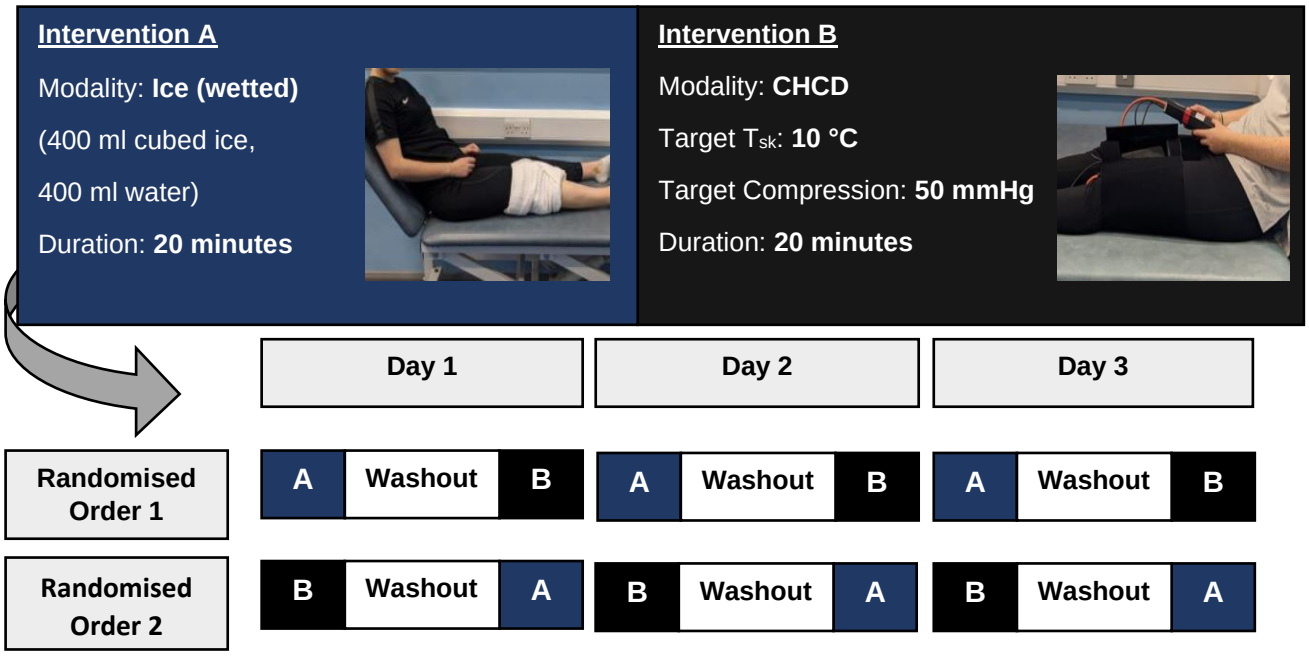

Figure 6.2: The randomisation plan for the interventions

6.3.3 Data Analysis

The most effective analysis techniques for single-case experiments are discussed in literature (Lobo *et al.*, 2017; Manolov and Onghena, 2018). Manolov and Onghena (2018) summarised the most common analysis techniques for alternating treatment design data below in Table 6.2.

Table 6.2: Common analyses techniques for alternating treatment designs, presented in a scoping review by Manolov and Onghena (2018)

Analyses performed in the studies	Frequency	Percentage
Visual analysis	36	76.60
Mean and mean difference	34	72.34
Variability (e.g., range)	24	51.06
Sessions to attain criterion	15	31.91
Percentage of nonoverlapping data	5	10.64
Percentage change	2	4.26
Standardized mean difference	2	4.26
Randomization test	1	2.13
Trend analysis	1	2.13

All data was entered into Microsoft Office Excel (Version 2019) for analyses. Visual analysis, mean, range, effect sizes, percentage change and percentage of nonoverlapping data were included as part of the analyses for this series of single-case experiments, which are all relevant analysis methods for single-case research using an alternating treatment design (Barker *et al.*, 2011). Visual analysis of graphical data was conducted for each individual. The graphical data consisted of 6 graphs for each single-case experiment, leading to a total of 66 graphs. As an example, for single-case experiment 1, all graphs are presented within the results section of this chapter. For the remaining 10 single-case experiments, all graphs are included in Appendix E.

Percentage of nonoverlapping data refers to the percentage of data post intervention which exceeds the baseline (pre-intervention) by a noteworthy point (Tarlow and Penland, 2016). In this instance, the noteworthy point was considered to be the relevant MCIC.

Each outcome measure (knee circumference, patient-reported pain, and stability) was also assessed for the clinical relevance using the relevant MCIC and global rate of change below:

Knee circumference = With no defined MCIC explicitly reported for swelling reduction, a reduction of 0.5cm in knee circumference was required to deem an intervention a clinically relevant treatment, as Sari et al. (2019) reported this figure following a standard clinical cold-pack treatment on patients with knee osteoarthritis.

Patient-reported pain = a 1.3-point change for acute pain in an emergency room population (Bijur, 2003) and a 1-point change for a population with patellofemoral pain (Piva et al., 2009) or chronic musculoskeletal pain (Salaffi et al., 2004).

Stability (11-point scale) = The global rate of change for an 11-point numeric rating scale is a 2-point change (Jaeschke, Singer and Guyatt, 1989).

6.4 Results

Eleven individuals (8 males, 3 females) with knee injuries or conditions were recruited. The average age of participants was 38.7 ± 19.2 yrs. The injuries were classified by a qualified healthcare professional with significant experience in management of knee injuries.

Sections 6.4.1 to 6.4.11 provide individual analysis of each single-case experiment. Each individual single-case experiment data table is reported in the order which the interventions were undertaken (i.e., either ABABA or BABABA) to provide a comprehensive overview of the intervention period that each participant had carried out. Sections 6.4.12 to 6.4.14 provide an overview of the changes to each outcome measure across the entire series of single-case experiments in a grouped approach. A summary of the grouped clinically important changes within the series of 11 single-case experiments is provided in Section 6.4.15.

A colour coding system has been used throughout this section to highlight where clinically important changes have occurred (green) and also changes which were positive but not quite deemed clinically important (yellow). It is important to remember that when analysing the colour coding, different MCIC values are available dependent on stage of injury. For example, a change of 1-point on the NPRS would be considered clinically important for a participant with chronic knee problems but not a participant with an acute knee injury.

6.4.1 Single-Case Experiment 1

Table 6.3: Participant Demographics and injury classification for single-case experiment 1

Participant Demographics		Injury Classification	
Age	24	**Injury Type**	Ligament
Gender	Male	**Grade**	3
Sport	Football	**Location**	Medial
Competitive Level	Amateur	**Group**	Chronic

Table 6.4: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 1.

Key

[a] Clinically important change

[b] Positive change but not clinically important

		Day 1		Day 2		Day 3	
		CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)
Swelling	Pre	39.0	38.5	37.5	37.5	37.5	37.5
	Post	38.5	38.5	37.5	37.5	37.0	37.5
	Change	-0.5	0	0	0	-0.5	0
Pain	Pre	2	2	2	2	2	2
	Post	1.5	1.5	2	2	2	2
	Change	-0.5	-0.5	0	0	0	0
	Pain Relief (%)	25	25	0	0	0	0
Stability	Pre	2	3	4	3	4	4
	Post	3	3	4	3	4	4
	Change	+1	0	0	0	0	0

Table 6.4 provides a breakdown of the pre and post intervention measurements over the three-day intervention period. The table reports the data in a chronological order, as this participant had a BABABA intervention order.

For the single-case experiment 1, the CHCD interventions were most effective for achieving reductions in swelling considered clinically important (Table 6.4). No other clinically important reductions were observed for participant-reported pain and stability following either intervention for this participant (see Tables 6.27-6.30). However, it is important to note that despite a -0.5 change on the NPRS scale not being considered

clinically important for chronic musculoskeletal injury, a clinically important change should consider the initial pain level and percentage improvement (Sloman *et al.*, 2006).

As this participant had a low baseline pain of 2, a 0.5-point decrease equates to 25% pain relief. This is illustrated in Graph C in Figure 6.3. Visual analysis of Graphs A-F in Figure 6.3 highlights that both interventions were generally more effective on the 1st day of intervention.

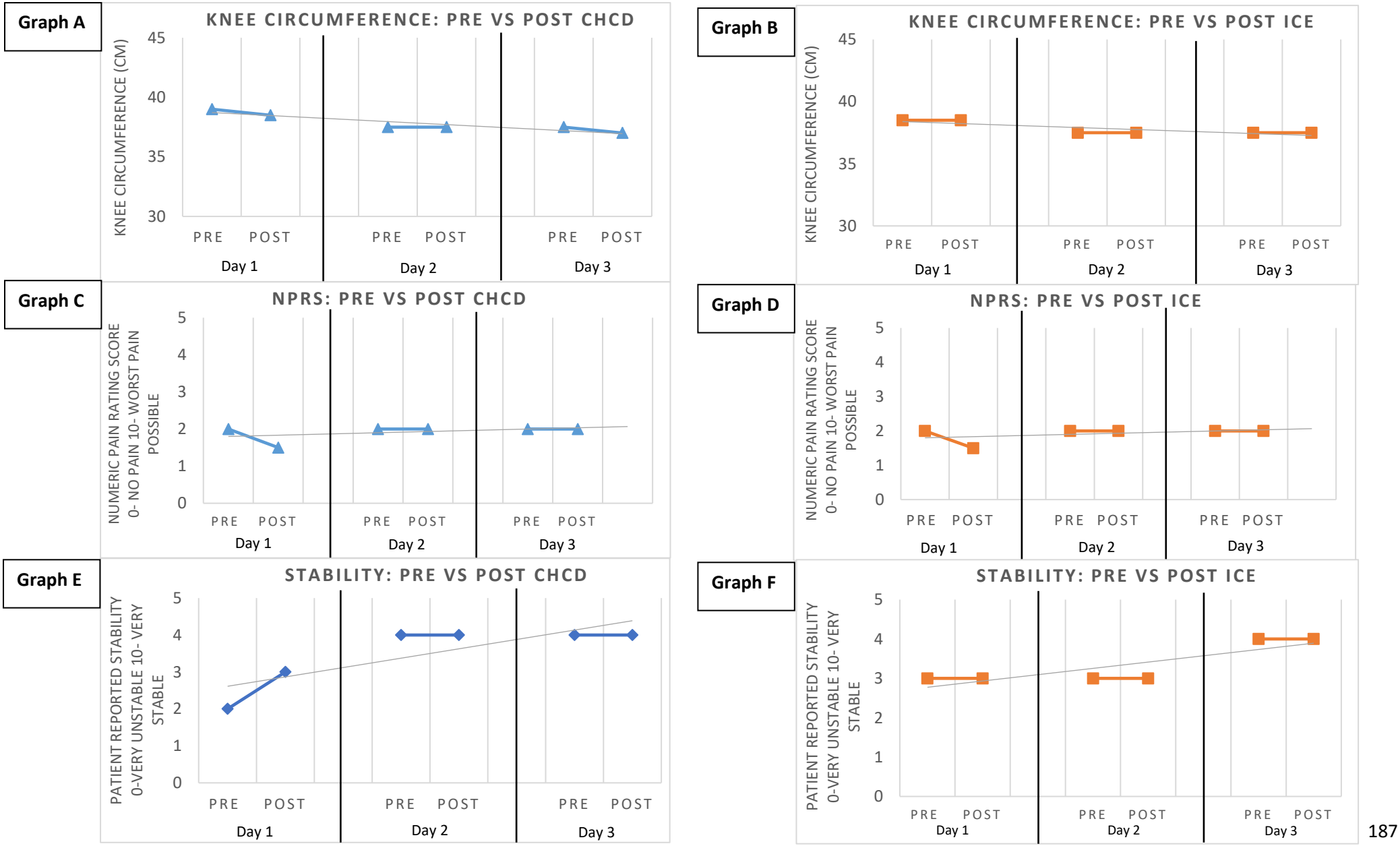

Figure 6.3: Graphs A-F used for visual analysis of each outcome measure of the three-day intervention period for Single-Case Experiment 1

6.4.2 Single-Case Experiment 2

Table 6.5: Participant demographics and injury classification for single-case experiment 2

Participant Demographics		Injury Classification	
Age	27	**Injury Type**	Meniscus
Gender	Female	**Grade**	1
Sport	Gym/Military Fitness	**Location**	Medial
Competitive Level	Amateur	**Group**	Sub-acute

Table 6.6: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 2.

		Day 1		Day 2		Day 3	
		CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)
Swelling	Pre	43	42	41	41	41	41
	Post	42	41	41	41	41	41
	Change	-1	-1	0	0	0	0
Pain	Pre	3	3	3	4	2	2
	Post	2	2	2	3	2	2
	Change	-1	-1	-1	-1	0	0
	Pain Relief (%)	33	33	33	25	0	0
Stability	Pre	3	5	6	6	8	9
	Post	5	6	6	7	8	9
	Change	+2	+1	0	+1	0	0

Single-case experiment 2 was the only participant to present with an injury in the sub-acute stage. Thirty-three percent of each CHCD and ice interventions produced a clinically important change in swelling for this participant (Table 6.6). Only one other meaningful improvement was reported for this participant, which was a clinically important increase in participant-reported stability following a CHCD intervention. However, despite only one clinically important increase in participant-reported stability, it is important to note that the baseline level of stability was 3 and the post three-day intervention period was 9 (10=very stable). This could have been a reflection of the rapid improvement of the injury throughout the sub-acute phase or a reflection of the effectiveness of the consecutive three-day cryotherapy intervention period. It is also important to note that 66% of both interventions reported a 1-point reduction in participant-reported pain, which would have been deemed clinically significant for a chronic injury. Whereas a reduction of 1.3 points is considered clinically significant for acute injury. In the absence of a reported MCIC in sub-acute musculoskeletal pain, acute injury MCIC was used for the individual with a sub-acute injury.

6.4.3 Single-Case Experiment 3

Table 6.7: Participant demographics and injury classification for single-case experiment 3

Participant Demographics		Injury Classification	
Age	25	**Injury Type**	Meniscus
Gender	Female	**Grade**	1
Sport	Football	**Location**	Medial
Competitive Level	Semi Pro	**Group**	Chronic

Table 6.8: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 3

		Day 1		Day 2		Day 3	
		Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)
Swelling	Pre	37.0	36.9	37	36.8	36.5	37.5
	Post	36.7	36.3	37	36.5	36.5	37.5
	Change	-0.3	-0.6	0	-0.3	0	0
Pain	Pre	3	3	4	3	2	2
	Post	2	2	3	2	2	2
	Change	-1	-1	-1	-1	0	0
	Pain Relief (%)	33	33	25	33	0	0
Stability	Pre	6	6	6	6	7	7
	Post	6	6	6	6	7	7
	Change	0	0	0	0	0	0

For single-case experiment 3, 66% of each CHCD and ice interventions produced a clinically important change in pain (Table 6.8). The device was the most effective intervention for reducing swelling for this participant, with one clinically important reduction recorded. However, both interventions had minimal effect on participant-reported stability for this participant.

6.4.4 Single-Case Experiment 4

Table 6.9: Participant demographics and injury classification for single-case experiment 4

Participant Demographics		Injury Classification	
Age	23	**Injury Type**	Ligament
Gender	Male	**Grade**	1
Sport	Football	**Location**	Medial
Competitive Level	Semi Pro	**Group**	Chronic

Table 6.10: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 4

		Day 1		Day 2		Day 3	
		CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)
Swelling	Pre	35.5	35	35	34.5	34	34
	Post	35.5	35	34.5	34.5	34.5	34
	Change	0	0	-0.5	0	+0.5	0
Pain	Pre	0	0	0	0	0	0
	Post	0	0	0	0	0	0
	Change	0	0	0	0	0	0
	Pain Relief (%)	0	0	0	0	0	0
Stability	Pre	3	2	3	3	5	5
	Post	3	3	4	3	4	4
	Change	0	+1	+1	0	-1	-1

Single-case experiment 4 recorded one clinically important change over the three-day intervention period, which was observed in swelling following one CHCD intervention (Table 6.10). However, it is important to note that the participant reported no pain prior to interventions and therefore improvement in pain was not possible for either intervention.

6.4.5 Single-Case Experiment 5

Table 6.11: Participant demographics and injury classification for single-case experiment 5

Participant Demographics		Injury Classification	
Age	28	**Injury Type**	Meniscus
Gender	Male	**Grade**	1
Sport	Football	**Location**	Medial
Competitive Level	Semi Pro	**Group**	Chronic

Table 6.12: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 5

		Day 1		Day 2		Day 3	
		Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)
Swelling	Pre	43	43	43	43	43	43
	Post	43	43	43	43	43	43
	Change	0	0	0	0	0	0
Pain	Pre	4	4	2	2	0	0
	Post	3	4	2	2	0	0
	Change	-1	0	0	0	0	0
	Pain Relief (%)	25	0	0	0	0	0
Stability	Pre	9	8	9	9	9	10
	Post	9	8	9	9	9	10
	Change	0	0	0	0	0	0

Single-case experiment 5 recorded one clinically important change during the three-day intervention period (Table 6.12). This clinically important change was observed in pain following an ice intervention, which was a percentage pain relief of 25%. However, interestingly the participant had actually reduced from a pain score of 4 to 0 by Day 3., despite no immediate intervention effects recorded. Despite no immediate effects following any intervention, the participants stability had also increased from an 8-9 to a 10 by the second intervention on Day 3. The knee circumference appeared stable throughout the three-day intervention period, with no changes to knee circumference reported following all interventions.

6.4.6 Single-Case Experiment 6

Table 6.13: Participant demographics and injury classification for single-case experiment 6

Participant Demographics		Injury Classification	
Age	31	**Injury Type**	Ligament
Gender	Male	**Grade**	1
Sport	Football	**Location**	Medial
Competitive Level	Semi Pro	**Group**	Chronic

Table 6.14: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 6

		Day 1		Day 2		Day 3	
		Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)
Swelling	Pre	41	40.5	40.5	41.5	39.5	39.5
	Post	40.5	39	40	40	39.5	39.5
	Change	-0.5	-1.5	-0.5	-1.5	0	0
Pain	Pre	4	6	4	7	2	2
	Post	3	4	2	5	1	1
	Change	-1	-2	-2	-2	-1	-1
	Pain Relief (%)	25	33	50	29	50	50
Stability	Pre	8	5	7	6	8	8
	Post	8	7	8	7	9	9
	Change	0	+2	+1	+1	+1	+1

Single-case experiment 6 recorded a substantial number of clinically important changes throughout the three-day intervention period following both interventions (Table 6.14). All three ice and all three CHCD interventions recorded by this participant produced a clinically important reduction in participant-reported pain and 66% of each intervention produced a reduction in swelling considered clinically meaningful. Only one clinically important change was reported for participant-reported stability throughout the three-day intervention period, which was observed following one CHCD intervention.

6.4.7 Single-Case Experiment 7

Table 6.15: Participant demographics for single-case experiment 7

Participant Demographics		Injury Classification	
Age	51	**Injury Type**	Knee Osteoarthritis
Gender	Male	**Grade**	1
Sport	-	**Location**	Medial
Competitive Level	-	**Group**	Chronic

Table 6.16: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 7

		Day 1		Day 2		Day 3	
		Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)
Swelling	Pre	40	40.1	40.5	40.5	40.5	40.5
	Post	40	40	40.5	40.5	40.5	40.2
	Change	-0.1	0	0	0	0	-0.3
Pain	Pre	6	5	6	3	3	0
	Post	5	4	1	2	2	0
	Change	-1	-1	-5	-1	-1	0
	Pain Relief (%)	17	20	83	33	33	0
Stability	Pre	5	7	7	7	7	9
	Post	7	7	7	8	8	9
	Change	+2	0	0	+1	+1	0

Within single-case experiment 7, both interventions produced clinically important reductions in pain, ice (3/3 interventions) and CHCD (2/3 interventions) (Table 6.16). However, minimal effects on participant-reported stability and swelling were observed. Only one clinically important change was reported for participant-reported stability, which was observed following one ice intervention and no clinically important reductions in swelling were reported for either intervention throughout the three-day intervention period.

6.4.8 Single-Case Experiment 8

Table 6.17: Participant demographics for single-case experiment 8

Participant Demographics		Injury Classification	
Age	21	**Injury Type**	Ligament
Gender	Male	**Grade**	1
Sport	Football	**Location**	Medial
Competitive Level	Semi Pro	**Group**	Acute

Table 6.18: pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 8

		Day 1		**Day 2**		**Day 3**	
		CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)
Swelling	Pre	36.7	36	35.7	35.7	35.7	35.4
	Post	35.7	35.7	35.7	35.7	35.4	35.4
	Change	-1	-0.3	0	0	-0.3	0
Pain	Pre	8	7	7	6	6	5
	Post	6	6	6	5	5	4
	Change	-2	-1	-1	-1	-1	-1
	Pain Relief (%)	25	14	14	17	17	20
Stability	Pre	5	6	7	7	7	7
	Post	5	6	7	7	7	7
	Change	0	0	0	0	0	0

Single-case experiment 8 reported a reduction in pain for all interventions carried out over the three-day period but only one reduction was considered clinically important for an acute injury (CHCD intervention on Day 1) (Table 6.18). A clinically important reduction to swelling was recorded on the first intervention on Day 1, which was the CHCD. Interestingly, the knee circumference never returned to the baseline value recorded prior to the interventions.

6.4.9 Single-Case Experiment 9

Table 6.19: Participant demographics and injury classification for single-case experiment 9

Participant Demographics		Injury Classification	
Age	73	**Injury Type**	Ligament
Gender	Male	**Grade**	2
Sport	-	**Location**	Medial
Competitive Level	-	**Group**	Chronic

Table 6.20: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 9

		Day 1		**Day 2**		**Day 3**	
	Order of intervention	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)
Swelling	Pre	41.5	40.5	40.5	40.1	40.5	39
	Post	40	40	39.6	39.1	39.2	38.5
	Change	-1.5	-0.5	-0.9	-1	-1.3	-0.5
Pain	Pre	8	5	7	5	7	5
	Post	3	5	5	5	5	6
	Change	-5	0	-2	0	-2	+1
	Pain Relief (%)	63	20	83	33	33	0
Stability	Pre	5	5	5	5	5	5
	Post	5	5	5	5	5	5
	Change	0	0	0	0	0	0

Single-case experiment 9 reported a clinically important reduction in swelling following all interventions (Table 6.20). Interestingly, all CHCD interventions also produced a clinically important reduction in pain, whereas ice interventions did not achieve a clinically important pain reduction. It is also worth mentioning that there was an increase in pain following the final ice intervention. Both interventions had minimal effect on participant-reported stability for this participant, which is comparable to other participants in this series of single-case experiments.

6.4.10 Single-Case Experiment 10

Table 6.21: Participant demographics and injury classification for single-case experiment 10

Participant Demographics		**Injury Classification**	
Age	57	**Injury Type**	Ligament
Gender	Female	**Grade**	1
Sport	Yoga/Gym	**Location**	Lateral
Competitive Level	Amateur	**Group**	Chronic

Table 6.22: pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 10

		Day 1		**Day 2**		**Day 3**	
	Order of intervention	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)
Swelling	Pre	38	38	38	38	37.5	37.5
	Post	38	38	38	37.5	37.5	37
	Change	0	0	0	-0.5	-1.3	-0.5
Pain	Pre	2	2	2	2	1	1
	Post	1	0	0.5	0	0	0
	Change	-1	-2	-1.5	-2	-1	-1
	Pain Relief (%)	50	100	75	100	100	100
Stability	Pre	10	10	10	10	10	10
	Post	10	10	10	10	10	10
	Change	0	0	0	0	0	0

Single-case experiment 10 reported clinically important reductions in participant-reported pain following all interventions. (Table 6.22). It is important to note that all CHCD interventions and one ice intervention provided complete pain relief. Sixty-six percent (2 out of 3) CHCD interventions produced a clinically important reduction in swelling. In contrast, 0% of ice interventions produced a clinically important swelling reduction. There were no clinically important changes reported for either intervention for participant-reported stability for this participant.

6.4.11 Single-Case Experiment 11

Table 6.23: Participant demographics and injury classification for single-case experiment 11

Participant Demographics		**Injury Classification**	
Age	66	**Injury Type**	Knee Osteoarthritis
Gender	Male	**Grade**	1
Sport	Gym	**Location**	Medial
Competitive Level	Amateur	**Group**	Chronic

Table 6.24: Pre and post intervention measurements for pain, swelling and stability over the three-day intervention period for single-case experiment 11

		Day 1		**Day 2**		**Day 3**	
	Order of intervention	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)	CHCD (B)	Ice (A)
Swelling	Pre	40	40	40	40	40	40
	Post	38	38	38	38	38	39
	Change	-2	-2	-2	-2	-2	-1
Pain	Pre	2.5	2.5	3	3	3.5	3.5
	Post	2	2.5	2	3	2.5	2.5
	Change	-0.5	0	-1	0	-1	-1
	Pain Relief (%)	20	0	33	0	29	29
Stability	Pre	3.5	3.5	3.5	3.5	2	2
	Post	3.5	3.5	3	3.5	2	2
	Change	0	0	-0.5	0	0	0

Similarly, both interventions produced clinically important reductions in swelling following all interventions for single-case experiment 11 (Table 6.24). Sixty-six percent (two of three) CHCD interventions produced a clinically important reduction in pain and 33% (one of three) ice interventions produced a clinically important pain reduction. There were no clinically important changes reported for either intervention for participant-reported stability.

6.4.12 Swelling

Tables 6.25 and 6.26 detail the pre and post intervention changes in knee circumference for each participant in the series of single-case experiments, as an indication of changes to local knee swelling.

Key

[a] Clinically important change

[b] Positive change but not clinically important

[c] Negative change but not clinically

Table 6.25: Summary of mean knee circumference changes following ice interventions, cm (n=11)

Injury stage		Acute	Sub-acute	Chronic									Mean ± SD	Effect size	Range
Participant		8	2	1	3	4	5	6	7	9	10	11			
Day 1	Pre	36.0	42.0	38.5	37.0	35.0	43.0	41.0	40.1	40.5	38.0	40.0			
	Post	35.7	41.0	38.5	36.7	35.0	43.0	40.5	40.0	40.0	38.0	38.0			
	Change	-0.3[b]	-1.0[a]	0.0	-0.3[b]	0.0	0.0	-0.5[a]	-0.1 [b]	-0.5[a]	0.0	-2.0[a]	-0.4 (±0.6)	0.2	-2 to 0
Day 2	Pre	35.7	41.0	37.5	37.0	34.5	43.0	40.5	40.5	40.1	38.0	40.0			
	Post	35.7	41.0	37.5	37.0	34.5	43.0	40.0	40.5	39.1	38.0	38.0			
	Change	0.0	0.0	0.0	0.0	0.0	0.0	-0.5[a]	0.0	-1.0[a]	0.0	-2.0[a]	-0.3 (±0.6)	0.1	-2 to 0
Day 3	Pre	35.4	41.0	37.5	36.5	34.0	43	39.5	40.5	39.0	37.5	40.0			
	Post	35.4	41.0	37.5	36.5	34.0	43	39.5	40.5	38.5	37.5	39.0			
	Change	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.5[a]	0.0	-1.0[a]	-0.1 (±0.3)	0.1	-1 to 0

Table 6.26: Summary of mean knee circumference changes following CHCD interventions, cm (n=11)

Injury stage		Acute	Sub-acute	Chronic									Mean ± SD	Effect size	Range
Participant		8	2	1	3	4	5	6	7	9	10	11			
Day 1	Pre	36.7	43.0	39.0	36.9	35.5	43.0	40.5	40.0	41.5	38.0	40.0			
	Post	35.7	42.0	38.5	36.3	35.5	43.0	39.0	40.0	40.0	38.0	38.0			
	Change	-1.0[a]	-1.0[a]	-0.5[a]	-0.6[a]	0.0	0.0	-1.5[a]	0.0	-1.5[a]	0.0	-2.0[a]	-0.7 (±0.7)	0.3	-2 to 0
Day 2	Pre	35.7	41.0	37.5	36.8	35.0	43.0	41.5	40.5	40.5	38.0	40.0			
	Post	35.7	41.0	37.5	36.5	34.5	43.0	40.0	40.5	39.6	37.5	38.0			
	Change	0.0	0.0	0.0	-0.3[b]	-0.5[a]	0.0	-1.5[a]	0.0	-0.9[a]	-0.5[a]	-2.0[a]	-0.5 (±0.7)	0.2	-2 to 0
Day 3	Pre	35.7	41.0	37.5	36.5	34.0	43.0	39.5	40.5	40.5	37.5	40.0			
	Post	35.4	41.0	37.0	36.5	34.5	43.0	39.5	40.2	39.2	37.0	38.0			
	Change	-0.3[b]	0.0	-0.5[a]	0.0	0.5	0.0	0.0	-0.3[b]	-1.3[a]	-0.5[a]	-2.0[a]	-0.4 (±0.7)	0.1	-2 to +0.5

6.4.13 Pain

Tables 6.27 and 6.28 detail the pre and post intervention changes in participant-reported pain scores across the series of single-case experiments. For participant perceived pain, two colour coding systems have been used in order to identify 1) clinically important changes and 2) percentage pain relief as reported in Sloman et al. (2006).

Key

[a] Clinically important change (positive)
[b] Positive change but not clinically important
[c] Clinically important change (negative)
[d] Negative change buy not clinically important`

Pain Relief Percentages (Sloman et al., 2006)

No pain
No relief - <35%
Minimal relief - 35%
Moderate relief - 67%
Much relief - 70%
Complete relief - 93%

Table 6.27: Summary of participant-reported pain score changes following ice (0=no pain, 10=worst pain possible) (n=11)

Injury stage		Acute	Sub-acute	Chronic									Average ± SD	Effect size	Range
Participant		8	2	1	3	4	5	6	7	9	10	11			
Day 1	Pre	7.0	4.0	2.0	3.0	0.0	4.0	4.0	6.0	5.0	2.0	2.5			
	Post	6.0	3.0	1.5	2.0	0.0	3.0	3.0	5.0	5.0	1.0	2.5			
	Change	-1.0[b]	-1.0[b]	-0.5[b]	-1.0[a]	0.0	-1.0[a]	-1.0[a]	-1.0[a]	0.0	-1.0[a]	0.0	-0.7 (±0.5)	0.3	-1.0 to 0.0
	Pain Relief	14%	25%	25%	33%	0%	25%	25%	17%	0%	50%	0%	19%		
Day 2	Pre	6	2	2	4	0	2	4	6	5	2	3			
	Post	5	1	2	3	0	2	2	1	5	0.5	3			
	Change	-1[b]	-1[b]	0	-1[a]	0	0	-2[a]	-5[a]	0	-1.5[a]	0	-1.0 (±1.5)	0.5	-5 to 0
	Pain Relief	17%	50%	0%	25%	0%	0%	50%	83%	0%	75%	0%	27%		
Day 3	Pre	5	1	2	2	0	0	2	3	5	1	3.5			
	Post	4	1	2	2	0	0	1	2	6	0	2.5			
	Change	-1[b]	0	0	0	0	0	-1[a]	-1[a]	+1[c]	-1[a]	-1[a]	-0.4 (±0.7)	0.2	-1 to +1
	Pain Relief	20%	0%	0%	0%	0%	0%	50%	33%	20%	100%	29%	23%		

Table 6.28: Summary of participant-reported pain score changes following CHCD (0=no pain, 10=worst pain possible) (n=11)

Injury stage		Acute	Sub-acute	Chronic									Average ± SD	Effect size	Range
Participant		**8**	**2**	**1**	**3**	**4**	**5**	**6**	**7**	**9**	**10**	**11**			
Day 1	Pre	8.0	5.0	2.0	3.0	0.0	4.0	6.0	5.0	8.0	2.0	2.5			
	Post	6.0	4.0	1.5	2.0	0.0	4.0	4.0	4.0	3.0	0.0	2.0			
	Change	-2.0[a]	-1.0[b]	-0.5[b]	-1.0[a]	0.0	0.0	-2.0[a]	-1.0[a]	-5.0[a]	-2.0[a]	-0.5[b]	-1.4 (±1.4)	0.5	-5.0 to 0.0
	Pain Relief	25%	20%	25%	33%	0%	0%	33%	20%	63%	100%	20%	31%		
Day 2	Pre	7.0	3.0	2.0	3.0	0.0	2.0	7.0	3.0	7.0	2.0	3.0			
	Post	6.0	2.0	2.0	2.0	0.0	2.0	5.0	2.0	5.0	0.0	2.0			
	Change	-1.0[b]	-1.0[b]	0.0	-1.0[a]	0.0	0.0	-2.0[a]	-1.0[a]	-2.0[a]	-2.0[a]	-1.0[a]	-1.0 (±0.8)	0.4	-2.0 to 0.0
	Pain Relief	14%	33%	0%	33%	0%	0%	29%	33%	29%	100%	33%	28%		
Day 3	Pre	6.0	1.0	2.0	2.0	0.0	0.0	2.0	0.0	7.0	1.0	3.5			
	Post	5.0	1.0	2.0	2.0	0.0	0.0	1.0	0.0	5.0	0.0	2.5			
	Change	-1.0[b]	0.0	0.0	0.0	0.0	0.0	-1.0[a]	0.0	-2.0[a]	-1.0[a]	-1.0[a]	-0.5 (±0.7)	0.2	-2.0 to 0.0
	Pain Relief	17%	0%	0%	0%	0%	0%	50%	0%	29%	100%	29%	20%		

6.4.14 Stability

Tables 6.29 and 6.30 detail the pre and post intervention changes in participant-reported stability scores across the series of single-case experiments.

Key

[a] Clinically important change (positive)
[b] Positive change but not clinically important
[c] Clinically important change (negative)
[d] Negative change buy not clinically important`

Table 6.29: Summary of participant-reported stability changes following ice (0=very unstable, 10=very stable) (n=11)

Injury stage		Acute	Sub-acute	Chronic									Average ± SD	Effect size	Range
Participant		8	2	1	3	4	5	6	7	9	10	11			
Day 1	Pre	6.0	5.0	3.0	6.0	2.0	9.0	8.0	5.0	5.0	10.0	3.5			
	Post	6.0	6.0	3.0	6.0	3.0	9.0	8.0	7.0	5.0	10.0	3.5			
	Change	0.0	1.0[b]	0.0	0.0	1.0[b]	0.0	0.0	2.0[a]	0.0	0.0	0.0	+0.4 (±0.7)	0.1	0.0 to +2.0
Day 2	Pre	7.0	6.0	3.0	6.0	3.0	9.0	7.0	7.0	5.0	10.0	3.5			
	Post	7.0	7.0	3.0	6.0	3.0	9.0	8.0	7.0	5.0	10.0	3.5			
	Change	0.0	1.0[b]	0.0	0.0	0.0	0.0	1.0[b]	0.0	0.0	0.0	0.0	+0.2 (±0.4)	0.1	0.0 to +1.0
Day 3	Pre	7.0	9.0	4.0	7.0	5.0	10.0	8.0	7.0	5.0	10.0	2.0			
	Post	7.0	9.0	4.0	7.0	4.0	10.0	9.0	8.0	5.0	10.0	2.0			
	Change	0.0	0.0	0.0	0.0	-1.0 [d]	0.0	1.0[b]	1.0[b]	0.0	0.0	0.0	+0.1 (±0.5)	0.0	-1.0 to +1.0

Table 6.30: Summary of participant-reported stability changes following CHCD (0=very unstable, 10=very stable) (n=11)

Injury stage		Acute	Sub-acute	Chronic								Average ± SD	Effect size	Range
Participant		8	2	1	3	4	5	6	7	9	10	11			
Day 1	Pre	5.0	3.0	2.0	6.0	3.0	8.0	5.0	7.0	5.0	10.0	3.5			
	Post	5.0	5.0	3.0	6.0	3.0	8.0	7.0	7.0	5.0	10.0	3.5			
	Change	0.0	2.0[a]	1.0[b]	0.0	0.0	0.0	2.0[a]	0.0	0.0	0.0	0.0	+0.5 (±0.8)	0.2	0.0 to +2.0
Day 2	Pre	7.0	6.0	4.0	6.0	3.0	9.0	6.0	7.0	5.0	10.0	3.5			
	Post	7.0	6.0	4.0	6.0	4.0	9.0	7.0	8.0	5.0	10.0	3.0			
	Change	0.0	0.0	0.0	0.0	1.0[b]	0.0	1.0[b]	1.0[b]	0.0	0.0	-0.5[d]	+0.2 (±0.5)	0.1	-0.5 to +1.0
Day 3	Pre	7.0	8.0	4.0	7.0	5.0	9.0	8.0	9.0	5.0	10.0	2.0			
	Post	7.0	8.0	4.0	7.0	4.0	9.0	9.0	9.0	5.0	10.0	2.0			
	Change	0.0	0.0	0.0	0.0	-1.0[d]	0.0	1.0[b]	0.0	0.0	0.0	0.0	0.0 (±0.4)	0.0	-1.0 to +1.0

6.4.15 Summary of Clinically Important Changes

Table 6.31 illustrates the total number of clinically important reductions to pain, swelling and instability. The table is colour coded to highlight the frequency of clinically important changes (0/3 – grey, 1/3 yellow, 2/3 – light green, 3/3 – dark green).

Table 6.31: Summary of the positive clinically important changes (out of three interventions) throughout the series of single-case experiments

Participant	**Randomised Order A= Ice B= CHCD**	**Positive Clinically Important Changes**					
		Ice			*CHCD*		
		Pain	*Swelling*	*Stability*	*Pain*	*Swelling*	*Stability*
1	BABABA	0/3	0/3	0/3	0/3	2/3	0/3
2	BABABA	0/3	1/3	0/3	0/3	1/3	1/3
3	ABABAB	2/3	0/3	0/3	2/3	1/3	0/3
4	BABABA	0/3	0/3	0/3	0/3	1/3	0/3
5	ABABAB	1/3	0/3	0/3	0/3	0/3	0/3
6	ABABAB	3/3	2/3	0/3	3/3	2/3	1/3
7	ABABAB	3/3	0/3	1/3	2/3	0/3	0/3
8	BABABA	0/3	0/3	0/3	1/3	1/3	0/3
9	BABABA	0/3	3/3	0/3	3/3	3/3	0/3
10	ABABAB	3/3	0/3	0/3	3/3	2/3	0/3
11	BABABA	1/3	3/3	0/3	2/3	3/3	0/3
Subtotal no. of positive clinically important changes:		13/33	9/33	1/33	16/33	16/33	2/33
Total no. of positive clinically important changes:			23			34	
Percentage of Nonoverlapping Data		39%	27%	3%	49%	49%	6%

In total 19 of the 33 interventions resulted in an immediate pain reduction following ice and 13 of these were clinically important changes. In comparison, 16 of the 22 reductions in pain following the 33 CHCD interventions were considered clinically important. Overall,

out of 12 reductions in swelling following ice interventions, 9 of these were clinically important changes. In comparison, 16 of the 19 reductions in swelling following the CHCD interventions were considered clinically important. Out of 8 reductions in instability following ice interventions, 1 was considered clinically important. In comparison, 2 of the 7 reductions in instability following CHCD interventions were considered clinically important.

Table 6.32: Summary of the negative clinically important changes (out of three interventions) throughout the series of single-case experiments

Participant	**Randomised Order A= Ice B= CHCD**	**Negative Clinically Important Changes**					
		Ice			*CHCD*		
		Pain	*Swelling*	*Stability*	*Pain*	*Swelling*	*Stability*
1	BABABA	0/3	0/3	0/3	0/3	0/3	0/3
2	BABABA	0/3	0/3	0/3	0/3	0/3	0/3
3	ABABAB	0/3	0/3	0/3	0/3	0/3	0/3
4	BABABA	0/3	0/3	0/3	0/3	0/3	0/3
5	ABABAB	0/3	0/3	0/3	0/3	0/3	0/3
6	ABABAB	0/3	0/3	0/3	0/3	0/3	0/3
7	ABABAB	0/3	0/3	0/3	0/3	0/3	0/3
8	BABABA	0/3	0/3	0/3	0/3	0/3	0/3
9	BABABA	1/3	0/3	0/3	0/3	0/3	0/3
10	ABABAB	0/3	0/3	0/3	0/3	0/3	0/3
11	BABABA	0/3	0/3	0/3	0/3	0/3	0/3
Subtotal no. of negative changes:		1/33	0/33	0/33	0/33	0/33	0/33
Total no. of negative changes:			1			0	

6.5 Discussion

This study aimed to determine the effects of two cryotherapy interventions on participant-reported pain, swelling and stability in individuals with a range of knee injuries, through a series of single-case experiments. The two interventions consisted of: *A)* wetted ice (400 ml cubed ice, 400 ml room-temperature water) and *B)* a novel cooling, heating, and compression device (CHCD) set to 10 °C and 50 mmHg compression.

The series consisted of 11 single-case experiments including 1 individual with an acute injury, 1 individual with a sub-acute injury and 9 individuals with a chronic injury or condition. The range of knee injuries consisted of medial collateral ligament (45%), lateral meniscus (9%), medial meniscus (27%), knee osteoarthritis (18%). Each single-case experiment was analysed individually through visual analysis and effect sizes, in order to determine the effects of each 20-minute intervention as applied to each individual. This is a common analysis approach for single-case experiments (Barker *et al.*, 2011). Visual analysis within previous single-case experiments identifies clinically significant changes opposed to statistically significant changes (Dallery, Cassidy and Raiff, 2013). Therefore, the total number of clinically important changes was also reported to indicate the overall success of each intervention.

6.5.1 Pain

Single-case experiments are useful designs for providing the preliminary evidence of the effectiveness or efficacy of interventions (Dallery, Cassidy and Raiff, 2013). This series of single-case experiments provides preliminary evidence of the effectiveness of a novel cooling, heating, and compression device on a population with soft tissue injuries, an intended end user group. This study reports the first findings of clinically meaningful pain relief following a targeted CHCD intervention for the majority of individuals with a range of knee injuries. Across the series single-case experiments, CHCD provided a clinically important reduction in participant-reported pain in 48% of the interventions. Medium to small effect sizes were observed through Days 1, 2 and 3 (d=0.5, d=0.4, d=0.2), with the greatest average reduction in pain seen on Day 1. In comparison, ice provided a clinically important reduction in participant-reported pain 39% of the interventions. Similarly, small to medium effect sizes were observed on Days 1, 2 and 3 (d=0.3, d=0.5, d=0.2) (Tables 2-7) but interestingly, the greatest average reduction in pain was seen on Day 2. Therefore, the 20-minute CHCD intervention provided a clinically important reduction in pain

associated with knee injuries, 9% more frequently than the 20-minute standard clinical treatment of ice.

6.5.2 Swelling

This study reports the first findings of clinically important swelling reduction following a targeted CHCD intervention for most individuals (73%) with a range of knee injuries. In 48% of the CHCD interventions applied in the series of 11 single-case experiments, a clinically important swelling reduction was observed. Whereas 27% of the ice interventions applied in the series of 11 single-case experiments provided a clinically important swelling reduction. For the CHCD interventions, medium to small effect sizes were observed for Days 1, 2 and 3 (d=0.3, d=0.2, d=0.1), with the greatest average reduction in swelling observed on Day 1. For the ice interventions, medium to small effect sizes were observed for Days 1, 2 and 3 (d=0.2, d=0.1, d=0.1), with the greatest average reduction in swelling observed on Day 1. Therefore, a 20-minute application of the device, set with a target T_{sk} of 10 °C with 50 mmHg compression, was more effective at reducing local knee swelling than a 20-minute application of the current standard clinical treatment of ice. This could have been due to the controlled compression used in conjunction with the cooling used within the CHCD intervention. This theory is supported by previous studies which have reported enhanced therapeutic effects from compressive cryotherapy in comparison with cryotherapy alone (Song *et al.*, 2016). These findings are comparable to Sari et al. (2019) which compared the effects of intermittent pneumatic compression (45 mmHg) and cold-pack treatments on clinical outcomes in patients with knee osteoarthritis. Significant improvements in range of motion, muscle strength, pain intensity, and functional status were reported for both treatment groups but interestingly, greater swelling reduction was observed in the intermittent pneumatic compression group compared to the cold-pack treatment group. Sari et al. (2019) reported an average reduction in knee swelling from pre-to-post treatment of 2cm (intermittent pneumatic compression) and 0.5cm (cold pack). However, it's important to note that both groups also used ultrasound, transcutaneous electrical nerve stimulation (TENS), and exercise, in addition to one of the interventions (either a cold-pack or the intermittent pneumatic compression).

6.5.3 Stability

The CHCD provided a clinically important increase in participant-reported stability 6% of the interventions and ice provided a clinically important increase in participant-reported stability 3% of the interventions. Only one small effect size was observed for average participant-reported stability within the series of single-case experiment which consisted of an increase in stability following the CHCD intervention on Day 1 (d=0.2). All other changes had no effect size (d<2). Therefore, both interventions provided little and comparable effects on participant-reported stability.

Overall, the CHCD intervention (target skin temperature of 10 °C and 50 mmHg) achieved clinically important changes in clinical outcomes more frequently than the ice interventions by 9% (participant-reported pain), 21% (swelling) and 3% (participant-reported stability), over the series of 11 single-case experiments on individuals with knee injuries. Regarding the sum of clinically important changes in participant-reported pain, stability and swelling, CHCD was the most effective intervention for 9 individuals and ice was the most effective for 2 individuals. These findings indicate that the CHCD intervention, set with a target T_{sk} of 10 °C and 50 mmHg compression, may be a beneficial self-management tool for a range of knee injuries. Despite Dallery et al. (2013) highlighting the symbiosis between single-case research and novel technology-based health interventions, there is currently a significant lack of research on soft tissue injury rehabilitation using this experimental approach. Currently most single-case experimental designs in rehabilitation focus on behaviour change and neurological conditions, therefore it is difficult to compare these findings to relevant previous literature using this design approach.

6.5.4 Limitations

A common limitation of the alternating treatment design threatening internal validity is the multi-treatment interference, which refers to the effect of one intervention interacting with the other intervention (Barker *et al.*, 2011). This was minimised by adopting a counterbalancing approach within this study, which involves randomising the order of interventions. Further to this, there was a minimum of 2-hour lightly active washout period between interventions to allow the rewarming of skin surface temperature and intramuscular temperature, in order to minimise the multi-treatment interference. Despite this series of single-case experiments providing preliminary

evidence of the effectiveness of the CHCD intervention on a small population with knee injuries, a larger study should be conducted to evaluate the effectiveness of these cryotherapy interventions on a wider population, with a range of soft tissue injuries. Similar to the studies reported in Chapters 4 & 5, a limitation of this study is the lack of a control group that did not receive a CHCD intervention within the series of single-case experiments. This was considered, however, as the participants were injured and in pain, there were some ethical concerns with providing participants a controlled condition with no cryotherapy, which would be against the clinical guidelines for acute injury management.

Further work should consider longer-term effects over a longitudinal study to identify the effects of targeted cryotherapy interventions throughout the rehabilitation period from the point of injury to 'return to play'. With the analyses of single-case experiments frequently focussing on clinically important changes and visual analysis, the statistical analysis is often limited to effect sizes and percentage of nonoverlapping data. This series of single-case experiments adopted this approach and therefore limited statistical analysis was conducted. However, through identifying clinically important changes, clinicians may be able to utilise relevant findings and implement optimal evidence-based interventions into applied practice.

6.6 Conclusion

Through the series of 11 single-case experiments using an alternating treatment design, it was observed that the 20-minute intervention using the CHCD set with a target skin temperature of 10 °C and 50 mmHg compression, achieved clinically important changes more frequently than a 20-minute application of ice for patient-reported pain (by 9%), swelling (by 21%) and patient-reported stability (by 3%). Both interventions created immediate positive effects on patient-reported pain and a limited positive effect on patient-reported stability. This study provides preliminary evidence of the effectiveness of the 20-minute CHCD intervention as a self-management tool for symptoms associated with knee injuries. This study also reports the first findings of a clinically meaningful pain relief and swelling reduction following the 20-minute CHCD intervention applied to individuals with a range of knee injuries. The enhanced swelling reduction observed

immediately following CHCD interventions could have been due to the addition of compression to the cooling. These findings support previous literature advocating the use of compression to aid reductions in knee swelling. The compressive cryotherapy intervention using the CHCD appeared more beneficial for the majority (82%) of individuals with knee injuries, due to the desired analgesic effect and increased swelling reduction compared to the current standard clinical treatment of ice. However, further research on a larger cohort and wider range of soft tissue injuries should be conducted to follow on from these preliminary findings. The preliminary findings indicate that higher levels of evidence would be warranted, such as a randomised control trial, to explore the use of different compressive cryotherapy interventions in soft tissue injury management further.

Chapter 7: Discussion

7.1 Introduction

This chapter will briefly summarise the findings from the three intervention studies outlined in Chapters 4, 5 and 6, and subsequently discusses the clinical implications associated with these findings. This chapter also outlines realisation of aims and objectives, as well as indicating possible strengths, weaknesses and limitations of the research undertaken. Recommendations for future research will also be discussed.

The main aim of this body of work was to explore parameters of temperature and compression, to inform the development of evidence-based, optimal protocols, using the CHCD. This thesis addressed a number of key objectives, through three intervention studies exploring a range of outcome measures on three participant groups:

1) Healthy participants (Chapter 4)
2) Healthy participants with induced pain (Chapter 5)
3) Participants with knee injuries and degenerative knee conditions (Chapter 6)

7.1.1 Realisation of Aims and Objectives

The ability of the CHCD to provide controlled temperature and compression, to reduce T_{sk} between 10-15 °C, was assessed in Chapter 4 (Objective 1). It was established that a temperature setting of 10 °C on the CHCD could achieve the desired T_{sk} in a healthy male population. Whereas a temperature setting of 15 °C could not achieve T_{sk} within the therapeutic range. Therefore, a temperature setting of 10 °C was used in the subsequent studies reported in Chapter 5 and Chapter 6.

The application of local contrast therapy is an area in research that is significantly lacking evidence, potentially due to the difficulty applying cold and heat therapy locally across the body. The CHCD provided the opportunity to explore the effects of contrast therapy, and therefore this study aimed to provide novel contributions to knowledge. Firstly, it was important to collate the current consensus of the use of contrast therapy in soft tissue injury management and post-exercise recovery. This was achieved through the creation of a scoping review titled *'The use of contrast therapy in soft tissue injury management and post-exercise recovery: a scoping review'* which was published in Physical Therapy Reviews (Objective 2).

The findings of the study reported in Chapter 4 informed the selection of the optimal CHCD intervention, which could then be compared to the most commonly used cryotherapy modality, ice in Chapter 5. The effects of two cryotherapy interventions (1) CHCD (10 °C and 50 mmHg) and (2) wetted ice, on muscle strength, pressure pain threshold, participant-perceived pain and joint position sense were explored on a healthy population with experimentally induced knee pain (Objective 3). The findings suggested that targeted compressive cryotherapy has the potential to achieve the desired analgesic effect on healthy participants with experimentally induced knee pain, whilst minimising the negative effects on muscle strength, dynamic stability and knee joint repositioning which has been reported in the literature previously.

These interventions were then explored in participants with a range of knee injuries and degenerative conditions, through a series of single-case experiments presented in Chapter 6 (Objective 4). The findings suggested that compressive cryotherapy, using the CHCD, appeared more beneficial for the majority (82%) of individuals with knee injuries, reducing swelling and pain, compared to wetted ice.

7.2 Healthy Participants (Chapter 4)

7.2.1 Summary

The first study reported in this thesis aimed to explore the effects of four CHCD interventions, on a range of outcome measures, on a healthy male population. The outcome measures consisted of both subjective (thermal sensation/comfort and pressure pain threshold) and objective measures (T_{sk}, SmO_2, joint position sense and strength). Within these measures, it was important to explore biomechanical (joint position sense), physiological (T_{sk}, SmO_2), perceptual (thermal sensation/comfort and pressure pain threshold) and functional (strength) factors, to provide a comprehensive understanding of the effect of each intervention, informing the development of optimal cryotherapy interventions.

This initial study indicated that the lower temperature (10 °C) was the most beneficial temperature to achieve the desired physiological, perceptual, biomechanical, and functional effects of the cooling intervention. However, it is difficult to conclude a single

optimal intervention from the results of this study alone as there were no significant differences found between the two pressure levels used (32 mmHg and 50 mmHg) with the 10 °C temperature setting. This finding refutes previous studies reporting an increased magnitude of cooling with the addition of compression (Song *et al.*, 2016; Alexander, Greenhalgh and Rhodes, 2020). As discussed in Chapter 4, one reason for this could be due to the design of the compression bladders in the prototype used, with the inflation of the air bladders hindering the contact of the cooling plate on the skin and impeding the rate of energy transfer. It is possible that a circumferential compression design may have provided greater therapeutic benefits as previous studies demonstrating greater therapeutic benefits with cooling and compression combined, have used a circumferential compression design (Song *et al.*, 2016; Alexander, Greenhalgh and Rhodes, 2020).

The findings from this study suggest that targeted cryotherapy, using the CHCD in a healthy male population, may minimise the inhibition to quadriceps function which has been reported following ice. A reduction in strength can lead to a reduction in functional performance and also increased risk of injury. This may facilitate an earlier return to weight-bearing activity and optimal loading, to promote early recovery. However, it is important to note that this study was carried out on a healthy male population. Although the focus of this thesis is injury management, it was important to validate the novel CHCD in a healthy population to obtain normative values and measure safety and performance prior to applying the device to symptomatic patients.

7.2.2 Clinical Implications

7.2.2.1 Skin Surface Temperature

Desired physiological effects of cooling interventions include decreased $T_{sk,}$ to induce a local analgesic effect, and decreased $SmO_{2,}$ to reduce metabolic activity and secondary damage (Bleakley and Hopkins, 2010) in order to possibly initiate these desired physiological effects of cooling, T_{sk} must be reduced to within the recognised therapeutic range of 10-15 °C (Kennet *et al.*, 2007).

As discussed in Chapter 4, T_{sk} was significantly reduced on the medial aspect of the knee up to 20 minutes post intervention, following all the compressive cryotherapy

interventions (interventions 1, 2 and 3). Interventions 1 (10 °C, 50 mmHg) and 3 (10 °C, 32 mmHg) also significantly reduced T_{sk} on the lateral aspect of the knee up to 20 minutes post intervention. This supports the hypothesis that there would be significant differences between temperature and/or compression settings on medial and lateral knee skin surface temperature, immediately post intervention or over a 20-minute rewarming period.

When comparing the immediate effects of the two temperature settings (10 °C and 15 °C), 10 °C significantly reduced T_{sk} greater than the 15 °C temperature setting. Findings indicate that CHCD interventions set at 10 °C (1 and 3) demonstrated a potential therapeutic effect throughout the 20-minute rewarming period on both the medial and lateral aspects of the knee. T_{sk} rewarming has been demonstrated to be a possible indication of deeper tissue cooling as superficial tissues draw heat from the deeper tissues in order to rewarm (Hardy and Woodall, 1998; Kennet *et al.*, 2007; Hardaker *et al.*, 2007). The rewarming curves reported in this study did not return to baseline 20 minutes post intervention (see section 4.3.3.1), which reflects published cryotherapy rewarming curves (Kennet *et al.*, 2007).

When comparing the immediate effects of the two compression settings (low: 32 mmHg and high: 50 mmHg), no significant differences in T_{sk} were found between low and high compression when the CHCD was set at 10 °C. Interestingly, it was noted that the lower compression achieved the lowest minimum T_{sk} immediately post treatment recorded within the study (12.2 °C). This highlights that the compression design within the device did not enhance the therapeutic cooling rate, which refutes previous studies reporting an increased magnitude of cooling with the addition of compression (Song *et al.*, 2016; Alexander, Greenhalgh and Rhodes, 2020). However, this could be due to the design of compression within the CHCD version used in this study (Table 3.1), which consisted of two air bladders applying pressure to either side of the knee, opposed to circumferential coverage. It was observed during the study that the air bladders hindered the contact of the cooling plate on the skin once inflated, particularly the lateral aspect of the knee and ultimately impeded the rate of energy transfer. Interestingly, studies which have demonstrated an increased magnitude of cooling with the addition of compression, have used a circumferential compression (Song *et al.*, 2016; Alexander *et al.*, 2021b). Therefore, a circumferential compression design may have led to greater reductions in

tissue temperature and SmO_2 and in turn may enhance the therapeutic impact of the targeted cryotherapy intervention.

The contrast therapy intervention (intervention 4) did not significantly affect medial and lateral knee T_{sk} immediately post intervention or over a 20-minute rewarming period, which supports the null hypothesis. As the temperatures were alternating every 3 minutes between 10 °C and 40 °C, the final cycle ended on a two-minute cold cycle, and this may not have been sufficient time to reduce T_{sk}. However, it is important to consider the aim of the intervention as Hing et al. (2008) suggested contrast therapy may offer beneficial effects functionally rather than the physiological outcome measures commonly evaluated in cryotherapy studies. This is one of the reasons why it was important to capture a wide range of outcome measures, to provide a comprehensive overview of the intervention effects. Interestingly, the rewarming curve for the contrast therapy intervention followed a different pattern to the compressive cryotherapy interventions (see section 4.3.3.1); T_{sk} appeared to fluctuate over the entire rewarming period. This is a novel contribution to knowledge as there are no published rewarming curves following contrast therapy currently in literature, to the authors knowledge.

The findings from this study indicate that research investigating T_{sk} during a contrast therapy intervention would be warranted, in order to assess the change in T_{sk} during and between cycles. It is difficult to conclude whether significant T_{sk} changes were achieved between the hot/cold cycles as T_{sk} was only measured over a 20-minute rewarming period. Future research should also explore different temperature, compression and time combinations used within a contrast therapy intervention, to determine the magnitude and speed of T_{sk} change for different cycle durations.

It is evident that more research is required to explore whether contrast therapy could be an effective adjunct for soft tissue injury management. Importantly, the scoping review that was carried out as part of this thesis identified that contrast therapy is more commonly used for the purpose of post-exercise recovery (Greenhalgh *et al.*, 2021) which has different therapeutic aims to knee injury management.

It is clear that there are a lot of factors still unknown which require further investigation, in order to determine the efficacy of contrast therapy for soft tissue injury management, such as:

- Optimal temperature for each cycle
- Optimal duration and number of cycles
- Optimal compression during each cycle

7.2.2.2 Thermal Sensation and Comfort

These outcome measures were captured to assess the subjective effects of each intervention, in a healthy population. Capturing thermal sensation provided an insight into how cold or hot the participant felt the intervention was, which could then be compared to the actual skin surface temperature recorded (Alexander *et al.*, 2021b). A decrease in thermal sensation indicates an increase in perception of cooling. This could be considered both therapeutically advantageous and disadvantageous, as an increased perception of cooling could increase intervention satisfaction but may also reduce compliance to withstand the intervention duration if the individual finds the intervention too cold. For this reason, thermal comfort was captured to provide a greater understanding of the effectiveness of each intervention. If an intervention is too cold to withstand and an individual does not complete the desired duration for this reason, the effectiveness of the intervention in applied practice is limited.

The results suggest that intervention 1 (10 °C and 50 mmHg) was considered 'slightly uncomfortable' in regard to thermal comfort. This is comparable to other local cryotherapy modalities such as wetted ice, which has also been reported as 'slightly uncomfortable' on a thermal comfort scale (Alexander *et al.*, 2020).

A limitation of these findings was that the measurements were recorded pre and post intervention at standardised intervals, as opposed to intermittently during the intervention. It was observed during data collection that participants appeared to become habituated to the constant thermal stimulus by the end of the 20-minute intervention and throughout the 20-minute rewarming period. On reflection, it may have been more interesting to capture these measurements immediately after the intervention was applied and in standardised periods throughout the intervention period.

7.2.2.3 Muscle Oxygenation

No significant main effects were found in tissue oxygenation (SmO_2) recorded at the tibialis anterior from pre- to post intervention across all interventions (p=0.414), which supports the null hypothesis. However, despite not being statistically significant, interventions 1, 2 and 4 demonstrated a trend of a decrease in SmO_2 from pre to immediately post intervention (Table 4.13), which is comparable to previous findings that cryotherapy reduces SmO_2 (Yeung *et al.*, 2016). It is generally accepted that tissue oxygenation reduces when cold is applied as vasoconstriction occurs which reduces local blood flow and tissue metabolism (Knight, 1995; Nadler, Weingand and Kruse, 2004; Yeung *et al.*, 2016; Alexander, Greenhalgh and Rhodes, 2020). The physiological benefits of reducing tissue oxygenation include minimising secondary damage following an acute trauma (Bleakley and Hopkins, 2010).

In contrast, compression has been shown to increase SmO_2 during and immediately post intervention (Neuschwander *et al.*, 2012), it is possible that the medial and lateral pressure applied in the CHCD prototype may not have been as effective as circumferential compression applied in other studies (Alexander *et al.*, 2021b). During intervention 2 SmO_2 continued to decline throughout the 20-minute rewarming period, which echoes findings reported in Alexander, Greenhalgh and Rhodes (2020). The continued decline may be because the cooling continues to penetrate deeper tissues after the intervention has been removed. This assumption is based on previous findings that intramuscular tissues continue to cool up to 40 minutes after the removal of the local cryotherapy modality (Zemke *et al.*, 1998; Hardaker *et al.*, 2007). However, as intramuscular temperature was not measured as part of this research, this is an assumption based on previous research.

Intervention 3 demonstrated an increase immediately post intervention, followed by a slight fluctuation in SmO_2. Interestingly, this intervention had a lower compression and produced the lowest minimum T_{sk} recorded in the study. Based on previous findings reported in the literature (Coza *et al.*, 2012; Alexander, Greenhalgh and Rhodes, 2020), higher compression would be expected to increase SmO_2 more than lower compression, so the findings from this study conflicts with previous research.

When comparing the immediate effects of compression (high and low) on muscle oxygenation, no significant differences were found (p=0.303). When comparing the immediate effects of temperature settings (10 °C and 15 °C) on muscle oxygenation, no significant differences were found (p=0.882). A possible suggestion for no significant differences being found following the compressive cryotherapy interventions would be the location of the oxygenation sensor. The sensor was placed on the tibialis anterior as the closest muscle belly distal to the area cooled on the knee joint line. Future work should explore the different measurement sites for the MOXY sensor, particularly over the cooling site directly. This wasn't possible during this study as it would have interfered with the thermal imaging measurements, as the MOXY sensor would have insulated the area being cooled. It is also possible that the effects of compression and cryotherapy counteracted each other as the literature presents opposite responses to SmO_2. More research is required in this field to establish the effects of compression and cryotherapy combined on SmO_2.

7.2.2.4 Muscle Strength

The findings from this study demonstrated no significant differences in quadriceps strength between time points or interventions in a healthy male population, which supports the null hypothesis. Therefore, post-hoc comparisons were not carried out. However, the intervention which achieved the lowest mean T_{sk}, reduced isometric quadriceps strength (peak moment) the most, which concurs with the findings reported in previous literature (Rhodes and Alexander, 2018; Alexander *et al.*, 2021b). Despite no statistically significant changes, there was a trend for the compressive cryotherapy interventions (1-3), demonstrating a reduction in quadriceps strength from pre- to post intervention (between 2-6% approximately).

In comparison, Rhodes and Alexander (2018) observed significant decreases of approximately 16% in quadriceps concentric peak and average moment following a 20-minute application of ice to the knee. The clinical implications of reduced quadriceps muscle strength include decreases in quadriceps functional performance, potentially leading to an increased risk of non-contact knee injury due to the loss of control to prevent excessive or abnormal movements (Shultz *et al.*, 2015; Rhodes and Alexander, 2018). Therefore, it is important to understand the magnitude of inhibition of different cryotherapy interventions in order to ensure a safe return to weight-bearing activity. The

findings from this study suggest that targeted cryotherapy may minimise the inhibition to quadriceps function in comparison to ice, which may facilitate an earlier return to weight-bearing activity and optimal loading.

On the other hand, contrast therapy (Intervention 4) had the opposite response, with an initial 5% increase in quadriceps strength post intervention, followed by a 3% decrease 20 minutes post intervention. No significant differences were found between the immediate effects of high and low compression on quadriceps strength (p=0.756). No significant differences were found between the immediate effects of temperature settings on quadriceps strength (p=0.256). This echoes the findings presented by Axman et al. (2013). Despite no significant difference statistically between groups, there was a general trend showing an increase in strength during knee extension following a 10-minute hot-pack application and a decrease in knee extension strength following 10-minute ice-pack application, in 35 healthy participants recruited within a university cohort. Therefore, depending on the therapeutic aim of the intervention (i.e., post exercise recovery or injury management), clinicians could consider utilising contrast therapy in order to encourage optimal loading and a safer return to weight bearing.

7.2.2.5 Joint Position Sense

It was important to consider biomechanical factors following cryotherapy interventions as previous research has found a significant decrease in dynamic stability following 20-minute applications of ice on the knee (Uchio *et al.*, 2003; Surenkok *et al.*, 2008; Costello and Donnelly, 2010; Rhodes and Alexander, 2018; Alexander *et al.*, 2018; Alexander *et al.*, 2021b). As previously discussed in Chapter 4, decreased dynamic stability and knee joint repositioning may cause a potential increased risk of re-injury when returning to weight-bearing activity (Arnason *et al.*, 2004; Alexander *et al.*, 2016; Alexander *et al.*, 2018). In turn, inhibition to joint position sense may discourage early activity or optimal loading post intervention.

The findings from this study showed no significant differences in maximum, minimum or ROM in the sagittal plane (knee flexion) between time points or interventions ($p>0.05$), which supports the null hypothesis. However, significant decreases were found in knee joint ROM in the coronal plane (knee abduction/adduction) from pre-intervention to post intervention. It is difficult to conclude the reasons for the reduction in coronal plane

ROM, however it could possibly indicate an increase in stability or stiffness following the cooling intervention. No significant differences ($p>0.05$) in maximum and minimum angles or ROM in the transverse plane (knee internal/external rotation) between time points or interventions. These findings conflict with previous research which has presented significant increases in the ROM in the transverse plane; causing significant reductions in the ability to replicate knee joint angle positioning accurately, 20 minutes following an ice application (Alexander *et al.*, 2016; Alexander *et al.*, 2018). Interestingly, the study by Alexander et al. (2018) reported similar knee T_{sk} immediately post intervention (14.2 °C) to the findings from this study, which suggests that the magnitude of T_{sk} reduction may not be the main factor negatively affecting dynamic stability. Thus, reducing the surface area being cooled around the knee, through targeted applications, could possibly be an important factor when considering the impact on knee joint dynamic stability following ice. Similar to the clinical implications of loss of strength, the clinical implications of minimising adverse effects on functional control potentially means that individuals could have a lower risk of re-injury when they return to weight-bearing following the cryotherapy intervention (Arnason *et al.*, 2004; Costello and Donnelly, 2010; Alexander *et al.*, 2016; Alexander *et al.*, 2018). This would allow individuals to return to rehabilitation exercises safer and earlier, which can encourage optimal loading where appropriate.

7.2.2.6 Pressure Pain Threshold

The findings from this study demonstrated significant main effects between PPT measurement sites on the medial aspect of the knee ($p<0.05$), in a healthy male population, which supports the hypothesis. PPT within the cooled area was significantly higher than the other measurement sites recorded. Significant differences were found between time points on both the medial and lateral aspects of the knee ($p<0.05$), which supports the hypothesis. These findings suggest that the cooling produced a local analgesic effect, which led to an increased pain threshold. However, from these results alone it is difficult to determine the optimal intervention for increasing pain threshold as no significant differences between interventions were found. This is important from a clinical perspective as an increase in PPT means that more adverse stimuli can be tolerated before a pain response is registered (Chesterton *et al.*, 2002).

Significant increases in PPT were found from pre-intervention to 20 minutes post intervention and post intervention to 20 minutes post intervention. Zemke et al. (1998)

reported that intramuscular temperatures (at 1cm) achieved their lowest temperatures at 17.9 ± 2.4 minutes with a 15-minute ice massage and 28.2 ± 12.5 minutes with a 15-minute application of an ice bag. Hardaker et al. (2007) reinforce this continuation of deep tissue cooling post removal of cryotherapy and demonstrated that intramuscular cooling (at 3cm) continues up to 30-40 minutes after removal. Additionally, Costello et al. (2012) found that intramuscular temperature (at 3cm) continued to decline up to 60 minutes after both whole-body cryotherapy and cold-water immersion and did not return to baseline temperature within the 60 minutes observed post intervention. With this in mind, it is possible to suggest that the effect of the cooling intervention was initially only superficial immediately post intervention and by 20 minutes post intervention, the deeper tissues may have decreased in temperature. However, as intraarticular temperature was not recorded as part of this thesis, this is only an assumption based on previous research.

Significant differences were found in PPT between the medial and lateral aspects of the knee, with the lateral PPT being higher, on average ($p=0.002$). On the medial aspect of the knee, the cooled area recorded the highest mean PPT, with the lowest PPT recorded below the cooled area. Whereas, on the lateral aspect of the knee, the cooled area recorded the lowest PPT, with the highest PPT being recorded below the cooled area. This may be due to the reduced contact of the cooling plate on the lateral aspect of the knee, as previously discussed.

On the other hand, no significant differences were found between PPT measurement sites on the lateral aspect of the knee. These findings echo Alexander et al. (2019), which reported that the medial aspect of the knee is significantly more sensitive than the lateral aspect of the knee. These findings also reinforce Part A (see Chapter 4, section 4.3.4), which identified that the desired cooling may have not been achieved on the lateral aspect of the knee and the contact of the cooling plate on the lateral side of the CHCD may need further improvement, in order to achieve the desired physiological effects.

7.3 Healthy Participants with Experimentally Induced Knee Pain (Chapter 5)

7.3.1 Summary

The second study reported in this thesis explored the effects of two cryotherapy interventions (1. wetted ice and 2. 10 °C and 50 mmHg using the CHCD) on strength, pain (NPRS and PPT) and joint position sense in healthy participants with experimentally induced knee pain. The findings of this study provide an insight into the effects of the optimal intervention identified in Chapter 4 and the current standard clinical treatment (ice), in a population with experimentally induced pain. This is the first study to date which explores the use of the novel CHCD on a symptomatic population, providing key information for informing the development of optimal cryotherapy interventions for knee injury management.

Capsaicin cream induced an average participant-reported pain of approximately 2 out of 10. Participant-reported pain was reduced by 100% (CHCD) and 91% (ice) 20 minutes post-cooling. Complete pain relief (≥93% pain reduction) was achieved immediately post-cooling in 7 participants for the CHCD and in 4 participants for ice. However, no statistically significant differences were found between interventions ($p>0.05$). Significant increases in PPT were found between post-capsaicin and post-cooling and between post-capsaicin and 20-minute post-cooling time points following the CHCD interventions. Whereas no significant differences were found in PPT between any time points following ice. Ice reduced quadriceps strength by 13% immediately post-cooling, however the CHCD had a negligible effect on muscle strength immediately post intervention (+0.3%). No statistically significant differences in muscle strength were found between interventions, the strength deficit post ice was almost double the percentage reduction (6%), which can be associated with a clinically important functional deficit in individuals with knee osteoarthritis (Ruhdorfer, Wirth and Eckstein, 2015). Significant increases were found in ROM in the coronal plane following the ice intervention, which indicates increased instability (adduction/abduction) following ice. No significant differences in maximum, minimum or ROM in the sagittal (knee flexion) or the transverse plane between time points or interventions were seen. However, there was a trend towards an increase in instability in the transverse plane from post-capsaicin to 20 mins post-cooling which was most apparent following the ice interventions ($p=0.053$).

Targeted compressive cryotherapy has the potential to achieve the desired analgesic effect on healthy participants with experimentally induced knee pain, whilst minimizing the negative effects on muscle strength and knee joint repositioning previously reported following ice applications.

7.3.2 Clinical Implications

7.3.2.1 Muscle Strength

The findings of this study were comparable to previous findings which reported significant reductions to quadriceps muscle strength (up to 16%) following 20-minute ice interventions (Alexander *et al.*, 2016; Alexander *et al.*, 2018; Rhodes and Alexander, 2018). A 13% reduction in quadriceps strength was reported following ice interventions, whereas the CHCD had a negligible effect immediately post intervention (+0.3%). However, despite a trend of a greater reduction following ice, no significant differences in strength were found between time points or interventions, which supports the null hypothesis.

However, it is important to note that this study was carried out on a symptomatic population as participants were induced with experimental knee pain, and therefore it may be a poor comparison as the previous studies mentioned were all carried out on a healthy population. With that being said, limited research is available in this field, so it is difficult to make a direct comparison. The strength deficit following ice was almost double the percentage reduction (6%), which can be associated with a clinically important functional deficit in individuals with knee osteoarthritis (Ruhdorfer, Wirth and Eckstein, 2015). As previously discussed, the clinical implications of decreases quadriceps muscle strength can lead to an increased risk of knee injury due to the loss of control to prevent excessive or abnormal movements (Shultz *et al.*, 2015; Rhodes and Alexander, 2018). Therefore, it is important to understand the magnitude of inhibition of different cryotherapy protocols in order to ensure a safe return to weight-bearing activities. These findings provide evidence supporting the use of targeted cryotherapy on a symptomatic population, to minimise the inhibition to quadriceps function in comparison to ice, which may facilitate an earlier return to weight-bearing activity and optimal loading.

7.3.2.2 Joint Position Sense

Previous studies have also demonstrated inhibition to knee joint repositioning following cryotherapy (Uchio *et al.*, 2003; Surenkok *et al.*, 2008; Costello and Donnelly, 2010; Alexander *et al.*, 2016; Alexander *et al.*, 2018). No significant differences in maximum, minimum values, or knee joint ROM in the sagittal plane (knee flexion) between time points or interventions were observed, which supports the null hypothesis. This highlights that adopting a targeted cooling approach may minimise this inhibition to knee joint repositioning and dynamic stability observed following other cryotherapy approaches. Significant increases were found in ROM in the coronal plane following the ice interventions, which indicates increased instability (adduction or abduction). Despite no significant differences in maximum, minimum or knee joint ROM in the transverse plane, there was a trend of increased instability in the transverse plane from post-capsaicin to 20 mins post-cooling, which was most apparent following the ice interventions (p=0.053). With a *p* value this close to significance, it would be interesting to explore this on a larger sample size, which may allow for further post hoc analyses. Increased instability 20-minutes post-cooling reflects previous literature, which has demonstrated that deeper intramuscular tissues (at 1cm) continue to cool after the cryotherapy intervention has been removed and achieve their coolest temperatures approximately 14 minutes post removal (Zemke *et al.*, 1998). Hardaker et al. (2007) reinforce this continuation of deep tissue cooling post removal of cryotherapy and demonstrated that intramuscular cooling (at 3cm) continues up to 30-40 minutes after removal. Decreased dynamic stability and knee joint repositioning may cause a potential increased risk of injury when returning to weight-bearing activity (Arnason *et al.*, 2004; Alexander *et al.*, 2016; Alexander *et al.*, 2018), and any inhibition to joint position sense may discourage early activity or optimal loading post intervention.

7.3.2.3 Participant-Reported Pain

The efficacy of ice treating soft tissue injury has recently been questioned due to the lack of high quality-evidence. However, evidence does exist to support the use of local cryotherapy for short-term pain relief. It is not yet known if reducing the surface area of the local cryotherapy application would significantly affect the ability to achieve a local analgesic effect to provide the desired short-term pain relief. Therefore, novel cryotherapy interventions which can provide the same desired analgesic effect achieved

through ice, whilst minimising these reported adverse effects to function, may be particularly beneficial in elite sport environments.

This study provides the first findings of potentially important and statistically significant pain relief following a targeted compressive cryotherapy intervention, using the CHCD. Experimental knee pain, using capsaicin cream, induced an average participant-reported pain of approximately 2 out of 10 on the Numeric Pain Rating Scale (NPRS) in this study. The increase in pain induced by the capsaicin cream was found to be statistically significant. The majority (80%) of participants experienced a burning sensation on application of the capsaicin cream during intervention sessions, which is comparable to previous studies (Chrubasik, Weiser and Beime, 2010).

Both interventions were effective in reducing participant-reported pain immediately post-cooling (ice - 76% and CHCD - 87%) and 20-minute post-cooling (ice - 91% and CHCD - 100%). It is important to note that both interventions achieved reductions in pain post-cooling which would be considered clinically important in an acute injury population. Complete pain relief was achieved by 20-minutes post-cooling for the CHCD intervention. Ice achieved 'much relief' (70%) by 20-minutes post-cooling.

Significant increases in participant-reported were found between pre and post capsaicin cream application. Significant decreases were found in participant-reported pain post-capsaicin to post-cooling, post-cooling to 20 minutes post-cooling and post-capsaicin to 20 minutes post-cooling. Thus, both interventions were effective at reducing short-term experimental knee pain. The induced analgesic effect and clinical evidence for ice reducing short term pain for soft tissue contusions and acute ankle injuries is discussed in the literature (Bleakley *et al.*, 2011). However, there is a lack of research investigating the effect of targeted cryotherapy approaches (cooling a smaller surface area) on short-term pain. This study provides the first findings of the effect on pain reduction following a targeted cryotherapy intervention, using the CHCD on the knee. The magnitude of pain relief would be considered clinically important in the management of acute injuries.

7.3.2.4 Pressure Pain Threshold

The application of capsaicin cream significantly decreased PPT ($p=0.019$), which indicates that the capsaicin cream may have caused an increase in superficial tissue sensitivity (Chrubasik, Weiser and Beime, 2010). Significant increases in PPT were found from post-

capsaicin (T2) to post-cooling (T3) and from post-capsaicin (T2) to 20-minute post-cooling (T4) following the CHCD interventions, which supports the hypothesis. This is in agreement with previous findings reporting significant increases in perceived pain threshold and tolerance, with a decrease in T_{sk} (Algafly and George, 2007). This suggests that a local analgesic effect occurred, and thus the targeted compressive cryotherapy approach may have the potential to provide short-term pain relief. Despite a trend of increase from post-capsaicin to post-cooling, no significant differences found between time points following ice interventions, which supports the null hypothesis. As this trend was close to statistical significance, any increase in sample size may show more main effects and allow further post hoc testing.

The average relative increases in PPT were 27% (CHCD) and 11% (ice). These relative increases are lower than values reported in the literature at the ankle (71%) (Algafly and George, 2007). However, as PPT varies significantly depending on anatomical location and with increases in PPT at the knee yet to be reported, it is difficult to make a comparison. The MDC for PPT at the tibialias anterior has been reported as 86.2 kPa. The decrease in PPT observed pre- and post-capsaicin application and the increase in PPT from post-capsaicin to post-CHCD intervention were both slightly higher than this (at 95 kPa and 94 kPa respectively). This indicates a potentially clinically meaningful increase in PPT following the CHCD intervention.

As previously discussed an increase in PPT is therapeutically beneficial because more adverse stimuli can be tolerated before a pain response is registered (Chesterton *et al.*, 2002). Therefore, the CHCD interventions could be considered the most effective intervention for pressure pain threshold in a symptomatic population with experimentally induced knee pain.

7.4 Participants with Knee Injuries or Conditions (Chapter 6)

7.4.1 Summary

The third intervention study reported in this thesis aimed to explore the effects of two cryotherapy interventions (1. wetted ice and 2. 10 °C and 50 mmHg using the CHCD) on pain (NPRS), swelling and participant-perceived stability in participants with a range of knee injuries and degenerative conditions. The findings of this study provide an insight into the effects of the optimal intervention identified in Chapter 4 and the current standard clinical treatment (ice), in an injured population. This study is the first study to report the use of the novel CHCD in an injured population, which provided key information for informing the development of optimal cryotherapy interventions for knee injury management.

Clinically important reductions in patient-reported pain were reported in 48% of CHCD interventions and 39% of ice interventions. Clinically important swelling reductions were recorded in 48% of CHCD interventions and in 27% of ice interventions. Only 3% of ice interventions and 6% of CHCD interventions observed clinically important increases in patient-reported stability. In regard to the sum of clinically important changes, CHCD was the most effective intervention for 9 individuals with knee injuries. Compressive cryotherapy, using the CHCD, appeared more beneficial for the majority (82%) of individuals with knee injuries, reducing swelling and pain, compared to wetted ice.

7.4.2 Clinical Implications

7.4.2.1 Swelling

This study reports the first findings of clinically important swelling reduction following a targeted CHCD intervention for most individuals (73%) with a range of knee injuries. In 48% of the CHCD interventions applied in the series of 11 single-case experiments, a clinically important swelling reduction was observed. Whereas 27% of the ice interventions applied in the series of 11 single-case experiments provided a clinically important swelling reduction. For the CHCD interventions, medium to small effect sizes were observed for Days 1, 2 and 3 (d=0.3, d=0.2, d=0.1), with the greatest average reduction in swelling observed on Day 1. For the ice interventions, medium to small effect sizes were observed for Days 1, 2 and 3 (d=0.2, d=0.1, d=0.1), with the greatest average reduction in swelling observed on Day 1. Therefore, a 20-minute application of the device,

set with a target T_{sk} of 10 °C with 50 mmHg compression, was more effective at reducing local knee swelling than a 20-minute application of the current standard clinical treatment of ice. This could have been due to the controlled compression used in conjunction with the cooling used within the CHCD intervention. This theory is supported by previous studies which have reported enhanced therapeutic effects from compressive cryotherapy in comparison with cryotherapy alone (Song *et al.*, 2016). These findings are comparable to Sari et al. (2019) which compared the effects of intermittent pneumatic compression (45 mmHg) and cold-pack treatments on clinical outcomes in patients with knee osteoarthritis. Significant improvements in range of motion, muscle strength, pain intensity, and functional status were reported for both treatment groups but interestingly, greater swelling reduction was observed in the intermittent pneumatic compression group compared to the cold-pack treatment group. Sari et al. (2019) reported an average reduction in knee swelling from pre-to-post treatment of 2cm (intermittent pneumatic compression) and 0.5cm (cold pack). However, it is important to note that both groups also used ultrasound, TENS, electrical stimulation, and exercise, in addition to one of the interventions (either a cold-pack or the intermittent pneumatic compression).

7.4.2.2 Pain

This study reports the first findings of clinically meaningful pain relief following a targeted CHCD intervention for the majority of individuals with a range of knee injuries and degenerative conditions. Across the series single-case experiments, CHCD provided a clinically important reduction in participant-reported pain in 48% of the interventions. Medium to small effect sizes were observed through Days 1, 2 and 3 (d=0.5, d=0.4, d=0.2), with the greatest average reduction in pain seen on Day 1. In comparison, ice provided a clinically important reduction in participant-reported pain 39% of the interventions. Similarly, small to medium effect sizes were observed on Days 1, 2 and 3 (d=0.3, d=0.5, d=0.2) (Tables 2-7) but interestingly, the greatest average reduction in pain was seen on Day 2. Therefore, the 20-minute CHCD intervention provided a clinically important reduction in pain associated with knee injuries, 9% more frequently than the 20-minute standard clinical treatment of ice. Ice has a widely accepted beneficial analgesic effect for pain relief (Bleakley *et al.*, 2011). However, the analgesic effect following targeted compressive cryotherapy interventions is less understood.

7.4.2.3 Stability

The CHCD provided a clinically important increase in participant-reported stability 6% of the interventions and ice provided a clinically important increase in participant-reported stability 3% of the interventions. Only one small effect size was observed for average participant-reported stability within the series of single-case experiment which consisted of an increase in stability following the CHCD intervention on Day 1 (d=0.2). All other changes had no effect size (d<2). Therefore, both interventions provided little and comparable effects on participant-reported stability.

7.5 Grouped Data

Table 7.1 presents a summary of the average pre- and post- measurements for each outcome measure and intervention for all three intervention studies. A colour coded system has been used throughout Table 7.1, to indicate clinically important changes and statistically important changes (see key below). As some outcome measures were collected in more than one study, Table 7.1 presents the opportunity to compare muscle strength, pressure pain threshold, joint position sense and numeric pain rating scale across different participant groups.

Key
Clinically Important Change
Statistically Important Change
Both Statistically and Clinically Significant

Table 7.1: A summary of grouped data within the three intervention studies presented in this thesis

		Healthy Participants (Chapter 4)				Induced Knee Pain (Chapter 5)		Knee Injuries (Chapter 6)	
		10/50 mmHg	15/50 mmHg	10/32 mmHg	10-40/25-50 mmHg	10/50 mmHg	Wetted ice	10/50 mmHg	Wetted ice
Thermal Comfort	Pre	0.0	0.0	0.0	0.0				
	Post	1.0	0.0	0.0	0.0				
	20 Mins Post	0.0	0.0	0.0	0.0				
	Pre-Post	**1.0**	**0.0**	**0.0**	**0.0**				
	Pre-20 Mins Post	**0.0**	**0.0**	**0.0**	**0.0**				
Thermal Sensation	Pre	0.2	0.5	0.3	0.1				
	Post	-1.2	-0.6	-0.5	0.1				
	20 Mins Post	0.2	0.1	0.2	0.0				
	Pre-Post	**-1.4***	**-1.1***	**-0.8**	0.0				
	Pre-20 Mins Post	**0.2**	**0.1**	**0.2**	**0.0**				
SmO_2 (%)	Pre	60.1 (14.1)	59.9 (14.5)	58.7 (12.8)	**0.0**				
	Post	57.5 (12.9)	57.9 (10.3)	61.3 (14.0)	56.8 (12.8)				
	20 Mins Post	59.3 (13.9)	49.1 (17.0)	59.9 (15.0)	53.6 (15.6)				
	Pre-Post	**-2.6**	**-2.0**	**2.6**	**-1.4**				
	Pre-20 Mins Post	**-0.9**	**-10.8**	**1.2**	**-4.6**				

T_{sk} (°C)	Pre	27.6 (1.4)	28 (1.6)	27.6 (1.1)	28.6 (1.3)			
	Post	14.2 (1.2)	17.9 (0.8)	14.3 (0.6)	27.5 (5.1)			
	20 Mins Post	25.2 (1.3)	26.3 (1.6)	25.4 (0.9)	28.9 (1.4)			
	Pre-Post	**13.4***	**10.1***	**13.3***	**1.1**			
	Pre-20 Mins Post	**2.5***	**2.1***	**2.3***	**-0.3**			
Strength (Nm/kg)	Pre	1.1 (0.3)	1.0 (0.2)	1.1 (0.3)	1.1 (0.2)	1 (0.2)	1.2 (0.3)	
	Post	1.1 (0.3)	1.0 (0.2)	1.0 (0.3)	1.1 (0.2)	1 (0.2)	1 (0.2)	
	20 Mins Post	1.1 (0.3)	1.0 (0.2)	1.1 (0.3)	1.1 (0.1)	1 (0.3)	1.1 (0.3)	
	Pre-Post	**0.0**	**0.0**	**-0.1**	**0.0**	**0.0**	**-0.2**	
	Pre-20 Mins Post	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
JPS (ROM, sagittal plane) (°)	Pre	43.6 (7.3)	46 (8.5)	42.9 (6.0)	49.2 (6.1)	43.1 (7.4)	42.9 (7.8)	
	Post	41.6 (7.9)	42.6 (6.3)	43.2 (8.1)	43.8 (5.5)	42.8 (5.1)	45.0 (8.6)	
	20 Mins Post	42.4 (7.0)	41.5 (6.5)	44.1 (6.1)	43 (6.0)	42.8 (6.8)	44.5 (7.6)	
	Pre-Post	**-2.0**	**-3.4**	**0.3**	**-5.4**	**-0.3**	**2.1**	
	Pre-20 Mins Post	**-1.2**	**-4.5**	**1.2**	**-6.2**	**-0.3**	**1.6**	

PPT (kPa)	Pre	374 (126.5)	387.7 (144.1)	435.4 (166.6)	445.9 (109.1)	347.9 (184.7)	356.5 (231.7)		
	Post	398.5 (148.7)	411.9 (185.3)	464.2 (196.6)	447.5 (137.4)	442.3 (224.8)	394.8 (240.3)		
	20 Mins Post	428.2 (150.1)	436.7 (233.4)	496.5 (214.7)	437.4 (132.6)	416.2 (217.6)	406.6 (212.1)		
	Pre-Post	**24.5**	**24.2**	**28.8**	**1.6**	**94.4***	**38.3**		
	Pre-20 Mins Post	**54.2**	**49.0**	**61.1**	**-8.5**	**68.3**	**50.1**		
NPRS	Pre					2.3	2.1	Day 1 Pre	4.1	3.6
	Post					0.3	0.5	Day 1 Post	2.8	2.9
	20 Mins Post					0.0	0.2	**Pre-Post**	**-1.3**	**-0.7**
	Pre-Post					**-2.0**	**-1.6**	Day 2 Pre	3.5	2.2
	Pre-20 Mins Post					**-2.3**	**-1.9**	Day 2 Post	2.5	1.7
								Pre-Post	**-1.0**	**-0.5**
								Day 3 Pre	2.2	2.2
								Day 3 Post	1.7	1.9
								Pre-post	**-0.5**	**-0.3**
Knee Circumference (cm)	Day 1 Pre								39.5	39.2
	Day 1 Post								38.7	38.8
	Pre-Post								**-0.7**	**-0.4**
	Day 2 Pre								39	38.9
	Day 2 Post								38.5	38.6
	Pre-Post								**-0.5**	**-0.3**

	Day 3 Pre			38.7	38.5
	Day 3 Post			38.3	38.4
	Pre-Post			**-0.4**	**-0.1**
	Day 1 Pre			5.2	5.7
	Day 1 Post			5.7	6.0
	Pre-Post			**0.5**	**0.4**
	Day 2 Pre			6.0	6.0
Stability	Day 2 Post			6.3	6.2
	Pre-Post			**0.2**	**0.2**
	Day 3 Pre			6.7	6.7
	Day 3 Post			6.7	6.8
	Pre-Post			**0.0**	**0.1**

Overall, Table 7.1 highlights that the compressive cryotherapy intervention, using the CHCD at 10 °C and 50 mmHg, recorded more statistically and clinically important changes than ice, in a symptomatic population (experimentally induced knee pain, knee injuries and degenerative conditions). The findings support previous literature advocating the use of cryotherapy to provide short-term pain relief (Bleakley, McDonough and MacAuley, 2006; Alexander, Allan and Rhodes, 2021; Allan *et al.*, 2022). Table 7.1 also highlights the justification for the selection of 10 °C and 50 mmHg as the optimal intervention from the study reported in Chapter 4, to then be explored further in Chapters 5 and 6.

Quadriceps strength was recorded in both a healthy male population (Chapter 4) and a healthy population with experimentally induced knee pain (Chapter 5). When comparing the grouped data in Table 7.1, the CHCD intervention set at 10 °C and 50 mmHg presented comparable strength measurements in both population groups (1.1 and 1.0 Nm/kg). This suggests that the experimentally induced knee pain using capsaicin cream, did not influence quadriceps strength, which conflicts previous research demonstrating that experimental knee pain reduced knee extension and flexion muscle strength (Henriksen, 2011). However, this may not be a true comparison as Henriksen (2011) used hypertonic saline (5.8% solution) injected into the infrapatellar fat pad, opposed to topical capsaicin cream.

Joint position sense was recorded in both a healthy male population (Chapter 4) and a healthy population with experimentally induced knee pain (Chapter 5). When comparing the grouped data for the healthy participant population and the healthy population with experimentally induced knee pain population, the CHCD intervention set at 10 °C and 50 mmHg presented comparable ROM in the sagittal plane in both population groups. Interestingly, ice interventions produced an opposite response, increasing ROM in the sagittal plane. This could suggest an increase in instability during knee flexion following ice interventions. However, it is important to note that this increase in ROM in the sagittal plane actually produced a joint angle closer to the target angle of 45° following ice.

Pressure pain threshold was recorded in both a healthy male population (Chapter 4) and a healthy population with experimentally induced knee pain (Chapter 5). When comparing the grouped data for the healthy participant population and the healthy participants with experimentally induced knee pain population, the CHCD intervention set

at 10 °C and 50 mmHg presented comparable PPT measurements in both population groups (PPT ranged from 374 to 428 kPa in a healthy population and 348 to 442 kPa in a population with experimentally induced pain). Interestingly, the CHCD intervention set at 10 °C and 50 mmHg achieved a greater increase in PPT in the healthy participants with experimentally induced knee pain population (+94 kPa) than the healthy male population (+24.5 kPa). This suggests that the cooling intervention may potentially be more beneficial when the subjects are symptomatic. Although, this may just be because the baseline value in the population with induced pain was lower due to the effect of the capsaicin cream and therefore, the change from pre- to post- appears more significant.

Participant-reported pain was recorded, using the numeric pain rating scale, in both a healthy population with experimentally induced knee pain (Chapter 5) and a population with knee injuries or degenerative knee conditions (Chapter 6). When comparing the grouped data for the healthy population with experimentally induced knee pain population and the participants with knee injuries, the CHCD intervention set at 10 °C and 50 mmHg presented different levels of NPRS pain. The healthy participants with experimentally induced knee pain presented lower NPRS scores, ranging between 0 and 2.3. Whereas the participants with knee injuries and degenerative conditions presented relatively higher NPRS pain scores ranging from 1.7 to 4.1.

7.6 Limitations & Strengths

7.6.1 Limitations

As with all research, it is important to consider and identify research limitations and discuss possible improvements for future research. Chapters 4, 5 and 6 addressed some of the research limitations associated with each individual intervention study. Despite data collection and analysis methods being controlled as much as possible, a number of limitations still exist and are discussed within this section.

One of the main limitations of the studies was that the novel CHCD used was a 'production quality prototype', which may have affected the performance of the device. Due to the nature of the product being in prototype stage, there were usability issues encountered such as straps slipping during compression and possible small leaks in the air bladder. This may have been a factor influencing the lack of significance across the different pressure levels and the ineffective compression applied in the first study. The compression design of the prototype was then amended for the following two studies.

Another limitation of the studies reported in this thesis were in relation to the samples investigated. The sample sizes used for Chapter 4 and 5 were calculated to be sufficient for measuring to provide adequate power of 80%. However, a larger sample would have provided greater power and may have provided more indication of strong trends which were observed for some outcome measures but found to be not statistically significant. In addition, a convenience sampling method was adopted, recruiting within the university staff and student populations in a sport and health science cohort. Despite never using this particular CHCD previously, most of the participants were familiar with cryotherapy interventions and had previous experience with other cryotherapy modalities. Convenience sampling of this nature can limit external validity, which limits the ability to generalise the findings to a wider population outside of the sport and health science cohort (Andrade, 2020). Furthermore, only healthy male participants were recruited for the first study reported in this thesis, which limits the transferability of these findings to a female population. Although, the subsequent two studies did recruit all genders.

Due to significant delays and changes to the medical device regulation processes following Brexit, the CHCD did not have a medical grade CE mark which meant that a

randomised controlled trial in a clinical setting was not yet possible. Therefore, in order to assess interventions on a symptomatic population, research design adaptations had to be made to address these restrictions. After discussions with the Medicines and Healthcare products Regulatory Agency (MHRA) and the U.S Food and Drug Administration (FDA), it was determined that the device could be launched as a 'wellness device'. It is also important to highlight that technical evaluations of earlier prototypes of the CHCD had demonstrated that the device was safe to use (Selfe *et al.*, 2017), in addition to the research carried out on a healthy population outline in Chapter 4. Therefore, the risk of adverse effects on population with knee injuries and degenerative conditions remained low, regardless of research design adaptations.

Chapter 6 addressed the main limitations associated with single-case experimental designs. The series of single-case experiments provided preliminary evidence of the effectiveness of the CHCD intervention on a small population with knee injuries, which indicates that a larger study is warranted to evaluate the effectiveness of these cryotherapy interventions on a wider population, and a wider range of soft tissue injuries. As the series of single-case experiments provided insight into clinically important changes for each individual, a randomised controlled trial would provide further statistical analyses to add to these preliminary findings.

All intervention studies within this thesis assessed the immediate effects of the interventions. Therefore, the author is unable to analyse if any changes were maintained over a longer period of time and if any longer-term effects occurred. Further work should consider longer-term effects over a longitudinal study to identify the effects of targeted cryotherapy interventions throughout the rehabilitation period from the point of injury to 'return to play'.

7.6.2 Strengths

The main strength of this thesis is that the research carried out is the first of its kind to utilise a novel CHCD which can accurately control time, temperature and pressure parameters, in order to explore a range of clinical interventions for knee injury management. This thesis highlighted the huge gap in the literature in relation to understanding the complex relationships between time, temperature and compression and this study provided an insight into the effect of different interventions as a first step to defining optimal evidence-based interventions for knee injury management.

The ability to accurately manipulate temperature and compression has not previously been possible with traditional methods of cryotherapy, such as ice. Therefore, the novel contributions to knowledge presented in this thesis can be used to inform and direct further investigations for future research aiming to define optimal interventions. In addition, this thesis explored a wide range of outcome measures which considered biomechanical, subjective, functional and physiological factors, across three different participant groups, and ultimately provided a comprehensive insight into the efficacy and effectiveness of the interventions for knee injury management. Although, it is important for future research to expand on these early indications, to further develop evidence-base interventions to allow clinicians to adopt a 'personalised' approach to cryotherapy intervention, based on robust evidence that particular injury or individual characteristics.

For the series of single-case experiments, multi-treatment interference was minimised by adopting a counterbalancing approach within this study, which involves randomising the order of interventions. Further to this, there was a minimum of 2-hour lightly active washout period between interventions to allow the rewarming of skin surface temperature and intramuscular temperature, in order to minimise the multi-treatment interference.

Lastly, the range of research designs included in this thesis (randomised crossover design and single-case experiments) facilitated a wider range of analysis techniques which considered both statistically important results and clinically important changes. Capturing both statistically important results and clinically important changes provided greater insight into both the efficacy and the effectiveness of the interventions, which ultimately

informed the development of optimal evidence-based interventions. Importantly, these findings can be implemented into clinical practice.

7.7 Contributions to Knowledge

With no optimal interventions defined in literature for cryotherapy or contrast therapy, this research aimed to create new knowledge through the development of evidence-based optimal clinical interventions using a novel CHCD on a range of participant groups and clinical outcomes. The CHCD offers full control on temperature (from 6 to 40°C), compression (from 20 to 75 mmHg) and time (from 1 to 20 minutes), enabling detailed study exploring the unknowns highlighted in purple in Chapter 1, Figure 1.3.

This thesis has provided preliminary evidence supporting the use of targeted cryotherapy, using a novel device set at 10 °C and 50 mmHg, to provide short-term pain relief and swelling reduction for knee injury management. Compressive cryotherapy, using the CHCD at 10 °C with 50 mmHg compression, appeared more beneficial for the majority (82%) of individuals with knee injuries, for reducing swelling and pain, compared to wetted ice.

Three conference abstracts have been presented as part of this PhD research degree at national physiotherapy conferences.

Physiotherapy UK 2020:

1) An exploration of targeted cryotherapy protocols, using the Swellaway Knee Unit, on healthy male subjects (Rapid 5)
2) An exploration into the effectiveness of cryotherapy modalities on patients with degenerative knee conditions, through a series of single-case experiments (Poster)

Physiotherapy UK 2021:

3) Exploring effects of cryotherapy modalities on pain, muscle strength and joint position sense in healthy participants with induced knee pain (Poster)

There is a significant lack of knowledge surrounding the use of contrast therapy for injury management. It has previously been difficult to apply controlled contrast therapy as a therapeutic option for soft tissue injury management and therefore therapists have not fully explored this treatment option. In turn, the limited literature available has used either water immersion or ice packs and hot packs (hydrocollator packs) to provide and explore contrast therapy. The novel device provided the ability to control temperature and compression parameters, and therefore this study can include controlled contrast therapy within the range of temperature and compression interventions explored. A scoping review titled 'The Use of Contrast Therapy in Soft Tissue Injury Management and Post-Exercise Recovery: A Scoping Review' has been published in Physical Therapy Reviews, as part of this thesis. Despite being a common therapeutic method used particularly in sporting settings, the scoping review highlights a lack of evidence, with the majority of research on contrast therapy using contrast water therapy, with a primary purpose of post-exercise recovery. This study presented the first rewarming curve following a local contrast therapy application. However, it is clear that further investigation is required in order to explore different contrast therapy protocols including, cycle durations, cycle temperatures and frequency of cycles.

7.8 Impact of COVID-19

This PhD commenced in April 2019 and therefore was inevitably impacted by the global pandemic, COVID-19. The pandemic struck mid-way through data collection for Study 2, which resulted in the suspension of face-to-face research and consequently, a delay to this particular study. Fortunately, data had just been collected for Studies 1 & 3, so I was able to analyse the data during the lockdown period, with remote support from my supervisory team. I completed COVID-19 risk assessments and put additional safety measures in place (i.e., personal protective equipment) to ensure a safe return to data collection in the lab as soon as possible. This pro-active approach meant that this was the first research project restarted at the university once the suspension of face-to-face research had been lifted.

Chapter 8: Recommendations for Clinical Practice

8.1 Introduction

This chapter discusses recommendations for optimal CHCD interventions for knee injury management based on the research undertaken. Recommendations for optimising clinical cryotherapy interventions are presented in the form of a new acronym '**OPTIMISE**'.

8.2 OPTIMISE - Considerations for optimising clinical cryotherapy interventions

Table 8.1 presents a summary of the 'OPTIMISE' acronym, designed to help clinicians remember the recommendations. Each recommendation is then discussed further within this chapter.

Table 8.1: Recommendations for optimising clinical cryotherapy interventions presented in the form of an acronym 'OPTIMISE'

'OPTIMISE' **An act, process, or methodology of making something as effective as possible**	
O	**Optimal Loading** The POLICE guidelines have been published to encourage early weight-bearing to promote early recovery. Targeted cryotherapy interventions have the potential to achieve short-term pain relief, whilst minimising these adverse effects to dynamic stability and muscle strength, to ensure a safer return to weight bearing and encourage optimal loading where appropriate. *Consider the patient's dynamic stability and strength following cooling interventions to ensure safer returns to weight-bearing exercises*

P	**Personalise** There is a growing realisation that a number of factors such as age, gender, adipose tissue and skin type have a significant bearing on the dose–response to cryotherapy. A 'one-size fits all' approach is unlikely to bring the optimal clinical benefits. Novel devices which can control temperature, time and compression provide an opportunity to personalise cryotherapy to individual. *Consider individual factors such as gender, BMI, age, skin type and injury location and tailor cryotherapy interventions using novel technology where possible.*
T	**Targeted Approach** A targeted cryotherapy approach may minimise adverse effects to muscle strength and dynamic stability, which has been reported following ice interventions. This approach may be more beneficial if you are able to diagnose and pinpoint the location of the injury, in order to return to optimal loading earlier. *Consider utilising a targeted cryotherapy approach to ensure a safer return to weight bearing and encourage optimal loading, where appropriate.*
I	**Ideal Therapeutic Range** An ideal therapeutic range for T_{sk} as 10-15 °C is well accepted in literature, due to the recognition of physiological responses to different skin and tissue temperatures. It is now a key parameter to assess the efficacy of a cooling intervention. This thesis identified that the optimal temperature setting on the CHCD is 10 °C, in order to achieve T_{sk} within the ideal therapeutic range to potentially initiate the desired physiological response to cooling. *Consider CHCD temperature settings in order to optimise the efficacy of a cooling intervention.*
M	**Multi-faceted** Research has stressed the importance of considering biomechanical, psychological and physiological factors when selecting a cryotherapy intervention, to provide a more comprehensive understanding of the effects of different compressive cryotherapy interventions. Clinicians can consider the effects on a range of factors in order to determine the most beneficial protocol, dependent upon the aim of the intervention. *Consider biomechanical, functional, psychological and physiological factors when selecting an intervention.*

I	**Injury Stage** Cryotherapy is advocated for acute injury management. Both cold, heat or contrast are advocated for chronic conditions such as knee OA. Evidence has suggested that the interventions success was dependent on individual preference and greater clinical improvements were observed when patients were using their preferred modality. This thesis identified that compressive cryotherapy using the CHCD may be more beneficial than ice, for the majority of individuals with knee injuries and degenerative knee conditions. However, as contrast therapy is also advocated for chronic stages of injury, future research should explore the use of heat and contrast therapy protocols for the management of degenerative knee conditions. *Consider whether cooling, heating or contrast therapies would be most beneficial for patients in sub-acute and chronic stages of injury.*
S	**Self-Manage** Patient-centred care is recommended for chronic conditions as a tool to increase patient empowerment and optimise self-management. Self-management of chronic conditions can improve the patient's quality of life, functional capacity, pain free days, autonomy and independence but also reduces the burden on the NHS. *Consider practical solutions for patients to manage their own chronic knee condition symptoms independently, to reduce the strain on the NHS and increase patient empowerment.*
E	**Evidence-Based** This thesis has provided evidence to support the use of a novel cooling, heating and compression device to achieve the ideal therapeutic range, in order to initiate a local analgesic effect. Defining optimal compressive cryotherapy interventions should adopt an evidence-based approach in order to optimise the efficacy and effectiveness of clinical protocols for knee injury management. *Consider if the intervention will achieve skin temperature within the ideal therapeutic-range or achieve the desired clinical effects.*

8.2.1 Optimal Loading

As discussed in Chapter 2, the update to change **PRICE** *(Protection, Rest, Ice, Compression and Elevation)* to **POLICE** *(Protection, Optimal Loading, Ice, Compression and Elevation)* was considered not only a guideline but also a reminder to clinicians to consider optimal loading for different patients and stimulus for new research. Optimal loading involves replacing rest with a balanced and progressive rehabilitation programme, aiming to promote early recovery with early activity and weight bearing (Bleakley, Glasgow and MacAuley, 2012). With the evidence of functional treatment methods including early mobilisation and weight bearing being more effective than immobilisation, 'tissue loading' is considered an essential part of soft tissue injury management (Bleakley *et al.*, 2011). Previous research has indicated inhibition to muscle strength and dynamic stability following local cryotherapy interventions and therefore advise players to be cautious returning to weight bearing activity, particularly following knee joint cooling (Alexander *et al.*, 2016; Rhodes and Alexander, 2018; Alexander *et al.*, 2018). Therefore, the ability to apply cooling to provide the desired short-term pain relief, whilst minimising the adverse effects to strength and dynamic stability, would have therapeutic benefits.

This thesis identified that targeted cryotherapy interventions have the potential to achieve short-term pain relief, whilst minimising these adverse effects. These findings reported in this thesis suggest that clinicians could consider using a targeted cooling approach, using the CHCD, to ensure a safer return to weight bearing and encourage optimal loading where appropriate.

8.2.2 Personalise

Chapters 1 and 2 highlighted the number of factors that affect an individual's response to thermal stress such as age, gender, adipose tissue and skin type (Fu *et al.*, 2016). There is a growing realisation these factors have a significant bearing on the dose–response to cryotherapy (Selfe *et al.*, 2020) and it has been highlighted that a 'one-size fits all' approach is unlikely to be effective across the entire soft tissue injury spectrum (Bleakley *et al.*, 2011). In turn, researchers have begun to consider these factors more closely in an attempt to 'personalise' cryotherapy to the individual (Selfe *et al.*, 2020).

Previously it has been difficult to control and maintain temperature, compression, and time parameters in order to achieve personalisation with cryotherapy. With the advancement in technology, the CHCD provides an opportunity to personalise cryotherapy. This thesis has provided an insight into the effects of different cryotherapy interventions across a range of population groups and has suggested that compressive cryotherapy may be more beneficial than ice alone. However, further research is required in this field to provide a greater understanding of the effects of gender, age, adiposity, and skin type, in order to inform optimal personalised protocols for different individuals and across a wider range of soft tissue injuries.

8.2.3 Targeted Approach

As discussed, previous research has indicated inhibition to muscle strength and dynamic stability following local cryotherapy interventions and therefore advise players to be cautious returning to weight bearing activity, particularly following knee joint cooling (Uchio *et al.*, 2003; Surenkok *et al.*, 2008; Costello and Donnelly, 2010; Alexander *et al.*, 2016; Rhodes and Alexander, 2018; Alexander *et al.*, 2018). Therefore, the ability to apply cooling to provide the desired short-term pain relief, whilst minimising the adverse effects to strength and dynamic stability, would have therapeutic benefits.

The findings outlined in chapters 4 and 5 identified that targeted cryotherapy interventions, using the CHCD, have the potential to achieve short-term pain relief, whilst minimising adverse effects to muscle strength and dynamic stability. Therefore, clinicians could consider utilising a targeted cryotherapy approach to achieve the desired short-term pain relief, whilst facilitating a safer return to weight bearing. It is important to consider that immediately following a trauma, it can be difficult to precisely diagnose injured tissue until further investigations are carried out. This does not militate against the use of the CHCD. Hypothetical deductive reasoning will consider the mechanism of injury and early examination findings which can suggest possible lesion/lesions and will identify heat, swelling and site of pain.

8.2.4 Ideal Therapeutic Range

Rivenburgh (1992) first proposed an ideal therapeutic range for T_{sk} as 10-15 °C, due to the recognition of physiological responses to different skin and tissue temperatures. It is now used as a key parameter to assess the efficacy of a cooling intervention (Kennet *et al.*, 2007; Selfe *et al.*, 2020).

This thesis identified that the optimal temperature setting on the CHCD is 10 °C, in order to achieve T_{sk} within the ideal therapeutic range to potentially initiate the desired physiological response to cooling such as a local analgesic effect, reduced blood flow, metabolic activity and secondary damage. T_{sk} within the ideal therapeutic range was not achieved when the device was set to 15 °C, and therefore would be considered an ineffective cryotherapy intervention.

With the advancement in technology offering the ability to control temperatures applied on the surface of the skin more accurately, future research should consider assessing whether the ideal therapeutic range is actually the optimum range for acute injury management. It is well accepted that metabolism is reduced with tissue temperatures between 5-15 °C and every 10 °C decrease in tissue temperature decreases the rate of chemical reactions by 2-to-3-fold according to Van't Hoff's law (Bleakley and Hopkins, 2010). Additionally, an analgesic effect has been demonstrated for skin temperatures below 13 °C (Bugai, 1975; Bleakley *et al.*, 2011). Although, it is important to consider that these values are not definite values and are based on averages provided from the best current evidence (Bleakley *et al.*, 2011). With that being said, it is reasonable to argue that T_{sk} between 13- 15 °C may not be as therapeutically beneficial as T_{sk} between 10-13 °C, as it could be less likely to induce an analgesic effect. Authors have advised that T_{sk} should not be reduced below 5 °C, as T_{sk} below this can cause adverse effects such as ice burns (Bleakley and Hopkins, 2010; Matos *et al.*, 2015). However, T_{sk} ranging between 5-10 °C should be considered in future research, now it is possible to explore this range in a controlled manner through new innovative technology.

8.2.5 Multi-faceted

Multifaceted interventions are defined as 'any intervention including two or more components' by Cochrane Effective Practice and Organisation of Care Group (Squires *et al.*, 2014). As previously discussed, the complex relationship between time, temperature and compression is yet to be fully understood. Alexander et al (2021a) highlighted the importance of considering biomechanical, subjective, functional and physiological factors, in order to provide a more comprehensive understanding of the effects of different compressive cryotherapy interventions and optimise outcomes dependent on the aim of the intervention. The following factors were considered in this thesis:

- Biomechanical factors through the assessment of joint position sense
- Functional factors through the assessment of muscle strength
- Physiological factors through the assessment of surface temperature and muscle oxygenation
- Subjective factors through the assessment of thermal sensation and comfort, pressure pain threshold and pain (NPRS)

Considering these factors contributes to a greater understanding of the efficacy and effectiveness of compressive cryotherapy interventions. This thesis presented the effects of a range of outcome measures on different population groups to contribute to the development of optimal clinical protocols. However, with the complex relationship between time, temperature, and compression yet to be fully understood, further research is required to provide a comprehensive understanding of dose-response on biomechanical, physiological, functional and psychological factors.

8.2.6 Injury Stage

Cryotherapy is advocated in the latest clinical guidelines for acute injury management (Bleakley *et al.*, 2011). Both cold, heat or contrast therapies are advocated for chronic conditions such as knee OA (NICE, 2014). Denegar et al. (2010) concluded that the selection of heat, cold or contrast on knee OA patients was dependent on individual preference. Greater pain relief and functional improvements were observed when patients were using their preferred modality.

This thesis explored the effects of different cryotherapy interventions on a range of knee injuries and the findings suggested that compressive cryotherapy using the CHCD may be more beneficial than ice, for the majority of individuals with knee injuries and degenerative knee conditions. However, as contrast therapy is also advocated for chronic stages of injury, future research should explore the use of heat and contrast therapy protocols for the management of degenerative knee conditions.

8.2.7 Self Manage

Patient-centred or person-centred care is recommended for chronic conditions as a tool to increase patient empowerment and optimise self-management (Pulvirenti, McMillan and Lawn, 2014). Patient self-management has been described as *"a set of tasks and processes that are used by a patient to maintain wellness in the presence of an ongoing illness" (Lorig and Holman, 2003).* Self-management of chronic conditions can improve the patient's quality of life, functional capacity, pain free days, autonomy and independence but also reduces the burden on healthcare system (NICE, 2014; Pulvirenti, McMillan and Lawn, 2014; Rochfort *et al.*, 2018). A core competency of healthcare professionals is the ability to 'promote patient empowerment and self-management', as set out by the World Organisation of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA, 2011). The Chronic care model (CCM) was developed more than a decade ago and is an internationally recognised model for the management of non-communicable diseases such as knee OA (Wagner, Austin and Von Korff, 1996; Rochfort *et al.*, 2018). The CCM aims to achieve optimum outcomes for patients through a productive interaction between "*an informed activated patient and a prepared proactive practice team" (Rochfort et al., 2018).* Through appropriate education from healthcare multidisciplinary teams, patients can often take ownership of managing the symptoms of their chronic condition, which in turn develops the patients understanding of their condition. This also enables patients to be more proactive and involved in treatment strategies and make informed lifestyle decisions to better self-manage their chronic condition (Pulvirenti, McMillan and Lawn, 2014; Rochfort *et al.*, 2018). Improvements in health care have contributed to an increase in people living with chronic conditions for longer (Grady and Gough, 2014).

This thesis identified that compressive cryotherapy may be more beneficial than ice alone, for the majority of individuals with knee injuries and degenerative knee conditions. In addition to chronic conditions, the clinical guidelines for acute injury management (POLICE) outlined in Chapter 2 (section 2.3.1), can also carried out independently by patients. The novel CHCD can be used by an individual at home on their own, without the assistance of a healthcare professional. It is easy to operate at home and when travelling and may be considered more practical as no ice, water or tethering to a plug socket is required. Therefore, the CHCD presents the opportunity for patients to manage their own symptoms independently, which in turn could contribute to reducing the strain on the NHS and empower the patient to take control.

8.2.8 Evidence-Based

An evidence-based approach to decision making is based on combining the best available evidence and critical thinking (Johnson, 2008; Carter and Lubinsky, 2015). This approach takes the dependance away from anecdotes and personal experience, which are less reliable sources on their own. It is often a misconception that evidence-base practice means 'evidence only', whereas the approach supports the use of three elements combined (Johnson, 2008; Carter and Lubinsky, 2015):

1) *Best evidence*
2) *Patient values*
3) *Clinical experience*

This thesis has provided evidence to support the use of a novel cooling, heating, and compression device to achieve the ideal therapeutic range, in order to initiate a local analgesic effect. Defining optimal compressive cryotherapy interventions will aid clinicians in developing personalised interventions for knee injury management.

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Appendix A: Consent and Screening Forms

Consent Forms

Study 1A

CONSENT FORM

Title of study: The development of optimal therapeutic protocols using the Swellaway Knee Unit, on healthy male subjects

Name of Researchers: Olivia Greenhalgh, Prof. Jim Richards, Jill Alexander-Riley

Please answer the following questions to consent to your participation in the study:

Please initial box

1. I confirm that I have read and understand the information sheet provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand what is required of me for the assessment, and the protocol has been explained to me fully ☐
3. I understand that my participation in this study is voluntary, and I am free to withdraw at any time without giving any reason and without my legal rights being affected. However, once my data has been anonymised it will not be possible to remove this. ☐
4. I agree to take part in the above study: ☐

Name of Participant	**Date**	**Signature**
Name of Person Taking consent (if not researcher)	**Date**	**Signature**
Name of Researcher taking consent	**Date**	**Signature**

Manchester Metropolitan University

V1: 06/02/19

PARTICIPANT CONSENT FORM

Title of study: The development of optimal therapeutic protocols using the Swellaway Knee Unit, on healthy male subjects

Name of Researchers: Olivia Greenhalgh, Prof. James Selfe, Dr Chris McCarthy, Prof. Jim Richards, Jill Alexander-Riley

Please answer the following questions to consent to your participation in the study:

Please answer the following questions by providing your initial in the boxes to determine your eligibility to take part in the research:

Please initial in boxes

☐ I confirm that I have read and understand the participant information sheet for the above study.

☐ I have the opportunity to consider the information, ask questions and have these answered satisfactorily.

☐ I have no known medical conditions which may affect my participation in this study.

☐ I understand that my participation in this study is voluntary and I am free to withdraw at any time without giving any reason, without my legal rights being affected.

☐ I agree to take part in the above study.

Thank you for taking the time to read about the study, if you have any questions please do not hesitate to ask.

_____	_____	_____
Name of Participant	**Date**	**Signature**

_____	_____	_____
Name of Researcher taking consent	**Date**	**Signature**

Main Contact:

Olivia Greenhalgh
O.Greenhalgh@mmu.ac.uk
Tel: 07765 696326

Study 2

V1: 20/05/19

PARTICIPANT CONSENT FORM

Title of study: The effectiveness of the Swellaway Knee Unit and wetted ice, on pain, joint position sense and muscle strength in healthy subjects with induced pain.

Name of Researchers: Olivia Greenhalgh, Prof. James Selfe, Dr Chris McCarthy, Prof. Jim Richards, Jill Alexander-Riley

Please answer the following questions to consent to your participation in the study:

Please answer the following questions by providing your initial in the boxes to determine your eligibility to take part in the research:

Please initial in boxes

☐ I confirm that I have read and understand the participant information sheet for the above study.

☐ I have the opportunity to consider the information, ask questions and have these answered satisfactorily.

☐ I have no known medical conditions which may affect my participation in this study.

☐ I understand that my participation in this study is voluntary and I am free to withdraw at any time without giving any reason, without my legal rights being affected.

☐ I agree to take part in the above study.

Thank you for taking the time to read about the study, if you have any questions please do not hesitate to ask.

_____	_____	_____
Name of Participant	**Date**	**Signature**

_____	_____	_____
Name of Researcher taking consent	**Date**	**Signature**

Main Contact:
Olivia Greenhalgh
O.Greenhalgh@mmu.ac.uk
OGreenhalgh@uclan.ac.uk

Appendix 6

Manchester Metropolitan University

uclan

CONSENT FORM

Title of study:
An exploration into the effectiveness of the Swellaway device through a series of n=1 experiments

Name of Researchers:
Prof. Jim Richards, Jill Alexander-Riley, Olivia Greenhalgh

Please answer the following questions to consent to your participation in the study:

Please initial box

1. I confirm that I have read and understand the information sheet provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand what is required of me for the assessment, and the protocol has been explained to me fully ☐
3. I understand that my participation in this study is voluntary, and I am free to withdraw at any time without giving any reason and without my legal rights being affected. However, once my data has been anonymised it will not be possible to remove this. ☐
4. I agree to take part in the above study: ☐

Name of Participant	**Date**	**Signature**
Name of Person Taking consent (if not researcher)	**Date**	**Signature**
Name of Researcher taking consent	**Date**	**Signature**

Par-Q+ Screening Form

CSEP approved Sept 12 2011 version

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

Regular physical activity is fun and healthy, and more people should become more physically active every day of the week. Being more physically active is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

SECTION 1 - GENERAL HEALTH

	Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1.	Has your doctor ever said that you have a heart condition OR high blood pressure?	☐	☐
2.	Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?	☐	☐
3.	Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4.	Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?	☐	☐
5.	Are you currently taking prescribed medications for a chronic medical condition?	☐	☐
6.	Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer NO if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.	☐	☐
7.	Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.

Go to Section 3 to sign the form. You do not need to complete Section 2.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow the Canadian Physical Activity Guidelines for your age (www.csep.ca/guidelines).
- You may take part in a health and fitness appraisal.
- If you have any further questions, contact a qualified exercise professional such as a CSEP Certified Exercise Physiologist® (CSEP-CEP) or CSEP Certified Personal Trainer® (CSEP-CPT).
- If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the questions above, please GO TO SECTION 2.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant – talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes – please answer the questions on Section 2 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity programme.

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SECTION 2 - CHRONIC MEDICAL CONDITIONS

		Please read the questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1.		Do you have Arthritis, Osteoporosis, or Back Problems?	☐ If yes, answer questions 1a-1c	☐ If no, go to question 2
	1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	☐	☐
	1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	☐	☐
2.		Do you have Cancer of any kind?	☐ If yes, answer questions 2a-2b	☐ If no, go to question 3
	2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?	☐	☐
	2b.	Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?	☐	☐
3.		Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm	☐ If yes, answer questions 3a-3e	☐ If no, go to question 4
	3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	3b.	Do you have an irregular heart beat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)	☐	☐
	3c.	Do you have chronic heart failure?	☐	☐
	3d.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer YES if you do not know your resting blood pressure)	☐	☐
	3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	☐	☐
4.		Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes	☐ If yes, answer questions 4a-4c	☐ If no, go to question 5
	4a.	Is your blood sugar often above 13.0 mmol/L? (Answer YES if you are not sure)	☐	☐
	4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet?	☐	☐
	4c.	Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?	☐	☐
5.		Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)	☐ If yes, answer questions 5a-5b	☐ If no, go to question 6
	5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	5b.	Do you also have back problems affecting nerves or muscles?	☐	☐

Please read the questions below carefully and answer each one honestly: check YES or NO.			YES	NO
6.	Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure		☐ If yes, answer questions 6a-6d	☐ If no, go to question 7
	6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	6b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	☐	☐
	6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	☐	☐
	6d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	☐	☐
7.	Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia		☐ If yes, answer questions 7a-7c	☐ If no, go to question 8
	7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	7b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	☐	☐
	7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	☐	☐
8.	Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event		☐ If yes, answer questions 8a-c	☐ If no, go to question 9
	8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	8b.	Do you have any impairment in walking or mobility?	☐	☐
	8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	☐	☐
9.	Do you have any other medical condition not listed above or do you live with two chronic conditions?		☐ If yes, answer questions 9a-c	☐ If no, read the advice on page 4
	9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months OR have you had a diagnosed concussion within the last 12 months?	☐	☐
	9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	☐	☐
	9c.	Do you currently live with two chronic conditions?	☐	☐

Please proceed to Page 4 for recommendations for your current medical condition and sign this document.

PAR-Q+

If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active:

- It is advised that you consult a qualified exercise professional (e.g., a CSEP-CEP or CSEP-CPT) to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually – 20-60 min. of low- to moderate-intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate-intensity physical activity per week.
- If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the follow-up questions about your medical condition:

- You should seek further information from a licensed health care professional before becoming more physically active or engaging in a fitness appraisal and/or visit a or qualified exercise professional (CSEP-CEP) for further information.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise profesional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes - please talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity programme.

SECTION 3 - DECLARATION

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The Canadian Society for Exercise Physiology, the PAR-Q+ Collaboration, and their agents assume no liability for persons who undertake physical activity. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.
- Please read and sign the declaration below:

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongfully disclose such information.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact:
Canadian Society for Exercise Physiology
www.csep.ca

KEY REFERENCES
1. Jamnik VJ, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the effectiveness of clearance for physical activity participation: background and overall process. APNM 36(S1):S3-S13, 2011.
2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document. APNM 36(S1):S266-s298, 2011.

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or BC Ministry of Health Services.

CSEP | SCPE
THE GOLD STANDARD IN EXERCISE SCIENCE AND PERSONAL TRAINING

CSEP approved Sept 12 2011 version

Appendix B: Ethical Approval

Study 1A

19 December 2018

Olivia Greenhalgh
School of Health Sciences
University of Central Lancashire

Dear Olivia

Re: STEMH Ethics Committee Application
Unique Reference Number: STEMH 953

The STEMH ethics committee has granted approval of your proposal application 'The development of optimal therapeutic protocols using the Swellaway Knee Unit, on healthy male subjects'. Approval is granted up to the end of project date*.

It is your responsibility to ensure that

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

Yours sincerely

Emma Bray
Deputy Vice Chair
STEMH Ethics Committee

Manchester Metropolitan University

01/04/2019
Project Title: Swellaway KTP

EthOS Reference Number: 7880

Ethical Opinion

Dear Olivia Greenhalgh,

The above application was reviewed by the Health, Psychology and Social Care Research Ethics and Governance Committee and, on the 01/04/2019, was given a favourable ethical opinion. The approval is in place until 01/05/2021 .

Conditions of favourable ethical opinion

Application Documents

Document Type	File Name	Date	Version
Additional Documentation	Appendix 10 - 1442 James Selfe Ethical Approval Memo	06/01/2017	V1
Consent Form	Appendix 3 - Consent Form V1	06/02/2019	V1
Recruitment Media	Appendix 6 - Poster MMU V1	06/02/2019	V1
Project Proposal	Appendix 1 - Proposal V2	08/03/2019	V2
Information Sheet	Appendix 5 - Participant Information V2	08/03/2019	V2

The Health, Psychology and Social Care Research Ethics and Governance Committee favourable ethical opinion is granted with the following conditions

Adherence to Manchester Metropolitan University's Policies and procedures

This ethical approval is conditional on adherence to Manchester Metropolitan University's Policies, Procedures, guidance and Standard Operating procedures. These can be found on the Manchester Metropolitan University Research Ethics and Governance webpages.

Amendments

If you wish to make a change to this approved application, you will be required to submit an amendment. Please visit the Manchester Metropolitan University Research Ethics and Governance webpages or contact your Faculty research officer for advice around how to do this.

We wish you every success with your project.

HPSC Research Ethics and Governance Committee

Manchester Metropolitan University

05/07/2019
Project Title: Swellaway Phase II

EthOS Reference Number: 10731

Ethical Opinion

Dear Olivia Greenhalgh,

The above application was reviewed by the Health, Psychology and Social Care Research Ethics and Governance Committee and, on the 05/07/2019, was given a favourable ethical opinion. The approval is in place until 01/05/2021 .

Conditions of favourable ethical opinion

Application Documents

Document Type	File Name	Date	Version
Recruitment Media	Appendix 6 - Poster MMU	20/05/2019	V1
Additional Documentation	Appendix 6 - Capsaicin_ Axsain 0.075pc PIL PL 16260-0016 Jan 2017	20/05/2019	V1
Consent Form	Appendix 3 - Consent Form V3	01/07/2019	3
Information Sheet	Appendix 5 - Participant Information V3	01/07/2019	3
Project Proposal	Appendix 1 - Proposal V3	01/07/2019	3

The Health, Psychology and Social Care Research Ethics and Governance Committee favourable ethical opinion is granted with the following conditions

Adherence to Manchester Metropolitan University's Policies and procedures

This ethical approval is conditional on adherence to Manchester Metropolitan University's Policies, Procedures, guidance and Standard Operating procedures. These can be found on the Manchester Metropolitan University Research Ethics and Governance webpages.

Amendments

If you wish to make a change to this approved application, you will be required to submit an amendment. Please visit the Manchester Metropolitan University Research Ethics and Governance webpages or contact your Faculty research officer for advice around how to do this.

We wish you every success with your project.

HPSC Research Ethics and Governance Committee

05 March 2020

Olivia Greenhalgh
School of Health Sciences
University of Central Lancashire

Dear Olivia

Re: Health Ethics Review Panel Application
Unique Reference Number: HEALTH 0039

The Health Ethics Review Panel has granted approval of your proposal application 'The effectiveness of the Swellaway Knee Unit and wetted ice, on pain, joint position sense and muscle strength in healthy subjects with induced pain.'. Approval is granted up to the end of project date.

It is your responsibility to ensure that

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

Yours sincerely

Julie Cook
Deputy Vice-Chair
Health Ethics Review Panel

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

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

Manchester Metropolitan University

10/10/2019
Project Title: Swellaway n=1 Experiments

EthOS Reference Number: 11729

Ethical Opinion

Dear Olivia Greenhalgh,

The above application was reviewed by the Health, Psychology and Social Care Research Ethics and Governance Committee and, on the 10/10/2019, was given a favourable ethical opinion. The approval is in place until .

Conditions of favourable ethical opinion
** If you are still recruiting, please add the current Manchester Met logos to the PIS and consent forms.

Application Documents

Document Type	File Name	Date	Version
Ethical Approval Supporting Information	Appendix 7- Risk Assessment V1	25/03/2019	V1
Ethical Approval Application Form	Swellaway - ETHICS_FORM_V4	01/04/2019	V4
Ethical Approval Supporting Information	Appendix 2 - Acute Assessment V4	01/04/2019	V4
Ethical Approval Supporting Information	Appendix 3 - Subacute assessment V4	01/04/2019	V4
Ethical Approval Supporting Information	Appendix 5 - Consent form	01/04/2019	V4
Ethical Approval Supporting Information	Appendix 6 - Data Protection Checklist	01/04/2019	V4
Ethical Approval Letter	STEMH 1010 Full Review Approval	31/05/2019	V1
Ethical Approval Supporting Information	Appendix 1 - Protocol V4	02/10/2019	4
Ethical Approval Supporting Information	Appendix 4- Participant Information Sheet V4	04/10/2019	V4

The Health, Psychology and Social Care Research Ethics and Governance Committee favourable ethical opinion is granted with the following conditions

Adherence to Manchester Metropolitan University's Policies and procedures

This ethical approval is conditional on adherence to Manchester Metropolitan University's Policies, Procedures, guidance and Standard Operating procedures. These can be found on the Manchester Metropolitan University Research Ethics and Governance webpages.

Amendments

If you wish to make a change to this approved application, you will be required to submit an amendment. Please visit the Manchester Metropolitan University Research Ethics and Governance webpages or contact your Faculty research officer for advice around how to do this.

We wish you every success with your project.

HPSC Research Ethics and Governance Committee

31 May 2019

Jim Richards/Olivia Greenhalgh
School of Health Sciences
University of Central Lancashire

Dear Jim and Olivia

Re: STEMH Ethics Committee Application
Unique Reference Number: STEMH 1010

The STEMH ethics committee has granted approval of your proposal application 'An exploration into the effectiveness of the Swellaway device through a series of n=1 experiments'. Approval is granted up to the end of project date*.

It is your responsibility to ensure that

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

Yours sincerely

Karen A. Rouse

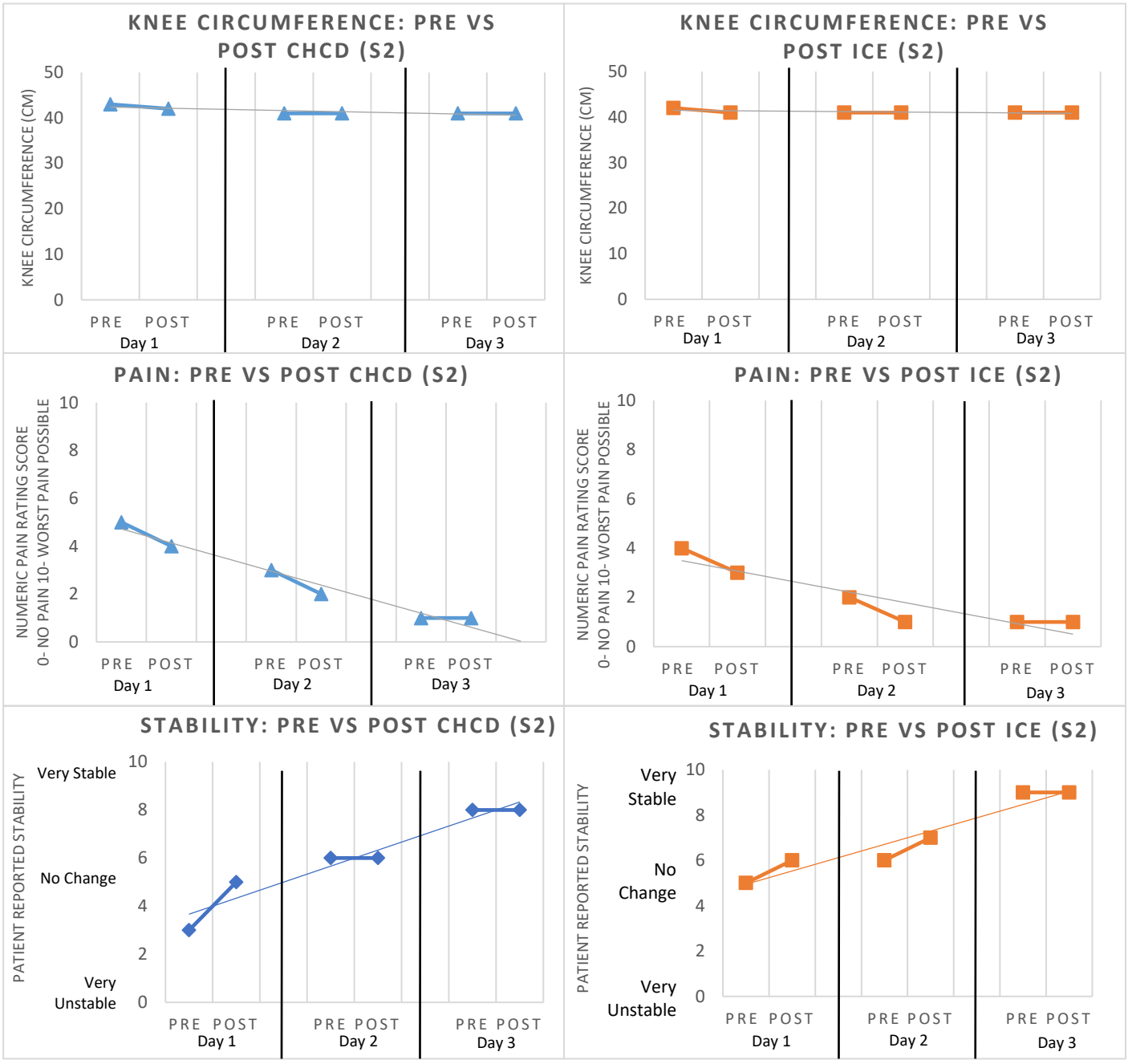
Karen Rouse

Chair
STEMH Ethics Committee

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

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

Appendix C: Single-Case Experiment Figures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PATIENT REPORTED STABILITY
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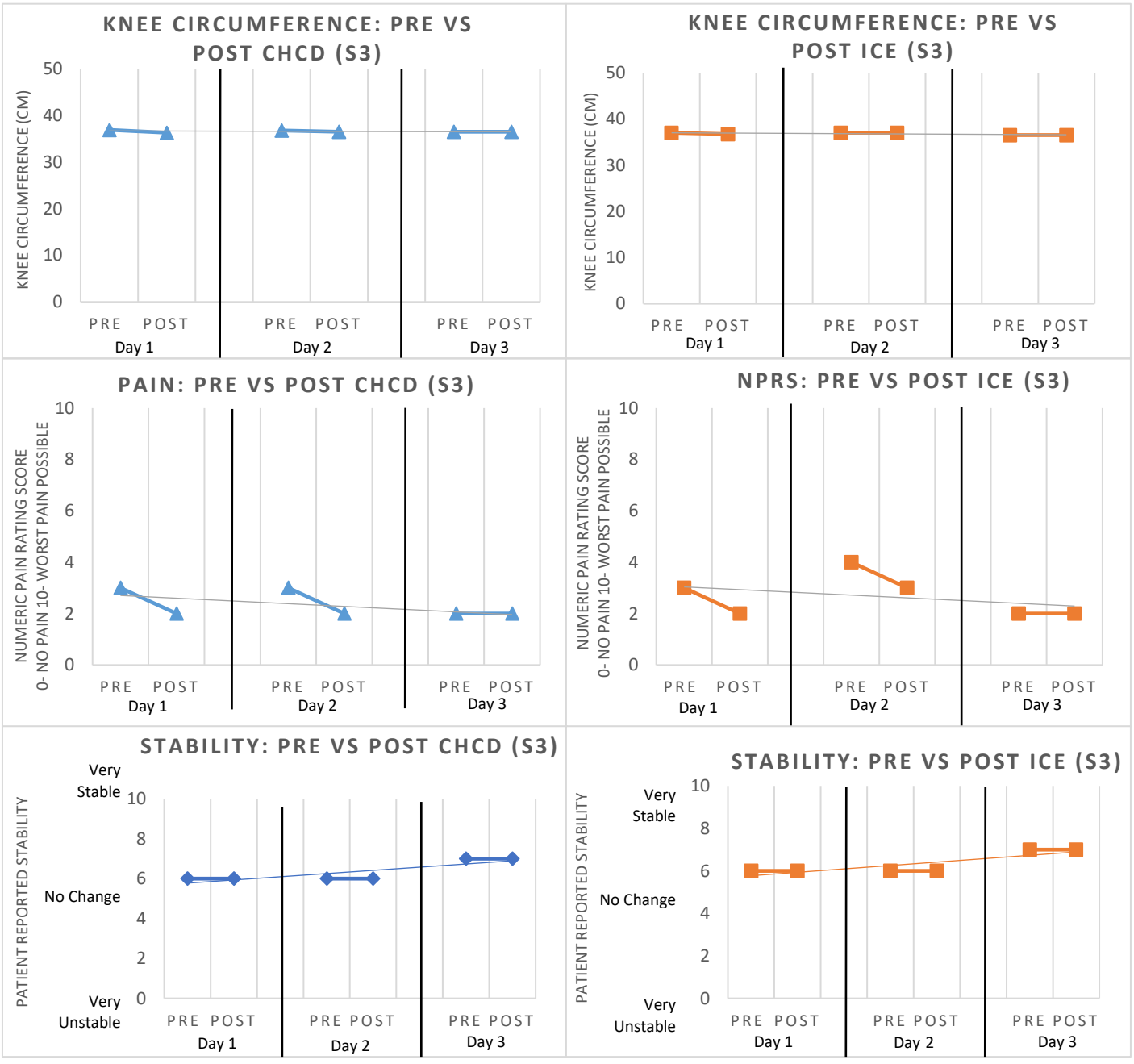
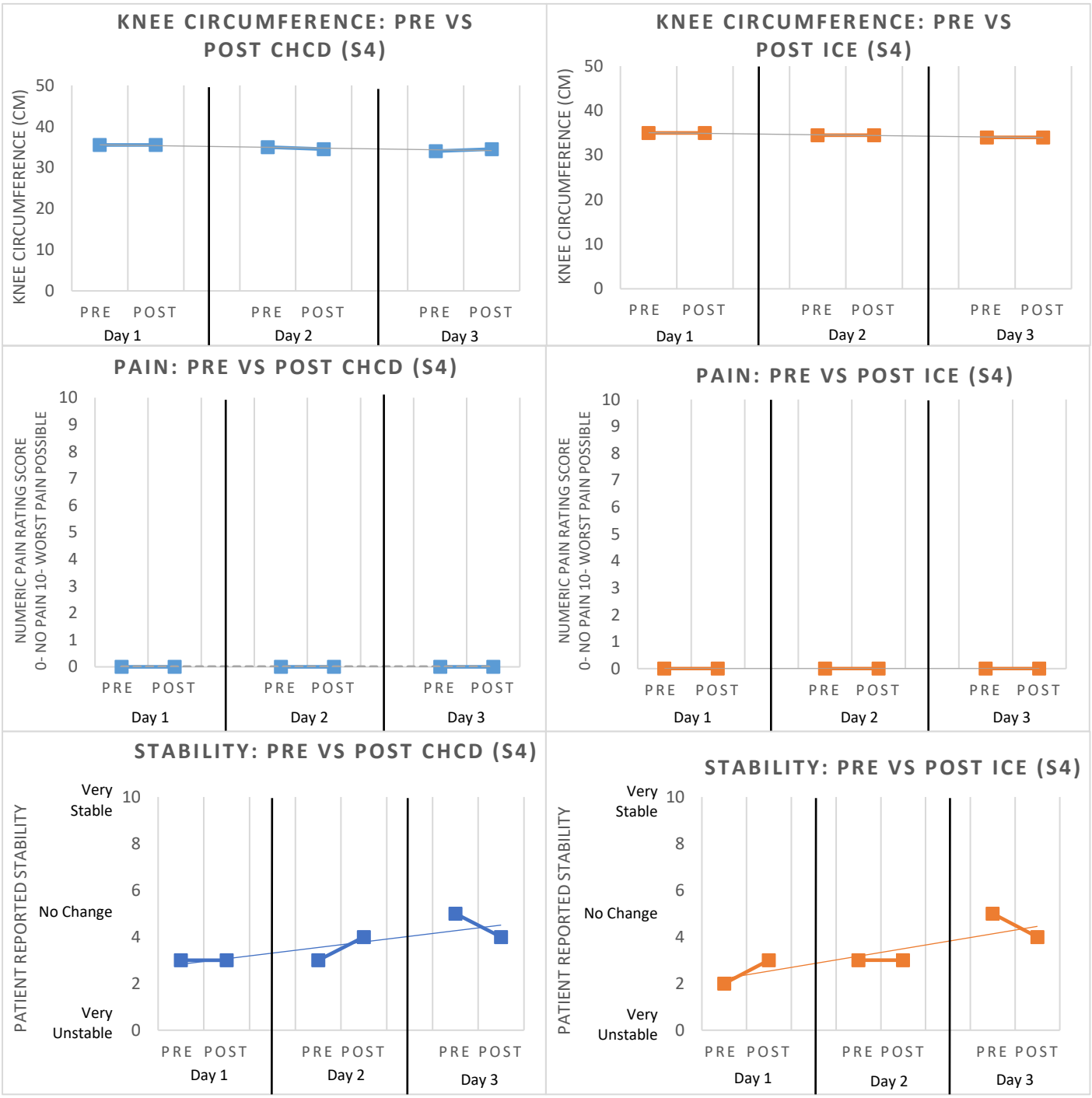
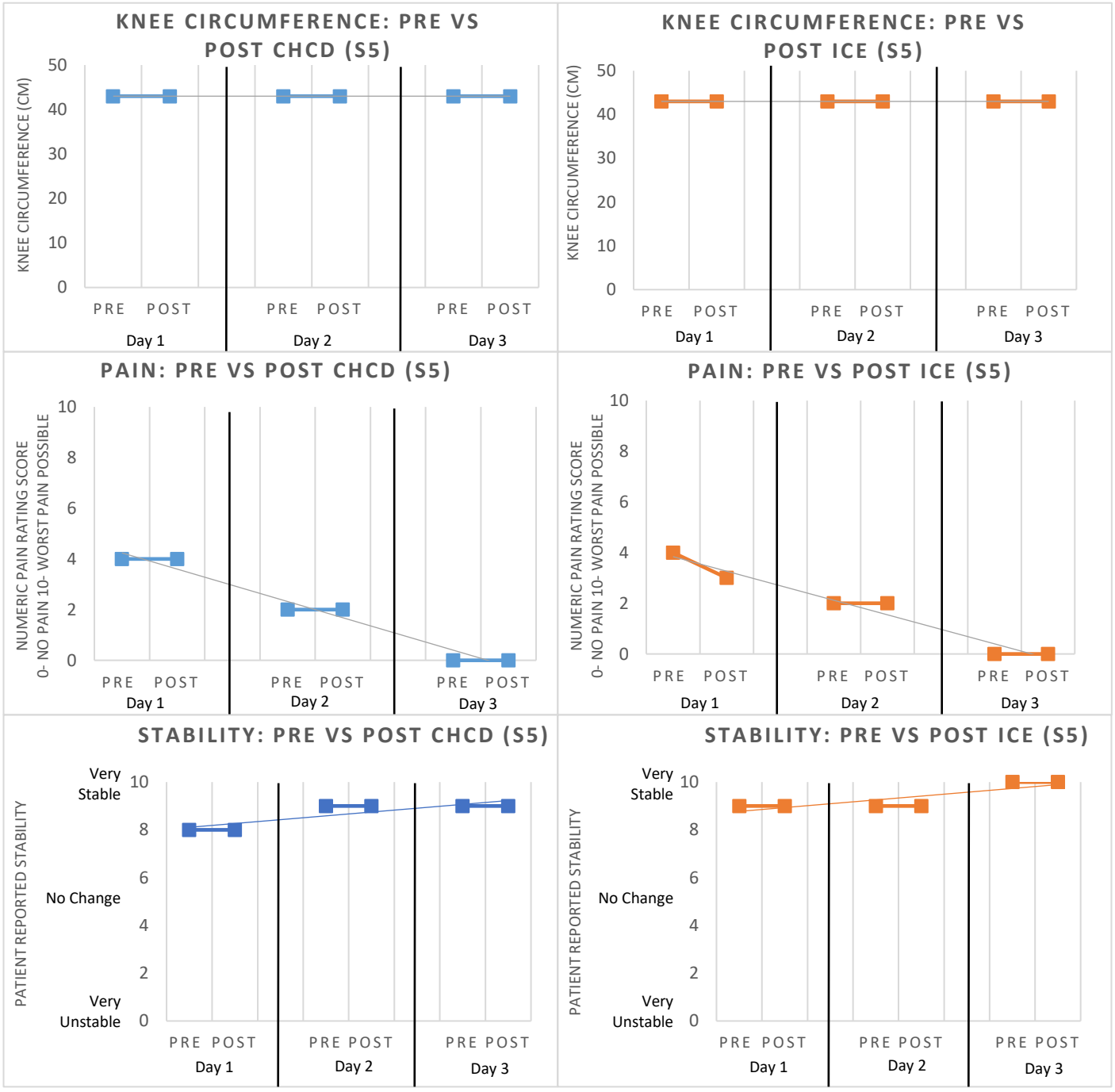
Single-Case Experiment 3

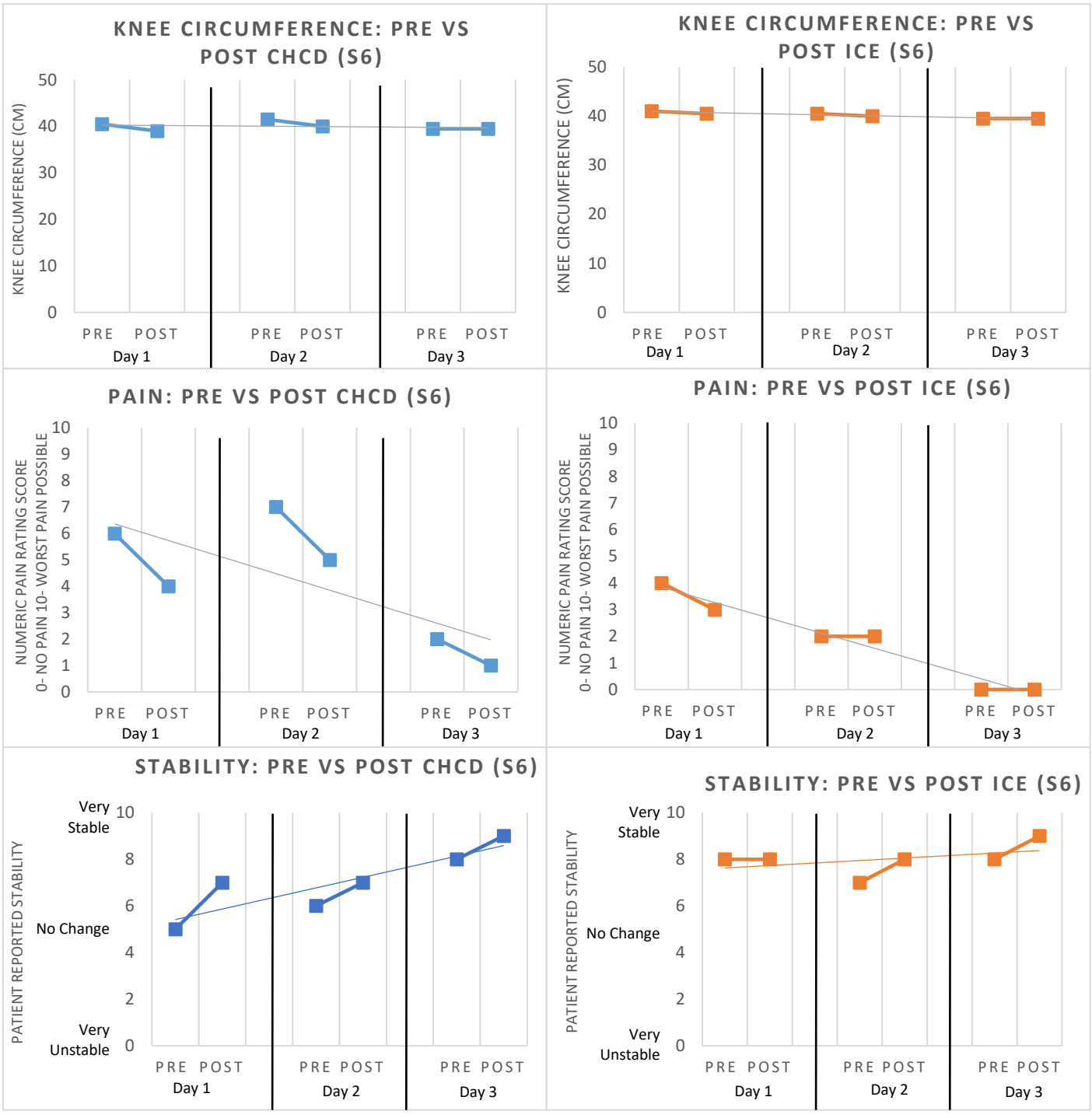


Single-Case Experiment 4



Single-Case Experiment 5

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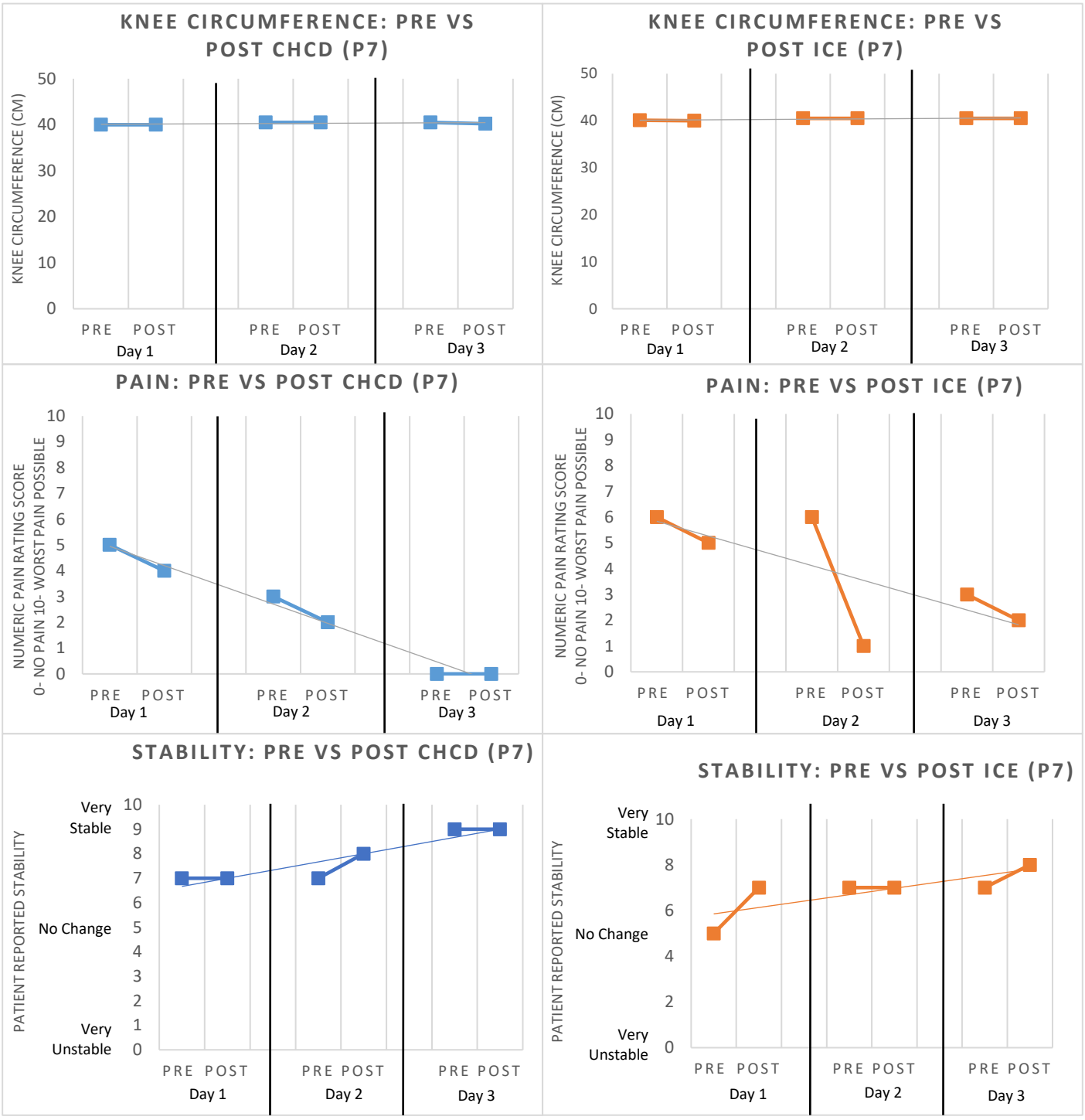
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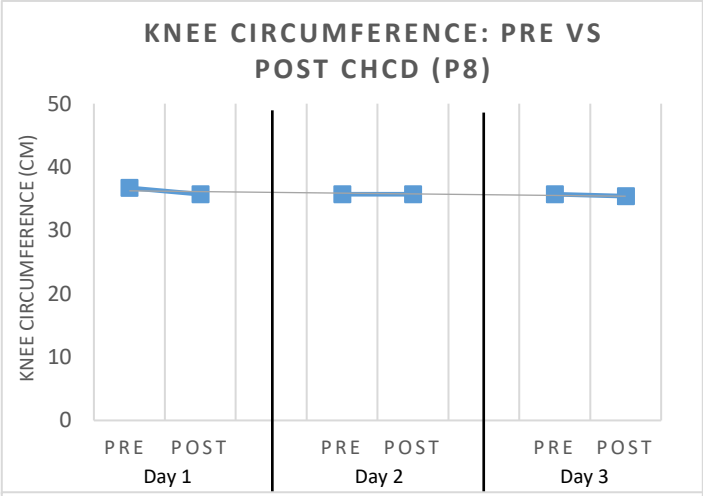
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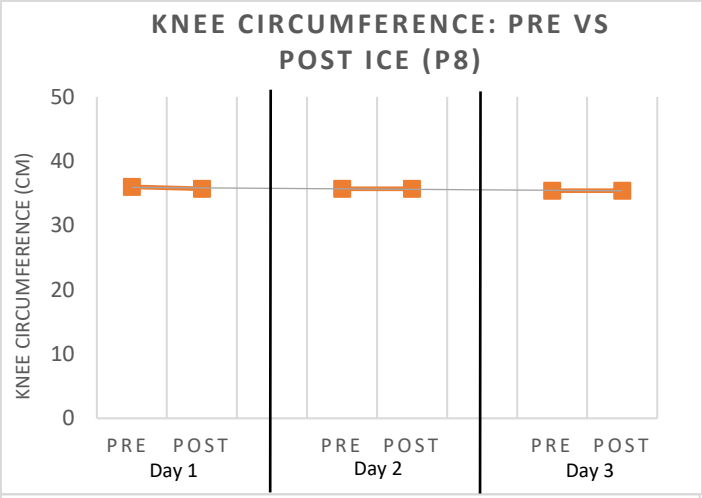
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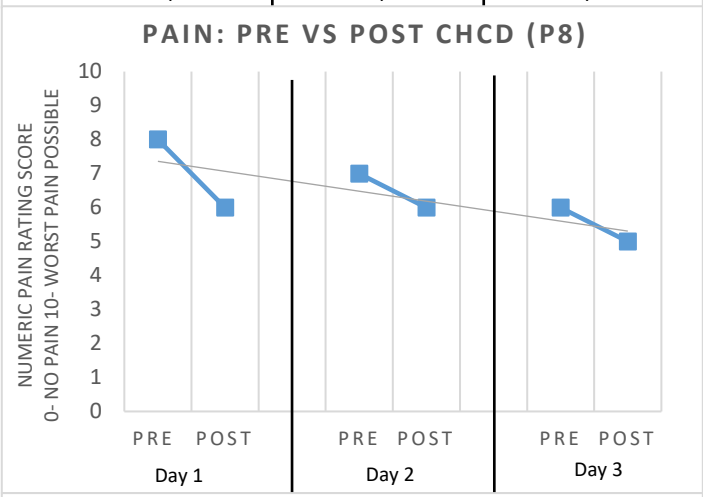
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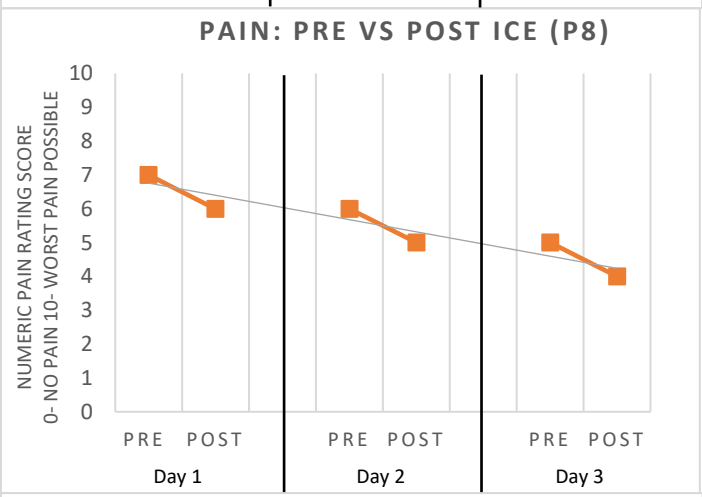
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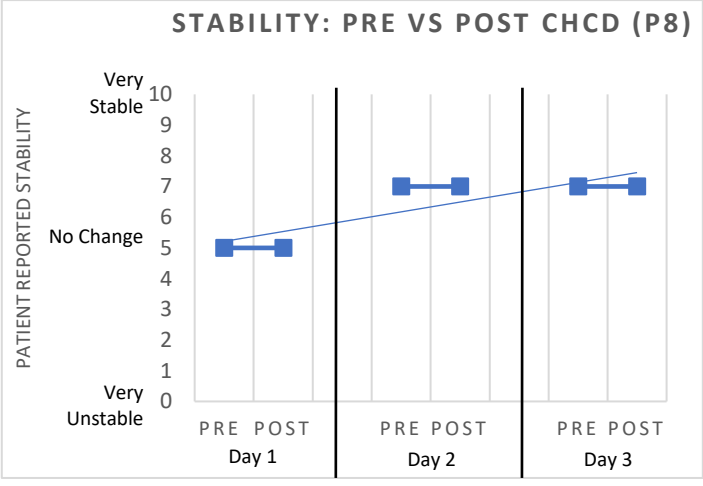
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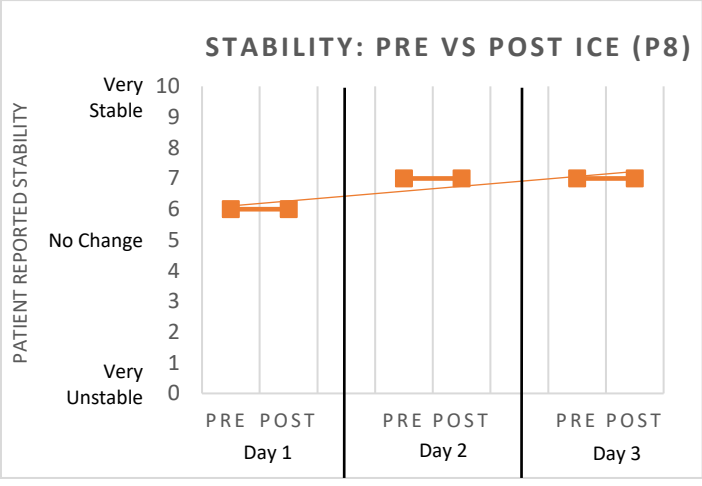
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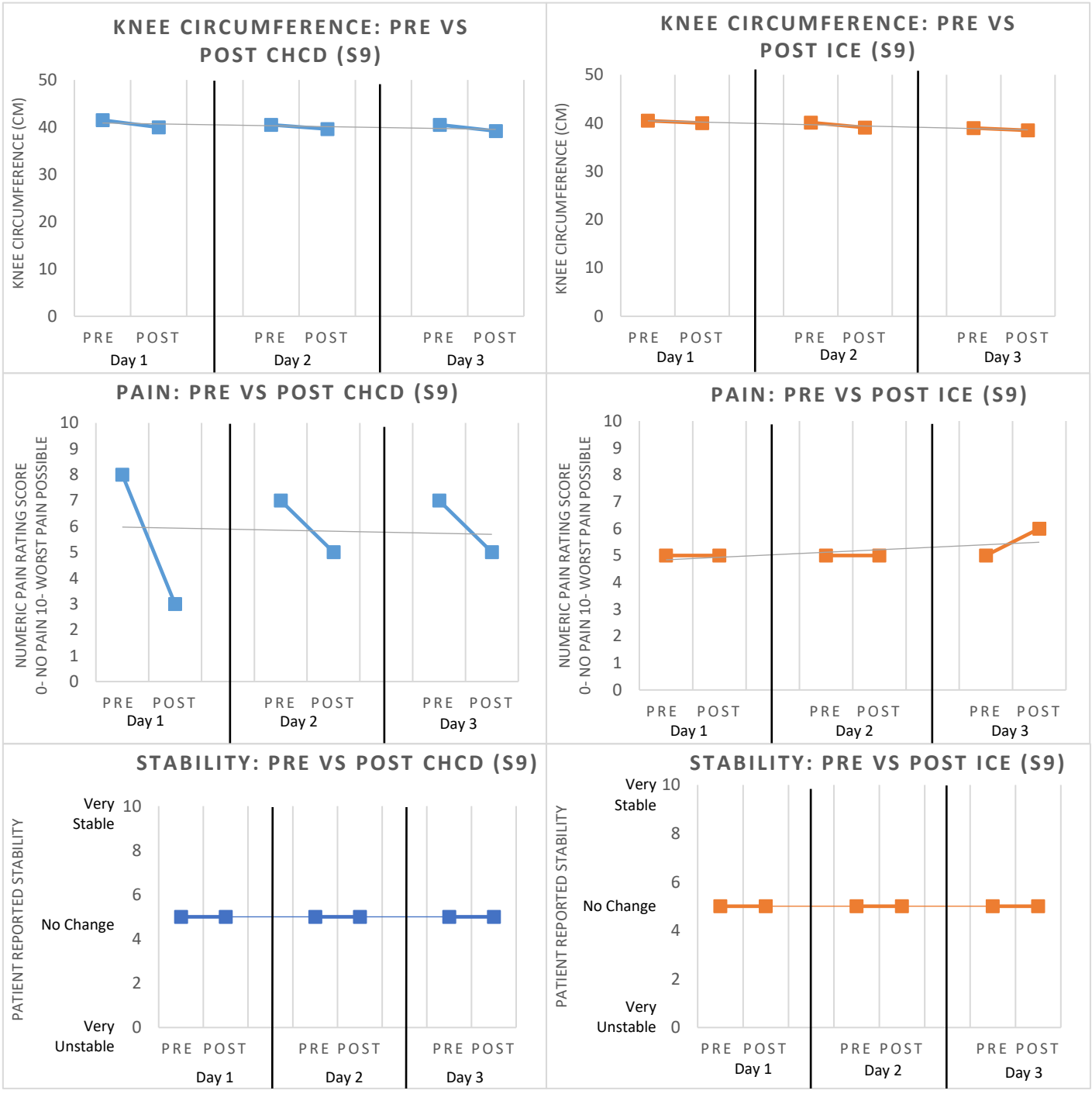
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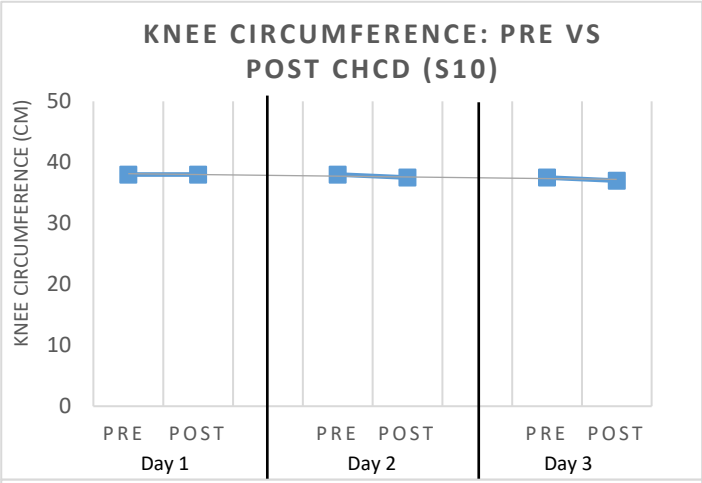
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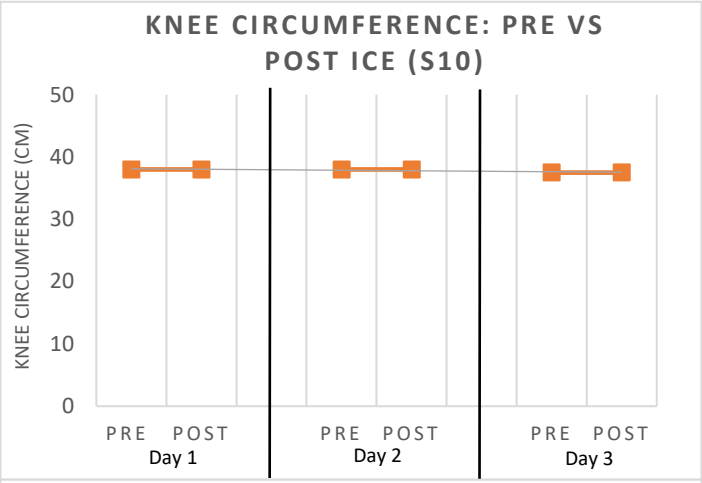
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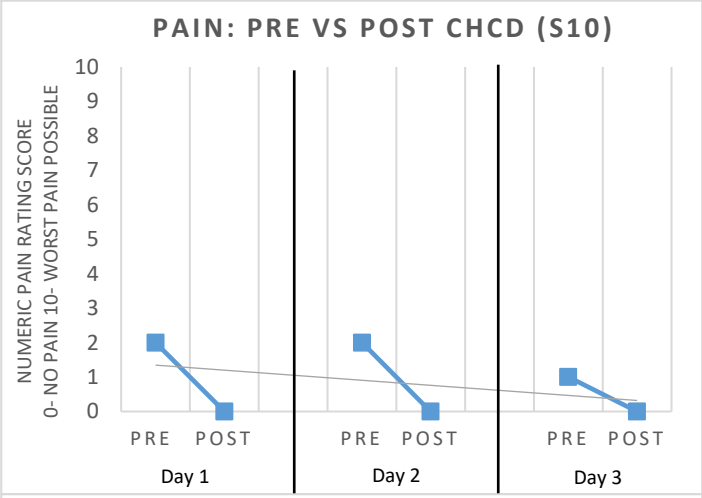
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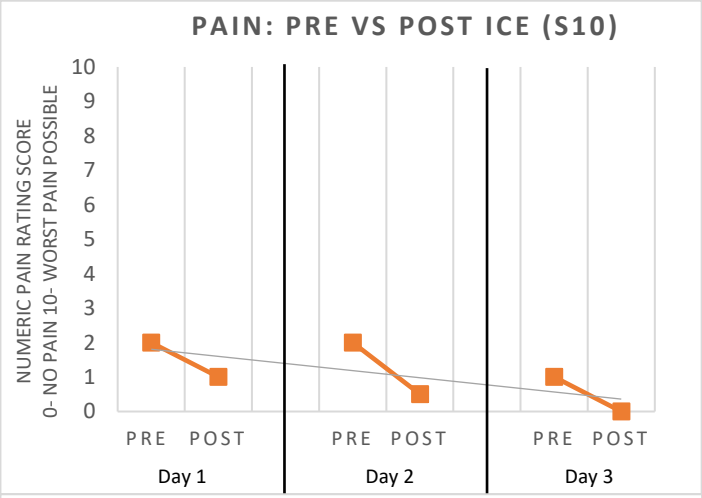
PAIN: PRE VS POST ICE (S10)
NUMERIC PAIN RATING SCORE
0- NO PAIN 10- WORST PAIN POSSIBLE
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PRE POST
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Day 1
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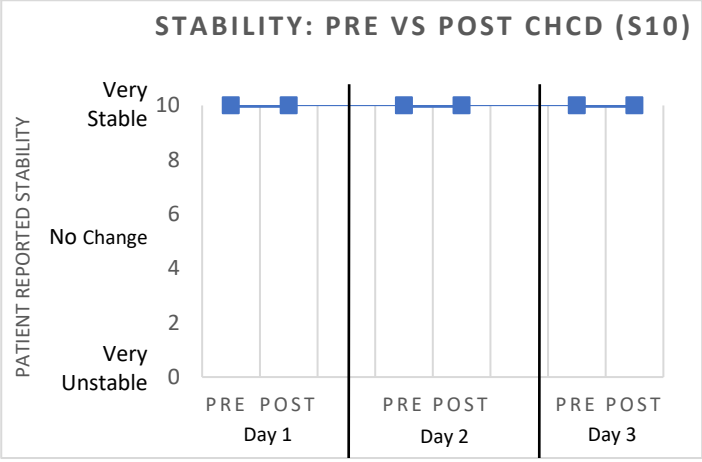
STABILITY: PRE VS POST CHCD (S10)
PATIENT REPORTED STABILITY
Very Stable
No Change
Very Unstable
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Day 1
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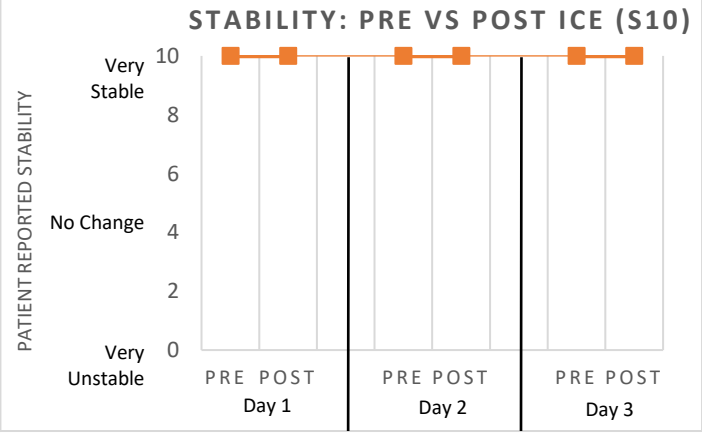
STABILITY: PRE VS POST ICE (S10)
PATIENT REPORTED STABILITY
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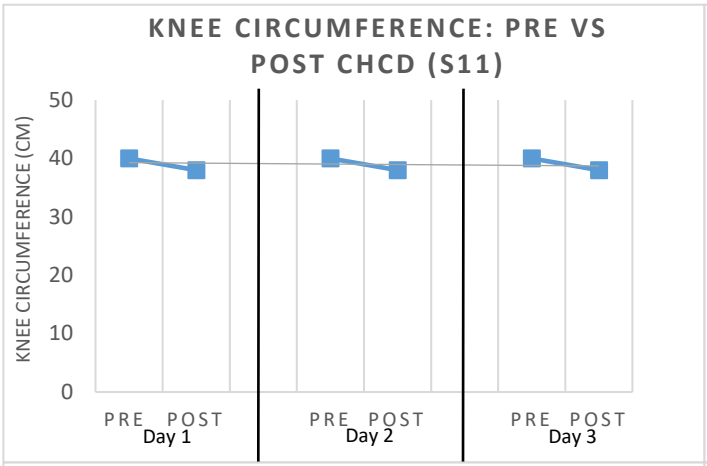
KNEE CIRCUMFERENCE: PRE VS POST CHCD (S11)
KNEE CIRCUMFERENCE (CM)
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10
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PRE POST
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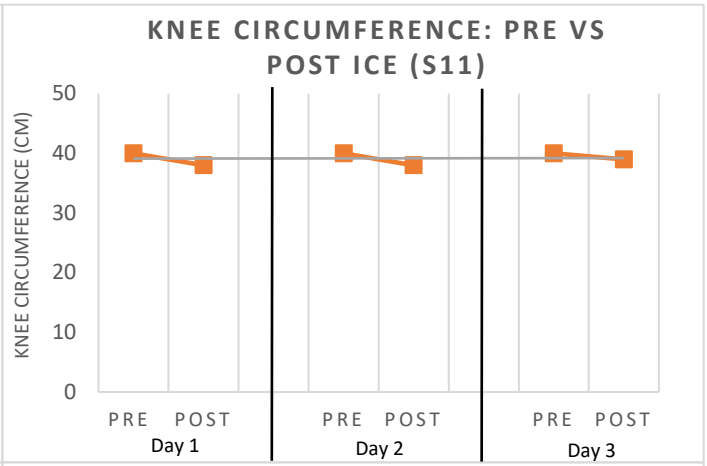
Day 2
PRE POST
Day 3


KNEE CIRCUMFERENCE: PRE VS POST ICE (S11)
KNEE CIRCUMFERENCE (CM)
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40
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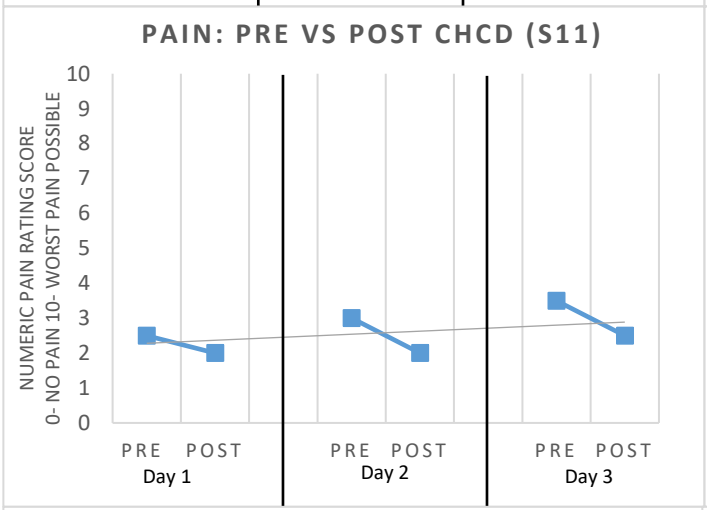
PRE POST
Day 1
PRE POST
Day 2
PRE POST
Day 3


PAIN: PRE VS POST CHCD (S11)
NUMERIC PAIN RATING SCORE
0- NO PAIN 10- WORST PAIN POSSIBLE
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PRE POST
Day 1
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Day 2
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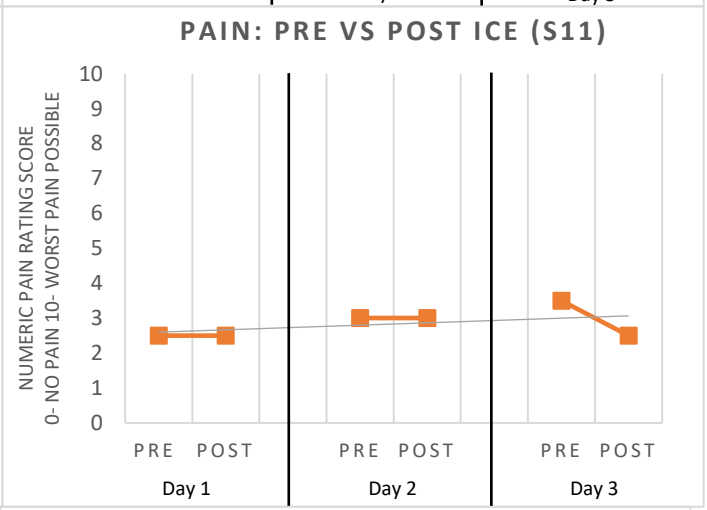
Day 3


PAIN: PRE VS POST ICE (S11)
NUMERIC PAIN RATING SCORE
0- NO PAIN 10- WORST PAIN POSSIBLE
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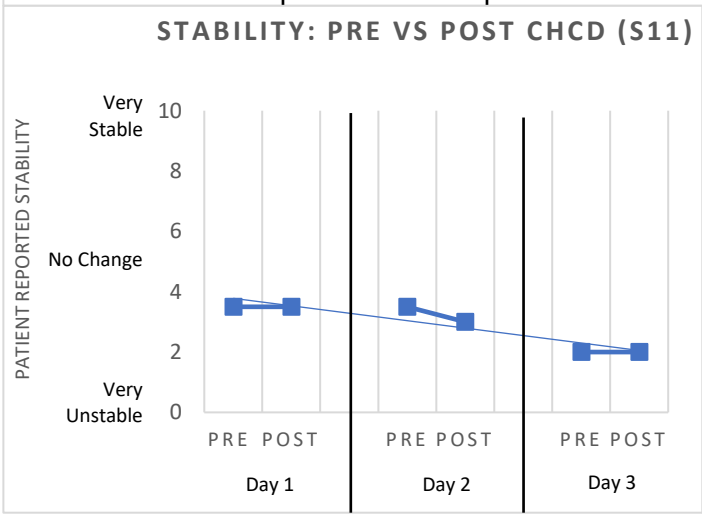
STABILITY: PRE VS POST CHCD (S11)
PATIENT REPORTED STABILITY
Very Stable
No Change
Very Unstable
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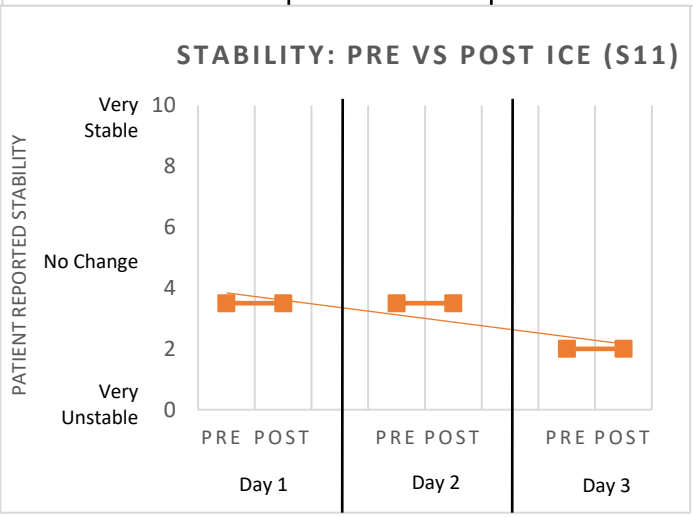
Day 3


STABILITY: PRE VS POST ICE (S11)
PATIENT REPORTED STABILITY
Very Stable
No Change
Very Unstable
10
8
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PRE POST
Day 1
PRE POST
Day 2
PRE POST
Day 3

Appendix D: Peer-reviewed publications relating to this thesis

Relevant to Chapter 2:

Greenhalgh, O., Alexander, J., Richards, J., Selfe, J. and McCarthy, C. (2021) 'The use of contrast therapy in soft tissue injury management and post-exercise recovery: a scoping review', Physical Therapy Reviews, 26(1), pp. 64-72.

PHYSICAL THERAPY REVIEWS
https://doi.org/10.1080/10833196.2020.1850163

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Check for updates

The use of contrast therapy in soft tissue injury management and post-exercise recovery: a scoping review

Olivia Greenhalgh[a], Jill Alexander[b], Jim Richards[b], James Selfe[a] and Chris McCarthy[a]

[a]Department of Health Professions, Manchester Metropolitan University, Manchester, UK; [b]Allied Health Research Unit, Faculty of Health and Wellbeing, University of Central Lancashire, Preston, UK

ABSTRACT

Contrast therapy is the alternation of thermotherapy and cryotherapy. Commonly used modalities of contrast therapy include contrast water therapy (CWT) and cold/hot packs. Despite a lack of research, it is widely used in clinical and sporting settings, particularly to aid recovery. The scoping review aims to provide a comprehensive overview of research surrounding the use of contrast therapy for soft tissue injury management and recovery. Twenty-nine full text papers were included, following a search of the databases listed: PubMed, Cochrane, SPORTDiscus, EBSCO, CINHAL and MEDLINE (via OVID). The majority of research on contrast therapy focuses on recovery, using contrast water therapy. Despite a consensus for contrast therapy temperatures of 10-15 °C (cold) and 38-40 °C (hot), significant variation amongst recovery protocols still exists, with temperatures ranging from 8-15 °C and 35.5-45 °C and duration ranging from 6 to 31 min. Generally, beneficial effects are reported to subjective measures such as self-reported perception of recovery, fatigue and muscle soreness following contrast therapy. However, the evidence is less clear regarding the influence on physiological measures and performance. Contrast therapy appears to be most commonly used in the form of contrast water therapy for post-exercise recovery purposes. There remains a significant lack of research surrounding the efficacy of contrast therapy for soft tissue injury management and the use of alternative modalities.

KEYWORDS

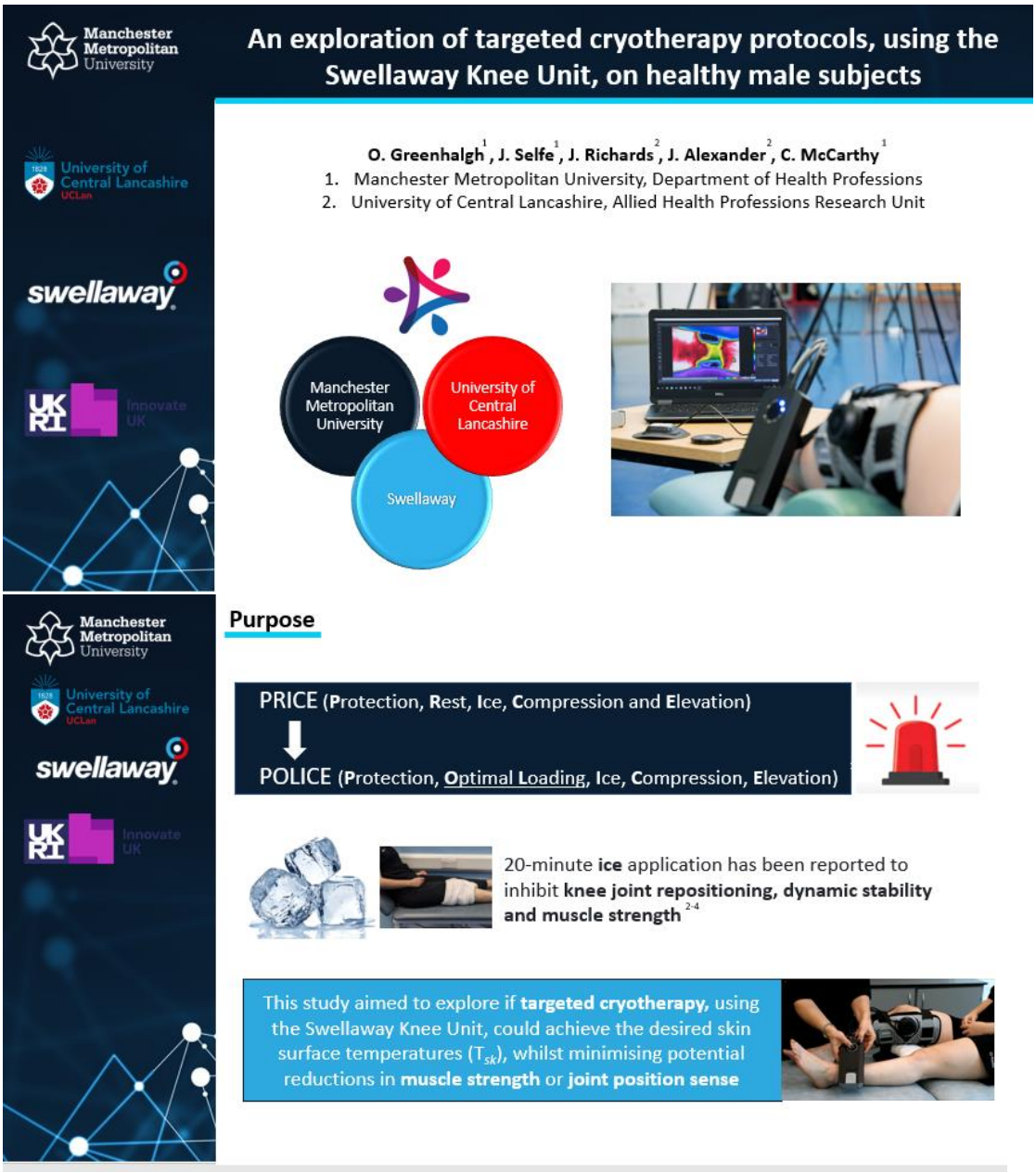
Contrast; cryotherapy; thermotherapy; rehabilitation; recovery

National conference presentations (2020 & 2021)

Relevant to Chapter 4:

Rapid 5 presentation:

Greenhalgh, O., Alexander, J., Richards, J., Selfe, J. and McCarthy, C. (2020) 'An exploration of targeted cryotherapy protocols, using the Swellaway Knee Unit, on healthy male subjects' Physiotherapy UK.



Methods

Part A

13 healthy male participants (21.5 ± 3.0 yrs)

- Skin surface temperature (T_{sk})
- Tissue oxygenation
- Thermal sensation/comfort

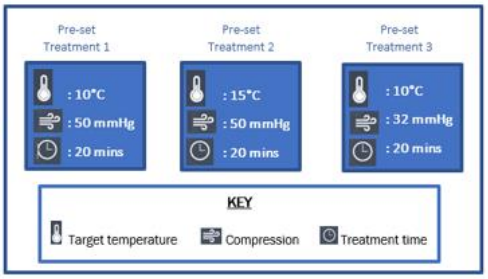
Part B

13 healthy male participants (25.3 ± 3.4 yrs)

- Quadriceps muscle strength
- Pressure pain threshold
- Joint position sense

All outcome measures were recorded **pre**, **post** and **20 minutes post-intervention**

Three compressive-cryotherapy interventions used in a **randomised crossover design:**



Results/Conclusions

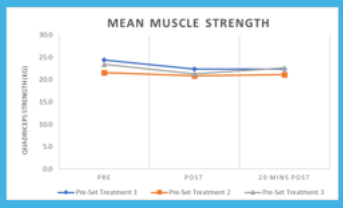
Part A

- Protocols set at 10°C achieved T_{sk} within the **therapeutic range** which may be considered an effective cryotherapy intervention. Protocols set at 15°C did not achieve T_{sk} within the therapeutic range

- Most participants described the compressive-cryotherapy interventions as thermally '**comfortable**' (80%) and '**slightly cool**' (50%)
- **No significant differences** (P>0.05) were found in tissue oxygenation between time-points or interventions

Part B

- **Isometric quadriceps muscle strength** decreased post-intervention by approximately **3-7%**. Previous literature has presented quadriceps muscle strength deficits of **16%** following ice interventions [2]



- **No significant differences** (P>0.05) were found in pressure pain threshold or maximum knee flexion between time-points or interventions. Previous literature has found **significant inhibition** to knee joint repositioning following ice interventions [3-4]

Implications

The targeted cooling approach, using the Swellaway Knee Unit, can achieve the desired cooling and appears to reduce the magnitude of inhibition to muscle strength and joint position sense reported following cryotherapy interventions

Key Point

Clinicians should consider utilising **targeted compressive-cryotherapy** to fulfil the 'IC' in 'POLICE', whilst minimising the reported **adverse effects** following cryotherapy, which may have previously discouraged **early optimal loading** 'OL' post-intervention

References

1. Bleakley CM, Glasgow P, MacAuley DC. PRICE needs updating, should we call the POLICE? British Journal of Sports Medicine. 2012;46(4):220-1.
2. Rhodes, D. & Alexander, J. The Effect of Knee Joint Cooling on Isokinetic Torque Production of The Knee Extensors: Considerations for Application. The International Journal of Sports Physical Therapy, 2018;13(6): 985.
3. Alexander J, Richards J, Attah O, Cheema S, Snook J, Wisdell C, May K & Selfe J. Delayed effects of a 20-min crushed ice application on knee joint position sense assessed by a functional task during a re-warming period. Gait & Posture. 2018. 62:173-178
4. Alexander J, Selfe J, Oliver B, Mee D, Carter A, Scott M, Richards J & May K, An exploratory study into the effects of a 20 minute crushed ice application on knee joint position sense during a small knee bend. Physical Therapy in Sport, 2016. 18;21-26

Relevant to Chapter 5:

Poster Presentation:

Greenhalgh, O., Alexander, J., Richards, J., Selfe, J. and McCarthy, C. (2021) Exploring effects of cryotherapy modalities on pain, muscle strength and joint position sense in healthy participants with induced knee pain. Physiotherapy UK.

2021 VPUK VIRTUAL PHYSIOTHERAPY CONFERENCE

Exploring effects of cryotherapy modalities on pain, muscle strength and joint position sense in healthy participants with induced knee pain

O. Greenhalgh[1], J. Selfe[1], J. Richards[2], J. Alexander[2], C. McCarthy[1]

1. Manchester Metropolitan University, Department of Health Professions, Manchester, UK
2. University of Central Lancashire, Allied Health Professions Research Unit, School of Sport and Health Sciences, Preston, UK

Purpose

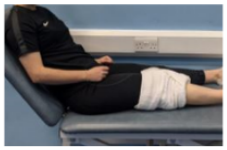
- '**Optimal loading'** has been introduced into the guidelines to facilitate early activity to optimise recovery.[1]
- Studies have identified potential adverse effects on muscle strength and dynamic stability following ice.[2]
- Evidence supports the use of cryotherapy to provide short-term pain relief.[1]

This study utilised a targeted compressive-cryotherapy approach on experimentally induced knee pain in healthy participants and explored the effects on muscle strength and joint position sense.

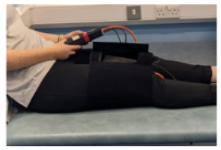
Methods

10 healthy participants (7 females, 3 males; 32.9 ± 11.6 years) were induced with experimental knee pain using capsaicin cream (0.075%) on the medial aspect of the non-dominant knee. A randomised crossover design was adopted to explore two 20-minute cryotherapy interventions. Repeated measures ANOVAs with post-hoc comparisons were used to assess changes between time points.

1) ice (wetted: 400g cubed ice, 400ml water)



2) *ProMOTION* EV1 (10°C, 50mmHg compression)



Four outcome measures were recorded pre-capsaicin, post-capsaicin, post-cooling and 20-mins post cooling:

i) Pressure pain threshold (PPT) **ii) Numerical pain rating scale (NPRS)**

iii) Quadriceps muscle strength **iv) Joint position sense (JPS)**

References

1. Bleakley CM, Glasgow P, MacAuley DC. PRICE needs updating, should we call the POLICE? British Journal of Sports Medicine. 2012;46:220-221.
2. Rhodes, D. & Alexander, J. The Effect of Knee Joint Cooling on Isokinetic Torque Production of The Knee Extensors: Considerations for Application. The International Journal of Sports Physical Therapy, 2018;13(6): 985.

This research was carried out as part of a Knowledge Transfer Partnership. Ethical approval was granted (EthOS 10731).
For more information, please contact **Olivia.Greenhalgh@stu.mmu.ac.uk**

Results

Key: Positive Effect / Adverse Effect

PPT

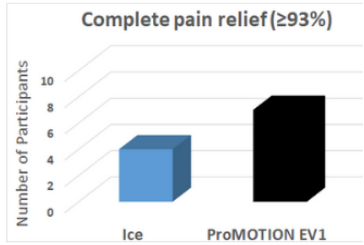
Ice
No significant differences were found in PPT

***ProMOTION* EV1**
Significant increases in PPT were found following:
1. Post-capsaicin and post-cooling (+27%)
2. Post-capsaicin and 20-minutes post-cooling (+20%)

NPRS

Ice
NPRS was reduced by **91%** 20-mins post-cooling.

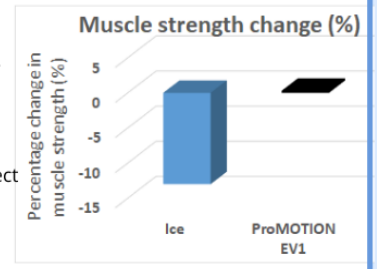
***ProMOTION* EV1**
NPRS was reduced by **100%** 20-mins post-cooling.



Quadriceps Muscle Strength

Ice
Reduced strength by **13%** post-cooling

***ProMOTION* EV1**
Had a negligible effect on strength (+0.3%) post-cooling



JPS

Ice
Significant increases were found in range of motion (ROM) in the coronal plane, which indicates **increased instability** (adduction/abduction).

Both interventions
A trend of increased instability (14%) in the transverse plane ROM 20-minutes post-cooling was most apparent following the ice (p=0.053).

Conclusions

- Targeted compressive-cryotherapy has the potential to achieve short-term pain relief, as demonstrated on healthy participants with experimentally induced knee pain
- A targeted approach may also minimise the negative effects on muscle strength and dynamic stability
- This would allow individuals to return to weight-bearing rehabilitation exercises earlier, at a lower risk of re-injury

Implications

Clinicians could consider utilising targeted compressive-cryotherapy to provide a short-term pain relief and minimise the reported adverse effects following cryotherapy, facilitating early weight-bearing rehabilitation.

ktn Knowledge Transfer Partnerships
Manchester Metropolitan University
University of Central Lancashire UCLan
ProMOTION RESEARCH & DEVELOPMENT BY SWELLAWAY LTD

Relevant to Chapter 6:

Poster Presentation:

Greenhalgh, O., Alexander, J., Richards, J., Jones, M., Selfe, J. and McCarthy, C. (2020) 'An exploration into the effectiveness of cryotherapy modalities on patients with degenerative knee conditions, through a series of single-case experiments' Physiotherapy UK.

An exploration into the effectiveness of cryotherapy modalities on patients with degenerative knee conditions, through a series of single-case experiments

O. Greenhalgh[1], J. Selfe[1], J. Richards[2], M. Jones[1], J. Alexander[2], C. McCarthy [1]
1.Manchester Metropolitan University, Department of Health Professions, Manchester, UK
2. University of Central Lancashire, Allied Health Professions Research Unit, School of Sport and Health Sciences, Preston, UK

Purpose

Knee osteoarthritis (OA) is a condition contributing to functional limitation, reduced quality of life and socioeconomic burden, largely due to pain (1). **Thermotherapy** (local hot or cold) is a NICE advocated, non-pharmacological self-management tool for knee OA (2). Optimal thermotherapy protocols are yet to be established.

This study aimed to explore the **effectiveness of two cryotherapy modalities** at reducing pain, swelling and instability in people with degenerative knee conditions, through a series of single-case experiments.

Methods

Ethical approval: University of Central Lancashire (STEMH 1010) and Manchester Metropolitan University (EthOS 11729)

- An **alternating-treatment design** was adopted, over a series of single-case experiments on four individuals (62.0 ± 9.3 yrs) with **degenerative knee conditions**
- Two 20-minute interventions were applied once a day for three days
- Interventions were applied in a randomised order (see below) with a minimum of two hours in between

Interventions

A	Wetted ice (400g cubed ice, 400ml water)
B	Swellaway (10°C with 50mmHg compression)

Randomisation

	Day 1		Day 2		Day 3	
Order 1	A	B	A	B	A	B
Order 2	B	A	B	A	B	A

Three outcome measures were recorded pre and post interventions:

- **Swelling** (knee circumference) using a tape measure
- **Patient-perceived pain** using the 11-point numeric pain rating scale (NPRS)
- **Patient-perceived stability** on an 11-point scale (very unstable-very stable)

The data was analysed using visual analysis of graphical data individually and collectively.

References

1. Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. Osteoarthritis and Cartilage, 1145-1153.
2. NICE. (2014, February 12). Osteoarthritis: care and management. Retrieved from National Institute for Health and Care Excellence: https://www.nice.org.uk/guidance/cg177/resources/osteoarthritis-care-and-management-pdf-35109757272517

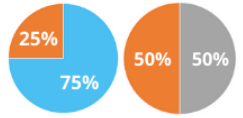
Results

Pain
- **83%** of Swellaway interventions and **58%** of ice interventions achieved a clinically important reduction in pain

Swelling
- **75%** of Swellaway interventions and **58%** of ice interventions reduced knee circumference

Stability
- Both interventions had limited effect on patient-perceived stability, only improving instability **8%** (Swellaway) and **16%** (ice) of total interventions

Overall
- **75%** of participants achieved the greatest reduction in pain and swelling following the Swellaway intervention
- **50%** of patients had a greater increase in perceived-stability following ice and **50%** of patients found the interventions equally as effective for perceived-stability



Swellaway | Wetted Ice | Equal effectiveness

Conclusions

- Both interventions achieved a **clinically important reduction in pain** for the majority of patients and interventions
- **Compressive-cryotherapy**, using the Swellaway, may be **more beneficial for reducing pain and swelling** in patients with degenerative knee conditions
- Ice appears **more effective at reducing patient-perceived instability**

A) Wetted Ice Intervention *B) Swellaway Device*

Implications

To optimise patients' ability to self-manage symptoms, **clinicians should consider exploring a range of thermotherapy modalities for patients with varying knee OA symptoms.** This is required in order to determine individual patients' most effective intervention, to utilise as a non-pharmacological **self-management tool.**

This research was carried out as part of a Knowledge Transfer Partnership. For more information, please contact ***O.Greenhalgh@mmu.ac.uk***

Appendix E: Additional Supporting Documentation

Algorithm to calculate the number of possible combinations

Table E.1: A summary of the start and end values calculated in order to determine the number of possible combinations of time, temperature and compression with the CHCD

	6 to 40	1 to 20	20 to 75	39200 combinations				
		Start					**End**	
No.	Temp	Time	Comp.		No.	Temp	Time	Comp.
1	6	1	20		39166	6	20	75
2	7	1	20		39167	7	20	75
3	8	1	20		39168	8	20	75
4	9	1	20		39169	9	20	75
5	10	1	20		39170	10	20	75
6	11	1	20		39171	11	20	75
7	12	1	20		39172	12	20	75
8	13	1	20		39173	13	20	75
9	14	1	20		39174	14	20	75
10	15	1	20		39175	15	20	75
11	16	1	20		39176	16	20	75
12	17	1	20		39177	17	20	75
13	18	1	20		39178	18	20	75
14	19	1	20		39179	19	20	75
15	20	1	20		39180	20	20	75
16	21	1	20		39181	21	20	75
17	22	1	20		39182	22	20	75
18	23	1	20		39183	23	20	75
19	24	1	20		39184	24	20	75
20	25	1	20		39185	25	20	75
21	26	1	20		39186	26	20	75
22	27	1	20		39187	27	20	75
23	28	1	20		39188	28	20	75
24	29	1	20		39189	29	20	75
25	30	1	20		39190	30	20	75
26	31	1	20		39191	31	20	75
27	32	1	20		39192	32	20	75
28	33	1	20		39193	33	20	75
29	34	1	20		39194	34	20	75
30	35	1	20		39195	35	20	75
31	36	1	20		39196	36	20	75
32	37	1	20		39197	37	20	75
33	38	1	20		39198	38	20	75
34	39	1	20		39199	39	20	75
35	40	1	20		39200	40	20	75

Package leaflet: Information for the user

Axsain® 0.075% w/w Cream

Capsaicin 0.075% w/w

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Axsain is and what it is used for
2. What you need to know before you use Axsain
3. How to use Axsain
4. Possible side effects
5. How to store Axsain
6. Contents of the Pack and other information

1. What AXSAIN is and what it is used for

The name of this medicine is Axsain cream. The active ingredient in this medicine is capsaicin which is a naturally occurring substance found in plants.
Axsain cream is used to relieve pain arising from nerves near to the surface of the skin. This can happen after having Shingles (Herpes Zoster).
Axsain cream is also used to relieve pain in patients who have nerve damage to their hands or feet caused by diabetes.

2. What you need to know before you use AXSAIN CREAM

Do not use Axsain cream:
- If you are **allergic** (hypersensitive) to capsaicin or any of the other ingredients (listed in section 6).
- On broken or irritated skin.

This medicine is not suitable for use in children.

Warnings and precautions

Talk to your doctor or pharmacist before using **Axsain cream**
- Keep away from the eyes, nose and mouth (if it does accidentally get into your eyes, nose and mouth or onto broken or irritated skin, wash off with plenty of water).
- Wash your hands immediately after applying the cream, unless the hands are treated areas, in which case, they should be washed 30 minutes after applying.
- Avoid hot baths or showers immediately before or just after applying Axsain cream.
- Do not apply tight bandages on top of Axsain cream.
- Avoid breathing in any vapours from the cream, as this can cause irritation of the eyes and breathing difficulties (including making asthma worse).

Other medicines and Axsain cream

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast feeding, think you may be pregnant or planning to have a baby, you should ask your doctor or pharmacist for advice before taking Axsain.

Axsain Cream contains cetyl alcohol

Axsain may cause local skin reactions (e.g. contact dermatitis) due to the product containing cetyl alcohol.

3. How to use AXSAIN CREAM

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
Axsain should be applied to the affected area 3 to 4 times a day, with a gap of at least 4hrs between each application.
A small amount of cream (about the size of a pea) should be rubbed onto the area to be treated with your fingers. Make sure that all the cream is rubbed in so it is no longer visible.
Wash your hands immediately after application of Axsain, unless you are treating nerve damage in your hands, when you should wait 30 minutes before washing your hands.
When using Axsain cream to relieve pain caused by nerve damage due to diabetes the treatment normally lasts for 8 weeks.

4. Possible side effects

Like all medicines Axsain can cause side effects, although not everybody gets them.
Axsain cream can cause a brief burning feeling when applied. This burning is more common when:
- The cream is used more than 4 times a day.
- Too much cream is applied.
- The cream is applied just before or after a hot bath or shower.

Rarely when Axsain cream is applied the vapour can cause brief irritation of the eyes, nose, and throat, such as runny nose, cough or sneezing, breathlessness or worsening of asthma.
Axsain may also cause irritation of the skin for example itching or stinging.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below)

United Kingdom
The Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;
Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AXSAIN CREAM

Keep this medicine out of the sight and reach of children.
Store below 25°C.
Do not use after the expiry date printed on the carton and tube.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Axsain contains

Axsain cream contains 0.075% capsaicin as the active ingredient. It also contains purified water, sorbitol solution, isopropyl myristate, cetyl alcohol, white soft paraffin, glycerol stearate, PEG-100 stearate and benzyl alcohol as the inactive ingredients.

What Axsain cream looks like and contents of pack

Axsain cream is a white cream packed in aluminium tubes with epoxyphenolic lining and polypropylene spiked cap containing 45 gm Axsain cream.

Marketing Authorisation Holder

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Manufacturer

Pharmasol Limited, North Way, Walworth Industrial Estate, Andover, Hampshire, SP10 5AZ, UK

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