PHYSIOLOGICAL AND CLINICAL EFFECTS OF RADIOFREQUENCY-BASED THERAPY

Binoy Radha Kumaran

Submitted to the University of Hertfordshire in partial fulfilment of the requirements of the degree of Doctor of Philosophy

PhD

February 2017

Abstract

Electrophysical agents (EPA) are a fundamental element of therapy practice and are vital for the treatment of a variety of conditions. Many of these agents employ some form of electromagnetic fields (EMF), in which radiofrequency (RF) is a major component. The therapeutic effects of RF are mainly linked to their effects on pain relief and potential effects on tissue repair. Although RF across various frequency ranges has been in use, reviews have shown that the frequency ranges currently used in therapy practice have narrowed to within 30 kHz–30,000 kHz (30 MHz). The most commonly used and hence the most commonly researched are shortwave therapies (SWT) that operate at 27.12 MHz, which is presently used predominantly in its pulsed form (PSWT).

In addition to SWT, devices employing significantly lower RF ranges have also been used widely despite their lack of evidence. Capacitive Resistive Monopolar Radiofrequency (CRMRF) that operates at 448 kHz is one such RF. This programme of research was designed to investigate the physiological and clinical efficacy of CRMRF delivered using the 'Indiba Activ 902' device. The project also evaluated the scope and evidence for RF-based EPAs in therapy, through a comprehensive review of literature. A total of 120 relevant clinical studies on either acute (30 studies) or chronic (90 studies) conditions were reviewed. Notable evidence was identified for chronic OA knee and acute postoperative pain and wound healing. Some evidence also exists for chronic low back pain and healing of chronic wounds. Only eight studies reported devices that employed RF outside the shortwave frequency band.

In a randomised crossover laboratory study on asymptomatic adults, the effects of contrasting doses of CRMRF on skin temperature (SKT), skin blood flow (SBF), nerve conduction velocity (NCV), deep blood flow and the extensibility of tissues were examined against a placebo dose and a control condition with no treatment. The study further compared CRMRF results with that of PSWT. The results showed that high (moderately thermal) and low (sub/minimally thermal) doses of CRMRF significantly enhanced and sustained SKT ($p<0.001$), while only the high dose meaningfully increased SBF ($p<0.001$). High dose PSWT increased SKT marginally ($p<0.001$) but did not sustain it. Further, the high and low dose CRMRF significantly enhanced blood flow volume at depth ($p=0.003$), while PSWT failed to show any significant impact. None of the treatments significantly affected deep blood flow velocity, tissue extensibility or NCV.

These results were reproduced on a cohort of patients affected by OA knee in a randomised controlled trial (RCT), and the effects appeared more pronounced in the patients than in the asymptomatic people. More importantly, the RCT showed that a four-week high dose CRMRF treatment (eight sessions) produced statistically and clinically significant gains in

pain and function associated with OA knee in the short to medium term ($p<0.001$), which was also significantly more pronounced than the gains produced by a placebo, or standard care ($p=0.001$for pain; $p=0.031$ for function). The findings of this study were considered promising. It is therefore suggested that CRMRF-based treatment can potentially be used as an adjunct to current therapeutic methods to enhance the clinical outcomes. However, further studies are needed to substantiate this, and the current results will provide credible baseline data for future research.

Acknowledgements

My sincere thanks to the following people without whom this work would have fallen short...

To Professor Tim Watson who has been inspirational and critical in the right measure, for being my perfect guide and best friend in this job for the last five years!

To Mr Roy Smith (CEO, Indiba S. A.), Dr Sebastia Sendros, Mr Xavier Rami and other colleagues at Indiba S. A., Barcelona for all their support and continued funding throughout the project.

To Dr Karen Beeton for her support on the provision of extended funding from the department.

To Mr Jon Woollard for being extremely helpful on the laboratory matters throughout, and for being the most prolific participant in my experiments.

To Mrs Diana Davis and other former and current colleagues at the University of Hertfordshire for their kind support and participation in the project.

To Dr Anthony Herbland for his invaluable expertise and help with the ultrasound image analysis.

To Dr Jane Simmonds for all her help, and for introducing me to this project in the first place.

To all the colleagues at the Safari Therapy Unit, Hemel Hempstead Hospital for their help and support for the clinical trial.

To all those patients at the Hemel Hempstead Hospital who kindly volunteered to participate in the clinical trial.

…and finally

To my parents who kept asking every other week that when was I going to finish this work!

To my seven-year-old son Sidharth for appreciating that I was working on ‘something big’!

To my wife Byju for all her patience and support (…and sometimes the lack of it)!

Thank God.

List of contents

Table of Contents

List of tables

List of figures

List of publications

1) Kumaran B, Watson T. Radiofrequency-based treatment in therapy-related clinical practice – a narrative review. Part I: acute conditions. Phys Ther Rev. 2015;20(4):241-54.

2) Kumaran B, Watson T. Radiofrequency-based treatment in therapy-related clinical practice – a narrative review. Part II: chronic conditions. Phys Ther Rev. 2016;20(5-6):325-43.

3) Kumaran B, Watson T. Thermal build-up, decay and retention responses to local therapeutic application of 448 kHz capacitive resistive monopolar radiofrequency: A prospective randomised crossover study in healthy adults. Int J Hyperthermia. 2015;31(8):883-95.

4) Kumaran B, Herbland A, Watson T. Continuous-mode 448 kHz capacitive resistive monopolar radiofrequency induces greater deep blood flow changes compared to pulsed mode shortwave: a crossover study in healthy adults. Eur J Physiother. 2017;19(3):137-46.

5) Kumaran B, Watson T. Skin physiological effects of 448 kHz Capacitive Resistive Monopolar Radiofrequency in healthy adults: A randomised crossover study and comparison with Pulsed Shortwave Therapy. Electromagn Biol Med. 2018; pp 1-12.

6) Kumaran B, Watson T. Treatment using 448 kHz capacitive resistive monopolar radiofrequency improves pain and function in patients with osteoarthritis of the knee joint: A randomised controlled trial *(in press).*

7) Kumaran B, Watson T. Capacitive resistive monopolar radiofrequency (CRMRF) therapy at 448 kHz: localized application significantly enhances and sustains skin physiological responses. Physiotherapy. 2015;101:e798. *(Abstract presented at the WCPT Congress 2015 in Singapore)*.

8) Kumaran B., Herbland A., Watson T. Capacitive Resistive Monopolar Radiofrequency (CRMRF) therapy at 448 KHz: The effects on deep blood flow and elasticity of tissues. *(Abstract presented at the CSP Physiotherapy UK 2015 Conference in Liverpool, UK)*.

SECTION I: INTRODUCTION AND OVERVIEW

1 Chapter 1 – Electromagnetism, radiofrequency and radiofrequency-based electrophysical agents: key concepts and project overview.

1.1 Research context

Capacitive Resistive Monopolar Radiofrequency (CRMRF) that operates at the base frequency of 448 kHz is a relatively newer type of electrophysical agent (EPA) used in therapy-related clinical practice. Although EPAs delivering CRMRF are commercially available, their evidence base for therapeutic use is largely anecdotal. This programme of research investigated the physiological effects of CRMRF on asymptomatic adults as well as their clinical effects on patients. Besides, the project also evaluated the scope and evidence for the use of all radiofrequency (RF)-based EPAs in therapy operating in the frequency range of 30 kHz – 30 MHz (RF-based EPAs outside of this range are seldom used) through a review of existing literature.

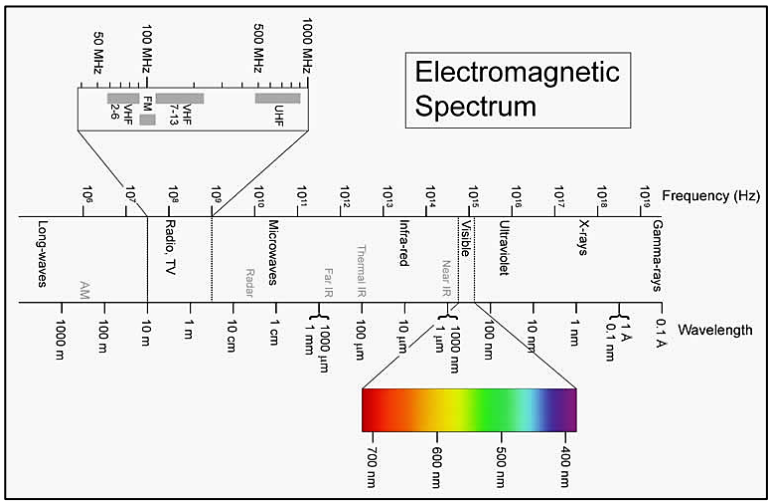
The CRMRF and other similar, but more commonly used EPAs such as shortwave therapies (SWT) employ electromagnetic fields (EMF) within the RF frequency range for their operation. The first chapter of this thesis will explore the background and basic principles that relate to EMF, RF and RF-based EPAs. An overview of the project with its rationale, aims and the key research questions that were addressed will also be presented.

1.2 Electromagnetic fields

Electromagnetic fields are omnipresent. Besides gravity and the weak and the strong nuclear forces, ‘electromagnetism’ is one of the four natural forces. They form an unavoidable part of life on earth. In layman terms, the electromagnetic waves/spectrum (EM waves/EM spectrum) (Figure 1.1) are a series of regular waves that travel at a constant velocity, the velocity of light (approximately 3×10^8 ms^{-1}). The main characteristic that defines an EM wave is its frequency (or the corresponding wavelength). The wave parameters wavelength and frequency are interconnected and are inversely related. The frequency of the wave is directly proportional to the energy the wave carries. Throughout this thesis, the EM waves in question will be identified based on their frequencies.

The EMF frequencies range from as low as 1 Hz of the Extremely Low Frequency (ELF) EMF to as high as 300 EHz (Exahertz, which is 10^{18} Hertz) of the Gamma rays. There are different ways of interaction of these EMFs with the living body depending on the wave frequencies. This concept will be further developed in the subsequent sections of this thesis.

Figure 1.1: A representation of the electromagnetic spectrum comparing wavelength and frequency



1.3 Radiofrequency

Radiofrequency radiations constitute a significant part of the EM Spectrum. They are undetectable to the human senses, unlike some of the other EM waves such as the visible radiation. There is a lack of consensus among the researchers on the frequency ranges that constitute RF. Although many investigators define RF energy as being specifically limited to the frequency range of about 30 kHz – 300 MHz (both CRMRF and shortwaves fall within this range), the Institute of Electrical and Electronics Engineers Inc. (IEEE) proposes a broader frequency range of 3 kHz – 300 GHz to define RF (Figure 1.2).[1,2] In addition to the usual range of 30 kHz – 300 MHz, IEEE proposes a more inclusive very low frequency (VLF: 3 – 30 kHz), the ultra-high frequency (UHF: 300 MHz – 3 GHz), the super high frequency (SHF: 3 – 30 GHz) and the extremely high frequency (EHF: of 30 – 300 GHz) ranges.[1] To put into context, the RF biological literatures that will be covered in this thesis were not collated based on the above frequency groupings. The emphasis placed on the literature within 30 kHz – 30 MHz was based on contemporary clinical practice.

Figure 1.2: Frequency distributions of RF as proposed by IEEE

	Radiofrequency range					
Infrared (**non-RF**)	EHF RF	SHF RF	UHF RF	**Normal range RF**	VLF RF	ELF EMF (**non-RF**)
Frequency above 300 GHz	30 - 300 GHz	3 - 30 GHz	0.3 - 3 GHz	**30 KHz - 300 MHz**	3 - 30 KHz	Frequencies below 3 KHz

Applications of RF are numerous. Their role is pivotal in communication, many industries, and in healthcare where they play a key role in various diagnostic, therapeutic and monitoring procedures in medicine. Whilst the RF literatures pertaining to these areas are

substantial, they are beyond the primary focus of this thesis. The focus of this project will largely be limited to the non-invasive use of RF for treatment in therapy-related clinical practice.

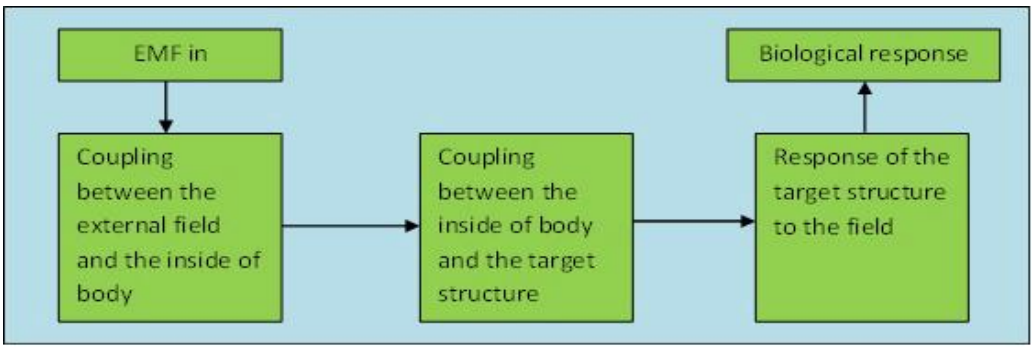
1.4 Radiofrequency and biological systems

To date, several thousand studies have examined the interactions between RF and biological systems, either advantageous or hazardous or both. Whether *in vitro* or *in vivo;* or whether in animals or in human beings, these studies have employed RF energy either in continuous or in pulsed modes. This section of the thesis will briefly discuss the interaction of RF with the biological systems, their underpinning mechanisms and effects.

1.4.1 RF-tissue interaction

The interaction between EMF (including RF) and biological systems is a process that occurs at three levels as illustrated in Figure 1.3 below. At first the external field couples with the field generated inside the body. Then this new induced field at the cellular or subcellular level couples with the target tissue, which then leads to a response from the target structure to the external field.

Figure 1.3: EMF – tissue interaction (adapted from Foster 2000)[3]



A biological response to an RF field must begin with the interaction of electric or magnetic field with an atom, molecule, or molecular system such as a cell membrane or neuron. This must be followed by a biochemical response leading to a functional alteration of the cell and/or organism (tissue response).[3-7]

The ELF EMF (non-RF) primarily flows through the extracellular space in the tissues as the cell membranes offer high impedance with the charges getting accumulated against them, whereas at higher frequencies of 100 – 1000 kHz (0.1 – 1 MHz), the field flows through intra as well as extracellular spaces.[3,4] Coupling the ELF field energy to the body (tissues) through air is difficult owing to the conductivity of body tissues. Hence in physical terms, if the body is considered a high-pass filter the cut off frequency for transmission is in the lower megahertz frequency range.[3] Ultimately, the level of biological effect is determined by the

level of absorption of the EM energy into the tissues and the properties of the exposed tissues that enable it.[8-11] The absorption can be quantified by a parameter known as the specific absorption rate (SAR). It is a numerical representation for the rate at which energy is absorbed by a known mass of tissue and varies by the frequency of the wave and the type of tissue.[3,12,13] The SAR is calculated in watts per kilogram (Wkg^{-1}).

1.4.2 Thermal versus nonthermal effects of RF

Many mechanisms, both ‘thermal’ and ‘nonthermal’ are proposed by which RF can interact with the biological systems regardless of whether they can produce any observable effects at practical exposure levels. However, the issue of 'nonthermal' effects is a matter of debate among the researchers, as to how much do they exist if they do, their possible health risks (for example harmful radiations from communication systems or health care systems), and the exposure conditions that might bring those effects.[3,4,6,14-17]

While the term 'nonthermal' should ideally refer to the mechanism of RF interaction with the tissues rather than the low magnitude of temperature increase from the exposure, a potential source of ambiguity is caused by many authors associating ‘nonthermal’ with the latter meaning. In therapy and biophysics, this is further compounded with the use of terms such as ‘microthermal’ or ‘quasithermal’ to refer to substantially low levels of thermal changes in tissues. Besides, there is the issue of ‘imperceptible’ thermal changes that may often be termed as nonthermal. That is, there is a real thermal change much as very small, but the therapist and the patient (recipient) are unable to perceive it.

Gross thermal effects might result from bulk temperature increase or from the rate of temperature increase even though the bulk temperature might be small. Non-thermal effects are thought to be evoked by SARs that do not cause a measurable rise in gross tissue temperature, and happen at cellular level, influencing the function of cell membranes and organelles.[3,4,16,18] Several thermophysiological responses are induced by the conversion of RF energy into heat energy in tissues[4,17,19,20] such as a rise in tissue temperature (both skin and deep), heat induced vasodilatation, increased blood flow (potentially both skin and deep blood flow), changes in the rates of biochemical reactions and changes in peripheral nerve conduction.[1,21,22] As suggested, the extent of these responses will depend on several factors (relating to the wave and tissues) that determine the SAR such as the frequency of the wave, the thermal conductivity and thermal capacity of the tissues that absorb the energy, the rate of energy absorption, the rate of metabolism in the treated tissues and whether the circulating blood is able to dissipate the generated heat effectively.[8-11]

Because of energy transfer into the tissues, all interactions between RF and biological systems are likely to increase tissue temperature. However, the nonthermal mechanisms are not believed to be directly associated with this temperature change. Other effects produced

by the RF fields in the tissues such as excitation of molecular vibrations, changes in protein conformation and changes to the behaviour of cell receptor proteins are proposed to be behind the nonthermal effects.[21,23,24] Nonetheless, this is potentially a complex issue since it may be argued that an increase in molecular vibration and production of heat are synonymous and not mutually exclusive.

At thermal doses, RF EMF evokes thermophysiological responses in the exposed tissues and the body as a whole.[17,20,22] While the majority of the research conducted in this area is on laboratory animals (mainly rodents), studies on human exposure have also been reported.[25-29] There are limitations to the extrapolation of the results obtained from animal models to human beings for most of the physiological systems. This is because the lab animals such as rodents are considered poor models for human beings owing to their limited physiological heat loss mechanisms. For example, while humans (wearing clothes) have a thermoneutral zone of 22–25 ^{o}C, rodents (mainly mice) have a higher thermoneutral zone of around 30 ^{o}C.[30-32] Their inability to sweat through the hairy skin might make pigs a better alternative in some work. Whether the research itself was carried out on hair free skin is another issue to be considered.

Some researchers argue that low-level nonthermal biological effects of RF do exist below a few megahertz and might be possible at frequencies as high as a few hundred megahertz (True nonthermal effects of RF might exist only below certain frequencies (<10 MHz) of the wave).[6,7] Others argue that *per se* the frequencies of RF higher than 10 MHz may not induce any physiological effect at cellular level in the absence of heating.[33] However, there is a lack of theoretical or experimental support for such effects between about 100 MHz and 150 GHz despite the extensive research in this area.[4-7,26,34,35] Furthermore, thermal effects can occur even at very low levels of thermal change, as cell metabolism can be affected by even fractional changes in temperature. Since biological systems are constructs of molecules held together and affected by 'Coulomb' forces, it is reasonable to expect that RF might interact with them. However, to affect these systems with external fields, energy must be pumped in either causing both conformation and functional change or imposing fields large enough to affect the function of one or more of the various endogenous fields.[5,20]

The endogenous fields that are linked to the biological processes can be disrupted or affected by the application of external fields on the same order of magnitude or greater, when applied with the proper direction, timing and frequency.[36] The applied fields that augment these endogenous fields promote the biological activity and the applied fields that diminish them will have a suppressive effect. Experiments in plant cells showed that nonlinear behaviour at cell membranes does not occur above approximately 10 MHz in the absence of heating, which were later supported by theoretical analysis and recent experimental work in humans.[33,37,38] RF fields at frequencies exceeding a few megahertz are

not rectified by the biological systems efficiently enough to affect endogenous fields, particularly by mechanisms involving electrical potential changes at the plasma membrane.[5,6] It is well known that a single RF photon is not energetic enough to cause ionization. Hydrogen bonds, considered the weakest of chemical bonds, are on the order of 1 – 5 kcal/mol, which would be equivalent in energy to a 10 THz (terahertz) photon. Much as RF cannot directly contribute to the breaking of chemical bonds, they are potentially capable of exciting molecules (cause them to vibrate). Such excitation and the associated heat mediated effects lead to changes in biochemical processes with demonstrable biological consequences.[6,7]

1.4.3 RF tissue absorption

During RF exposure, energy may be selectively deposited in specific tissue beds, their pattern varying with many physical factors of both the radiation and the target tissue. RF exposure may or may not produce a warm environment in the tissue depending on many parameters of the signal such as the frequency, intensity of application, duration of exposure, as well as the body locus and the exposed surface area. Higher RF frequencies (10 GHz or above) generally have a similar absorption profile as infrared (IR), getting absorbed in the most superficial layers of the skin. However, lower RF frequencies will be absorbed in complex patterns at other depths. In humans, a prediction of the ensuing thermal sensation is difficult because of the lack of thermoreceptors at depth. Irradiation of small skin areas by three or 10 GHz pulsed microwave (PMW) had to last at least five seconds for the minimal intensity to evoke a thermal sensation and the exact intensity depended on the area stimulated.[3-5,14,21,39,40] Historically, pulsed wave (PW) radiation has been found more likely to produce certain biological effects than continuous wave (CW) radiation at the same average incident PD, with support from several studies.[22,41]

1.4.4 Biological effects of RF

There is extensive literature surrounding the effects of RF on biological systems. The literature relating to the health effects of RF can be classified as those studies that investigate the physiological / clinical responses due to intended exposure and those that investigate their adverse / undesirable effects, mainly due to occupational / unintended exposure to RF. The adverse health effects due to occupational or experimental exposure have been studied for several decades. They include numerous studies and their reviews on physiological systems such as the central nervous (CNS), cardiovascular (CVS), endocrine, reproductive and immunological systems; and specific conditions such as cancer and tumours.[2,42,43]

A significant proportion of the experimental research on the biological effects of RF has been conducted on laboratory animals, with emphasis on rodents. A large proportion of

epidemiological studies published in recent years have addressed the potential health concerns from mobile phones. Although RF could cause various biological changes, the consensus is that either the epidemiological studies or the human exposure experiments does not suggest an actual health risk [1,21,44-46] from RF in general, or specifically from low frequency RF (<10 MHz).[1,47] Furthermore, distinguishing the normal biological effects from adverse health effects is crucial, since many reported effects were within the normal physiological ranges. The relevance to health hazards is therefore uncertain.[1,48]

The issue of the biological effects of RF formed the basis of this research project, which was investigated in multiple stages. As stated at the beginning of this chapter, the pertinent literature on all RF-based EPAs in therapy-related clinical practice and associated literature from experimental studies were reviewed. The physiological and clinical effects of RF at 448 kHz were investigated in laboratory and hospital-based settings on asymptomatic adults and adult patients respectively. The rest of this chapter will provide a brief overview of the project and its development, its rationale, the research questions and overall aims.

1.5 Overview of the project

1.5.1 Development and sequencing

The funding for this study was provided by the external stakeholder (commercial organisation), who are a device manufacturer based in the EU (Indiba S. A., Barcelona, Spain). The manufacturer wished to conduct a study to investigate the clinical efficacy of CRMRF in a patient population. Upon discussions between Professor Tim Watson and Indiba S. A., it was concluded that the study should address wider issues including both physiological and clinical effects of CRMRF owing to its lack of evidence in the contemporary literature. At the time, it was also agreed that the study will be further developed and conducted as a PhD project. A draft outline of the main aims of the project and the potential phases of study were proposed by the principal supervisor (Professor Tim Watson) prior to the involvement of the research student (Binoy Radha Kumaran). These proposals were further developed by the student into a project containing three phases (phases I – III) in a logical order, to investigate the theoretical construct, existing evidence and the physiological and clinical effects of CRMRF-based therapy.

In phase I, a general review of the relevant RF literature in relation to its biological effects and theoretical underpinning; and a detailed review of the relevant evidence base for the use of RF-based treatment in therapy-related clinical practice were planned. The findings from phase I were expected to inform the content and design of a phase II study, where a series of laboratory experiments were planned. A robust evaluation of the physiological effects of CRMRF in asymptomatic volunteers was expected to enable a fundamental consideration of the primary effects of this therapy. The phase II involved a step by step investigation of the

optimum dosage and delivery methods for CRMRF and the various skin and deep physiological effects to its multiple doses of delivery. Further, the findings from phase II was expected to help design a clinical study (as phase III) involving an appropriate patient group. CRMRF being an EPA designed to be used in the realm of therapy-related clinical practice, the researchers concluded that it was imperative to investigate the effects in a clinical population, regardless of the outcomes of the physiological studies in phase II. The aim was to conduct a robust randomised controlled trial (RCT) with sufficient statistical power; however, the researchers were aware that time and funding constraints could lead to the phase III being limited to a pilot or a feasibility study. In the end, with the help of extended time as well as extended funding, the project could achieve an adequately powered RCT in phase III.

This research project started in February 2012. The phase I was completed by May 2013. The phase II was completed by December 2014. In phase III, the clinical trial endured substantial and unforeseen delays owing to several administrative hurdles. Eventually, it started in January 2016 and was completed by the end of October 2016. The content reported in this thesis is solely the work designed, carried out, analysed and written by the research student and the external stakeholder had no role in the process.

1.5.2 RF-based treatment in therapy-related clinical practice

RF-based EPAs have been used in physiotherapy since the early decades of last century.[49-54] Three types of RF modalities, which operated on three distinct frequency ranges in the RF spectrum, were mainly in use. Longwave diathermy (0.5 – 1.0 MHz) became obsolete in the 1950s owing to its interference with the communication and broadcasting frequencies.[55] Shortwave therapy (SWT) (otherwise known as shortwave diathermy, or SWD) (27.12 MHz) and Microwave therapy (otherwise known as microwave diathermy, or MWD) (up to 2.45 GHz) became more established. The literature on microwave therapy and longwave diathermy will not be considered in this thesis since the focus here is on EPAs that are still frequently used in therapy practice. Evidence suggests that microwave therapy is currently not commonly used in many countries.[56-59]

Although historically SWT was used in several different frequencies, they were not the same in all countries. In 1947, three frequencies at the short end of the RF band (40.68 MHz, 27.12 MHz and 13.56 MHz) were assigned by the Federal Communication Commission of the United States Government for the medical use of shortwave. This was done as an attempt to regulate the use of high frequency currents in different disciplines.[60] The allocation of these frequencies relates to international regulation rather than their clinical efficacy. Of the three frequencies, 27.12 MHz is the most widely used in current clinical practice.[18]

There are two modes of SWT: continuous (CSWT) and pulsed (PSWT). The CSWT was the first to have become available, being widely used by clinicians since the early decades of 20th century.[49-54] However, the evidence suggests that CSWT has now become less popular and rarely used (especially in the western world).[56,61] It may be argued that this drop in popularity is partly linked to a 'fashionable shift' since there is in fact an evidence base in favour of CSWT.[18] On the other hand, PSWT, which was developed in the 1940s, is still in use among about 11% of outpatient clinics in the UK.[56,61,62]

1.5.3 Rationale

In addition to the above three modalities, RF-based devices operating at significantly lower frequency ranges (below 1 MHz) have also been used. However, despite a lack of robust research evidence such EPAs have become commercially available and used by therapists worldwide since many years. The CRMRF is one such relatively newer type of low frequency (448 kHz) RF used in the realm of physiotherapy and rehabilitation in many countries in Europe (e.g. Spain, Italy, Germany, France) and elsewhere (e.g. Singapore, Japan, Brazil). Consistent with the above statement the CRMRF evidence base for therapeutic use is largely anecdotal. This programme of research was designed to investigate the physiological effects of CRMRF on asymptomatic adults as well as their clinical effects on patients. Besides, the project also evaluated the scope and evidence for the use of all RF-based EPAs generally used in therapy practice, through a comprehensive review of existing literature.

Throughout the various study elements of the project, CRMRF was delivered using the device named 'Indiba Activ 902', which is a commercially available kit manufactured by Indiba S. A., Barcelona, Spain. The project itself is funded by Indiba S. A.; however, the industry funders had no role in the designing and overall administration of the study, collection and analysis of data, or in the preparation of this thesis.

The key aims, and research questions of this project are listed below. To address those aims three phases of research were undertaken: literature review, laboratory-based physiological study and hospital-based clinical study. These are covered in detail in the chapters that follow.

1.5.4 Key aims and research questions

1.5.4.1 Primary research questions

1) How robust is the evidence base to support the use of RF-based treatment in therapy-related clinical practice?

2) What are the effects of 448 kHz CRMRF on the skin and deep physiological parameters in an asymptomatic population, and how do they compare with that of PSWT?

3) Do the above-mentioned physiological effects vary between asymptomatic adults and patients?

4) Does 448 kHz CRMRF therapy provide increased clinical benefits in patients with osteoarthritis of the knee joint when compared to the current exercise-based standard care or to a placebo?

1.5.4.2 Overall aims of the programme of work

1) Investigate the theoretical construct and the physiological and clinical effects of RF-based EPAs in therapy-related clinical practice through a review of existing literature.

2) Design a robust methodology and investigate the physiological effects of CRMRF on asymptomatic adults in a laboratory-based study and compare those effects to those obtained with existing similar RF-based EPAs such as PSWT.

3) Based on the methodology evolved from the laboratory study, investigate the physiological and clinical effects and efficacy of CRMRF therapy in a randomly selected cohort of patients with knee osteoarthritis.

4) Contribute to the body of existing evidence through dissemination of the above research findings and make recommendations for future research.

1.6 Conclusions

Radiofrequency energy is omnipresent and is inseparable from our everyday lives. The biological effects of RF are proposed to be thermal, nonthermal, or both. While the thermal mechanisms of action are well established, the ‘so called’ nonthermal mechanisms are less clearly understood and are hence controversial. There is an extensive literature base that covers the biological effects of RF, although only part of it is specifically relevant to the purpose of this research project. Among the innumerable applications of RF, their use in therapy-related clinical practice forms the basis of this thesis. The current chapter provided an insight into the physics and theoretical underpinning of RF in general and the principles of RF-tissue interaction. The chapter has also laid down the rationale and key aims of this research project. The chapters in Section II will discuss the biological and clinical literature concerning RF in greater detail.

SECTION II: THE LITERATURE

2 Chapter 2 – Literature review on the biological effects of radiofrequency: methodology and main results.

2.1 Introduction

While the previous chapter provided a brief overview of RF as a whole, its physics and underpinning theory, the present chapter aimed to identify the literature directly relevant to the research questions addressed in this project. There is extensive literature on the biological effects of RF in the high frequency band (Microwaves: 300 MHz – 300 GHz). The smaller RF bands (10 – 100 MHz) that include the shortwaves and frequencies below shortwaves (30 kHz – 10 MHz) have also been studied, although to a lesser extent. These smaller frequency bands are mainly of use in present day therapy practice.[1,19,63-107] Radiofrequencies below the shortwave frequency band are the least researched of all.

As stated in the previous chapter, three types of RF-based EPAs have mainly been used since their inception: Longwave diathermy, microwave diathermy, and pulsed / continuous SWT, of which PSWT is the most commonly used in contemporary practice. Besides PSWT, pulsed RF at 27.12 MHz is also employed by devices bearing other names such as pulsed electromagnetic energy (PEME), pulsed electromagnetic field (PEMF), pulsed high frequency electromagnetic energy (PHFE) or pulsed radiofrequency energy (PRFE). Such diverse nomenclature is a reason for confusion within the existing literature, not just because of the multiple names used for potentially similar devices, but also because some of these devices employ EMF outside of the shortwave frequency band[108-120] while some use an RF frequency of 27.12 MHz.[121-133] The devices that use 27.12 MHz as their operating frequency are fundamentally similar to PSWT. The dissimilar names appeared potentially because of some of the device manufacturers using different terms instead of the more generic PSWT. Throughout this thesis the term PSWT will be used collectively for devices that use a pulsed RF frequency within the shortwave frequency band to ensure consistency.

The RF currently used in therapy-related clinical practice (based on literature published in English) is predominantly in the shortwave frequency band and largely limited to PSWT as a delivery mode.[18,56,61,134-136] As stated in Chapter 1 RF-based devices operating at significantly lower frequency ranges (below 1 MHz) have also been reported and used in clinical practice despite a lack of robust evidence. The use of SWT for various specific clinical conditions have been well reviewed,[49,61,135,137-139] although no one review covered all the therapy-related clinical literature in this frequency spectrum. Owing to the lack of clinical literature, no similar reviews are available for RF-based EPAs below the shortwave frequencies. This literature review aimed to:

1) Identify all relevant RF publications covering the frequency range of 30 kHz – 30 MHz including clinical and non-clinical literature.

2) Undertake a detailed narrative review of all relevant therapy-related RF clinical studies conducted on human patients.

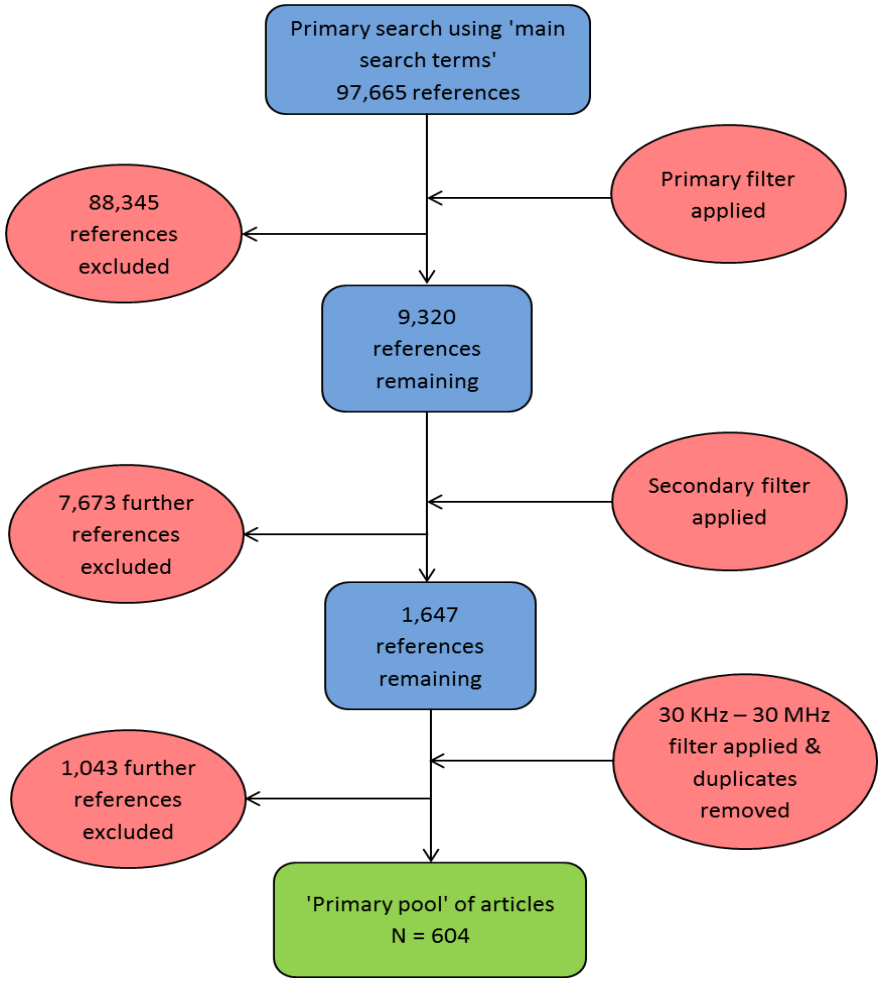
2.2 Methods

2.2.1 Search strategy and reference management

Multiple sources, including the core subject specific electronic databases, printed publications, text books and other online resources were searched to identify peer-reviewed and published literature as well as the grey literature. Online bibliographic databases PubMed, Scopus, ISI Web of Science and CINAHL Plus were used for the electronic searches. Google Scholar was also used as an additional source and a source to identify the grey literature. Further hand searching of the reference lists of relevant publications and texts helped in revealing papers those were initially not identified through the electronic searches. EndNote X6 (Thomson Reuters) software package was used to manage the references.

Publications from all the years to date (October 2016) were identified using key word (main search terms) searches. The results were then filtered using additional words/terms (primary filter). A ‘primary pool’ of articles dealing with the RF frequency range of 30 kHz – 30 MHz was then formed using a string of filter terms (secondary filter) and removing the duplicates using the EndNote filter. The full list of key words and filter words/terms used for searching the literature is given in Appendix 2.1. This pool contained all kinds of clinical, non-clinical, and review articles. The flowchart given in Figure 2.1 works through the process of literature searching.

Figure 2.1: Schematic representation of the literature search process



2.2.2 Narrative review

From the clinical studies in the primary pool, all studies that met the following criteria were selected for the narrative review.

1) Published in English.

2) Relating to any condition in therapy-related clinical practice.

3) Conducted on human patients *in vivo*.

4) Non-invasive and non-ablative methodology.

An all-inclusive methodological approach was followed for this review. This was different to the methodology of a systematic review in that it did not exclude studies based on their study design or overall quality, which is usually the norm. Related and unrelated examples of several such all-inclusive reviews that adopted a similar methodology can be found in contemporary therapy literature.[140-143]

The included clinical studies were stratified as shortwave or non-shortwave (based on the frequency of RF employed), and as acute or chronic (based on the type and duration of clinical condition involved). Shortwave studies were those which employed devices generating RF waves of 10 – 30 MHz and non-shortwave studies were those which employed devices generating RF waves of 30 kHz – 10 MHz. Further stratifications were also done based on the study design (clinical trial, cohort study, case series) and the clinical category (pain and inflammation, tissue healing, others (all other less reported conditions, e.g. – acute pneumothorax)).

An 'acute' condition was considered as a condition not older than 4 – 6 weeks and a 'chronic' condition as a condition older than six weeks. Categorising studies in to distinct acute and chronic groups solely based on the duration of condition or the nature of the clinical category may not always be a valid method. This is because some of these conditions may overlap to a varied extent. However, there is no explicit definition given to the terms 'acute' and 'chronic' in the existing literature.[144,145] Personal opinion or anecdotal evidence has tended to have played a major role in the durations used for such classification.[146]

The methodology described above, which was used for categorising the included studies, was adopted in this review based on clinical practice. There are no specific guidelines available in this regard. Acute and chronic is potentially the commonest form of distinct categorisation employed in therapy practice since treatment goals, strategies, methods and outcomes could vary greatly between the two and it is important to approach them differently. Likewise, RF-based EPAs appeared to have been used mostly for conditions relating to either pain and inflammation or tissue healing (results of the review explained below). Hence, grouping the studies based on these categories was considered prudent and more relevant to clinical practice than any other potential forms of classifications.

2.2.3 Quality assessment of studies

The Cochrane risk of bias assessment tool[147] (where appropriate) (Appendix 2.2) was used to screen the methodological quality of the studies, and the checklist proposed by Downs and Black[148] for randomised and non-randomised studies (Appendix 2.3) was used to score them. The Downs and Black checklist contains 27 items concerning the quality of reporting, validity, bias and statistical power of the studies (maximum score of 32; higher the score better the quality of the study), and is a valid tool for assessing the methodological quality.[149] Modified versions of this checklist have also been used by some authors as a more appropriate tool, which was done by simplifying the 'item 27' (originally scored 0–5) that assesses statistical power.[150,151] This is because the assessment of statistical power in the original version of the checklist is complex and is difficult to be applied to many studies. A

similar modified version was used in the current review. The item 27 was rated as either ‘zero’ (insufficient power) or ‘one’ (sufficient power) for this review. The maximum possible score was hence 28.

2.3 Main results

The ‘primary pool’ obtained after the broad literature search and the subsequent filtering to exclude the duplicates and irrelevant literature contained 604 articles within the 30 kHz – 30 MHz frequency range. The flow chart that explains the stages of the filtering is given in Figure 2.2. Figure 2.3 provides the breakdown of the types and numbers of articles in the primary pool. The clear majority of these (567 articles, 94%) were shortwave studies and only 51 were non-shortwave studies. A few of them (14 articles) overlapped these nominal groupings.

Figure 2.2: Stages of filtering from the ‘primary pool’ of articles

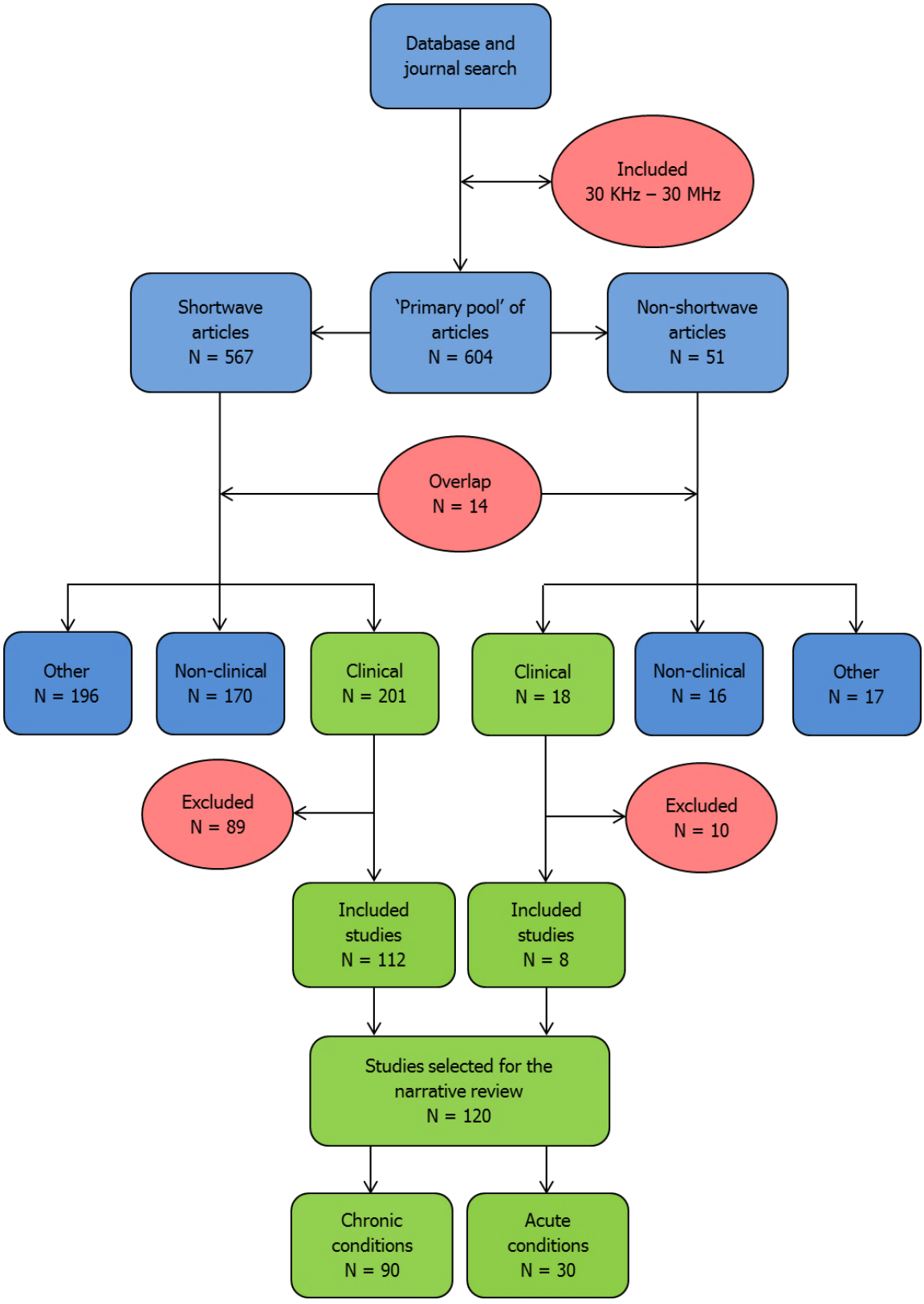
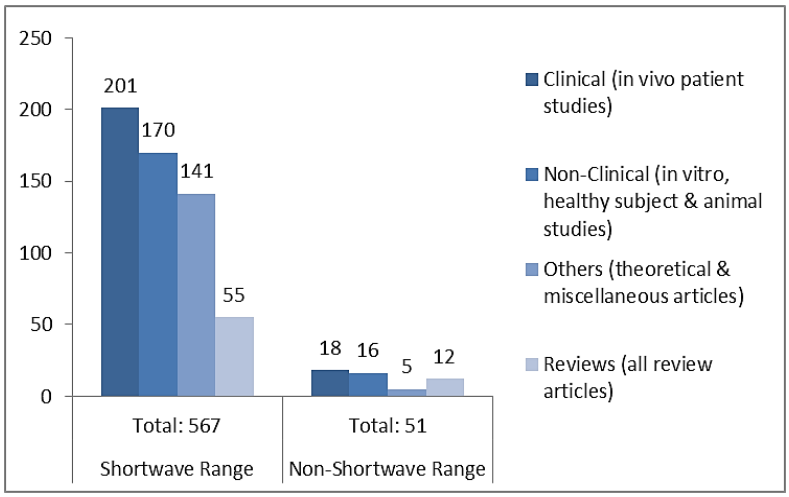
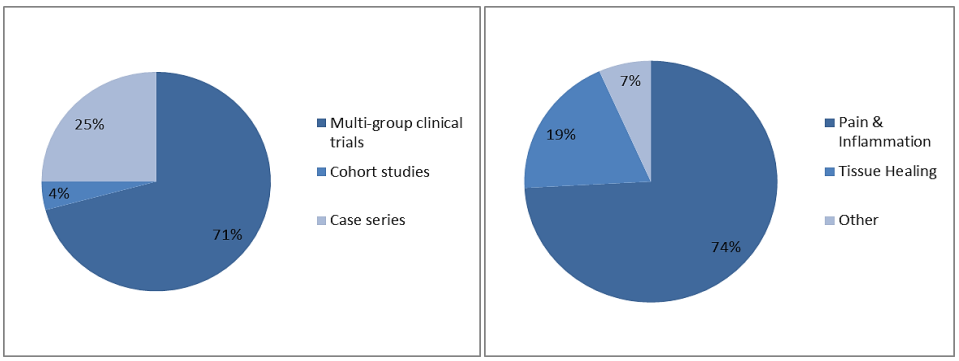


Figure 2.3: Types and numbers of articles in the primary pool



After the exclusions 120 clinical studies met the four criteria set for the narrative review. While 112 (93%) of these were shortwave studies, only eight were non-shortwave studies. Two potentially suitable studies employing shortwave were excluded as they had no proper abstracts and their full-texts were unavailable through the available resources.[152,153] Overall 89 studies related to pain and inflammation and 23 to conditions of tissue healing. A mixture of eight studies relating to less reported conditions (e.g. acute pneumothorax) was classed as 'others'. Similarly, while 85 studies were multi-group trials, 30 were case studies and the remaining five of them were cohort studies (Figure 2.4). However, as identified, clearly there was potential overlap among the clinical application categories, such as between studies that considered tissue healing and that considered pain and inflammation. The allocation of papers to their groups was based on the primary outcome(s) as identified by their authors (e.g. pain, rate of healing). Only a third the studies (30 studies, 25%) investigated acute clinical conditions whereas the remaining 90 studies employed chronic clinical conditions. Except for five studies[154-158] the full texts were available for all the studies included in the review. The abstracts of these five studies were available; hence the main results reported in those abstracts were drawn for this review.

Figure 2.4: Clinical application categories and types of studies



The clinical studies will be reviewed in detail as acute and chronic categories in chapter 3. The rest of this chapter will briefly explore the RF-based studies outwith the clinical literature although a detailed review was not intended.

2.4 Radiofrequency-based treatment: the non-clinical literature

This section will identify the relevant non-clinical RF literature outside of the 120 studies included in the narrative review. They include all the animal studies, healthy-human studies and the *in vitro* studies conducted on human or animal cell/tissue models. A limited number of experimental animal studies that simulated certain clinical conditions were also identified in both acute and chronic categories. Such studies will be discussed in more detail, so that comparisons with clinical studies can be drawn.

2.4.1 Human studies *in vivo* on asymptomatic people

The studies that investigated the physiological effects of RF on healthy people can be classified into various groups depending on the physiological parameters that were being investigated. Predominantly, the effects relating to thermophysiological responses such as tissue temperature,[81,83,89,95,96,105,159-172] blood flow,[19,79,86-88,90,92,173-184] or both temperature and blood flow[77,80,85,104,185-187] were investigated. Many studies have also investigated connective tissue (e.g. muscle and tendon) responses to RF exposure,[82,84,91,94,101,106,188-190] while some other studies investigated physiological responses such as the effects on peripheral nerves[78,191,192] and immunological markers.[193] None of the above *in vivo* studies employed RF below the shortwave frequency band.

Many of the above studies employing RF devices that investigated the human thermophysiological responses such as temperature, blood flow and nerve conduction were comparable to the studies carried out in this project.[77,80,85,86,187,192] Several of these studies that mostly employed RF at the shortwave frequency band investigated skin and/or deep thermal responses of humans to RF exposure.[77,80,81,83,85,95,96,105,194] Among them many of the earlier published studies[77,81,85,96] reported a significant rise and maintenance of both skin and intra-muscular temperatures. A more recent study that closely related to the methodology employed in this project was the study by Bricknell and Watson (1995).[105] They employed incremental doses of PSWT on asymptomatic participants and reported their dose parameters that produced a 'possible thermal perception' (Mean 'mean power (MP)' of 6.58 (±3.50) W) and a 'definite thermal perception' (Mean MP 10.88 (±3.32) W) on the skin.

In another study, which was conducted at the University of Hertfordshire, Al-Mandeel and Watson[80,192] reported significant rises in the skin temperature with high and low doses of PSWT (MP dose of 24 & 3 W respectively). Draper et al. (1999)[83] investigated the temperature changes inside the gastrocnemius muscle in response to a 20-minute PSWT exposure (MP dose of 48 W). A mean (SD) temperature rise of 3.49 (±1.13) ^{o}C was reported

after the treatment and a decay of 1.78 (±0.69) ^{o}C was reported in the first 10 minutes post-treatment. The methodology of this study was unrelated to that used in the current project as it was an invasive study (discussed in Section III).

Likewise, among the studies that investigated the effects of PSWT on blood flow, some studies have proposed a significant rise in skin and/or muscle blood flow after treatment with PSWT[19,176] while it has been disputed by others.[90] Similar to the rise in tissue temperature as mentioned above, Al-Mandeel and Watson[80,192] also reported a significant rise in blood flow in the skin during treatment with PSWT (MP dose of 24 W). However, this response dropped significantly once the PSWT exposure was stopped. Besides the studies on PSWT, further shortwave studies were reported employing CSWT, which suggested a high and/or sustained increase in temperature,[81,96] blood flow,[79,86] and both temperature and blood flow.[77,85] Comparison of the effects of similar average doses of PSWT and CSWT on blood flow are also available.[19]

Studies employing shortwave that investigated blood flow in deeper tissues and conducted on either healthy subjects[19,77,91,195] or patients[196-198] have also been reported similar to the current project. The current evidence available from the literature on the deep circulatory effect of PSWT is mixed.[19,90] Morrisey (1966)[90] reported that while irradiation of the calf muscles or abdomen using PSWT for 15 min at 40 W did not have any significant influence on the volume of blood flow in the leg, an 80 W exposure to the calf caused a significant increase in the blood flow. Similar increase in calf and foot blood flow after a 20-min abdominal exposure to PSWT at 65 W was reported by Silverman and Pendleton (1968),[19] while a 15 W abdominal exposure did not have any significant impact. These results demonstrated a dose response relationship.

As evident from the main results of this review, overall a very low number of non-clinical studies employed RF below the shortwave frequency band. No *in vivo* human studies relating to this research project were found among them.

2.4.2 Animal studies, *in vitro* studies on cell and tissue models

Several RF studies conducted on either animals or *in vitro* tissue models have been reported over the past century. Unlike the healthy-human studies identified above, some studies that employed RF below the shortwave frequency band have also been identified in this category,[98-100,102,199-205] all of which were *in vitro* studies unrelated to therapy practice. The animal studies belonging to the shortwave frequency band were related to a variety of experimental conditions such as the effects on bone and joint tissues,[73,74,76,103,206-209] muscle and tendon,[67,68,75,188,210] neural tissues,[121,122,211,212] blood,[70,213] tumours,[165,214] histamine,[215,216] cardiorespiratory system,[217] metabolism,[218] wound healing,[69] skin flaps[219] and infection.[93]

Several *in vitro* studies conducted on human or animal tissue substrates employing RF within the shortwave frequency band were also identified.[64,202,220-225]

2.4.3 Experimental animal studies simulating acute clinical conditions

Six animal studies were identified in total, of which four studies investigated the effects of SWT on healing of acute experimental wounds. Two of these studies were based on the healing of skeletal muscle injuries[67,68] and one study each was found on bone injury[103] and skin wound.[69] Of the remaining two studies, one study each investigated the resolution of experimental haematomas[70] and arthritis[73] with the application of PSWT.

Hutchison (1951)[103] conducted two experiments on adult dogs with bilateral tibial grafts and adult male rabbits with radial fracture. Conventional CSWT was used in both experiments at a 'mild thermal' dose (20 minutes twice daily). In both experiments, the authors concluded that CSWT 'significantly delayed' the healing of fractures and bone grafts compared to the untreated control group animals. These findings are contrary to the findings of the clinical study by Cameron (1964)[226] (discussed in Chapter 3). Similarly, rabbits with skin cuts and guinea pigs with third degree skin burns were subjected to PSWT (38 W MP for 10 minutes once daily) by Constable and colleagues.[69] Unlike the results from the clinical studies discussed in Chapter 3, PSWT did not improve wound healing in either of the animal groups.

Calf muscle injury in rabbits, which was induced by injecting 'xylocaine' was treated by PSWT (dose parameters not fully reported) for 20 minutes twice daily for either eight or 16 days in the study by Brown and Baker (1987).[68] While the 8-day treatment failed to influence muscle healing, a trend towards enhanced healing was observed with a 16-day treatment programme. In another study on the effects of CSWT (five minutes daily for seven days at an intensity producing 'bearable heat') on induced biceps femoris muscle injury in adult dogs, Bansal and colleagues[67] demonstrated early maturation of the collagen fibres at the healing site as well as regeneration of the injured muscle fibres. It is unclear how the authors could adjust the dose as 'bearable heat' in an animal model. Both the above studies were comparable to the clinical studies on postoperative wound healing discussed later in Chapter 3, though the results were conflicting.

Fenn (1969)[70] reported the effects of PSWT (30 minutes twice daily for 9 days; dose parameters not fully reported) on experimental haematomas induced in the ears of 30 male rabbits. Fifteen actively treated animals demonstrated a significantly faster resolution of the haematoma compared to another group treated with a placebo. Similarly, Nadasdi (1960)[73] used PSWT (10 minutes for up to four times; dose parameters not fully reported) in rats with experimentally induced arthritis of the tibio-calcaneal joint. Significant inhibition of arthritis was obtained with PSWT when compared to the non-treated group. In another study, Silverman (1964)[93] showed that either CSWT or PSWT was no different to a control or a

placebo condition in treating infected mice. Mice inoculated with pneumococcus bacterial colonies were irradiated for 15 minutes twice daily for three days or till the animals died. The treatment failed to improve the survival rate or time. No clinically relevant human studies were identified under any of these three conditions.

2.4.4 Experimental animal studies simulating chronic clinical conditions

Unlike for acute conditions, the researcher identified only one animal study[74] that evaluated the effects of RF-based therapy that was directly relevant to chronic clinical conditions. Vanharanta (1982)[74] investigated the effect of continuous shortwave therapy (CSWT) on the joint mobility and radiographic changes during the development of osteoarthritis (OA) of the knee joint. The authors developed an experimental model of OA knee by periodically immobilising the knee joints of rabbits. They were then treated with CSWT (55 sessions in 11 weeks, 5 minutes per session) and compared with an identical group of non-treated rabbits in a control group. The groups did not show any significant difference between them post treatment, in terms of joint mobility or radiological changes. A lack of further animal studies relevant to chronic conditions made it difficult to draw a definite comparison with human studies.

2.5 Conclusions

The methods adopted to identify the relevant RF literature within the frequency range of 30 kHz – 30 MHz and the overall results of the literature search have been explained in this chapter. The results showed that 120 studies were conducted on patients using some form of RF therapy. Apart from the clinical studies, several experimental studies that were carried out on a non-clinical sample (tissue models, animals, asymptomatic subjects) were also identified. The next chapter in this section of the thesis will discuss in detail the RF clinical studies identified on acute and chronic conditions.

3 Chapter 3 – Radiofrequency-based treatment in therapy-related clinical practice.

3.1 Studies on acute conditions

As described in Chapter 2, out of the total of 120 relevant clinical studies that were identified for the narrative review, 30 studies were related to acute clinical conditions. Each of those studies will be considered in detail in the sections below. No studies employing a frequency below the shortwave range was identified among the acute conditions. All 30 studies used devices operating at 27.12 MHz. Conditions pertaining to pain and inflammation was reported by 22 studies.[124-127,130,131,227-242] Tissue healing[129,154,155,226,243-245] was reported by seven studies and one study reported other less reported conditions (acute pneumothorax).[246] The main characteristics of all these studies along with their Downs and Black scores are reported in Table 3.1.

Table 3.1: RF studies on acute therapy-related conditions

Study	Diagnostic category	Outcomes measured	Study type, sample size and number of groups	Type of RF used	RF dose parameters					Number and duration of sessions	Did RF improve the outcomes significantly?	Downs and Black score (out of 28)
					CSWT Power (W)	PSWT						
						PP (W)	PD (μs)	PRR (pps)	MP (W)			
Kaplan and Weinstock 1968	Foot surgery	Pain, oedema and erythema	RCT; 100 subjects; 2 groups	PSWT		975/ NR	65	600/ 400	38/ NR	≥7 (over 3 days); 10–15 min/session	Yes	15
Aronofsky 1971	Dental surgery	Pain, inflammation and 'healing rate'	Non-RCT; 90 subjects; 3 groups	PSWT		975	65	600	38	≤6 (over 4 days); 10–15 min/session	Yes	9
Hutchison et al. 1978	Dental surgery	Pain, swelling, trismus, analgesic intake and complications	RCT; 82 subjects; 2 groups	PSWT		NR	65	500	NR	5 (over 4 days); 10 min/session	No	12
Santiesteban and Grant 1985	Foot surgery	Analgesic intake and hospital stay	RCT; 50 subjects; 2 groups	PSWT		120	95	700	8	2 (over 1 day); 30 min/session	Yes	16
Reed et al. 1987	Inguinal herniorrhaphy surgery	Pain and analgesic intake	RCT; 43 subjects; 2 groups	PSWT		1	60	320	0.02	≥4 (over 2 days); 15 min/session	No	17
Heden and Pilla 2008	Breast augmentation surgery	Pain and analgesic intake	RCT; 42 subjects; 3 groups	PSWT		2	2000	2	0.01	31 (over 8 days); 30 min/session	Yes	22
Rohde et al. 2010	Breast reduction surgery	Pain, interleukin 1-β level and analgesic intake	RCT; 24 subjects; 2 groups	PSWT		2	2000	2	0.01	12 (over 2 days); 20 min/session	Yes	23
Rawe et al. 2012	Breast augmentation surgery	Pain and analgesic intake	RCT; 18 subjects; 2 groups	PSWT		98×10^{-4}	100	1000	0.001	7 (over 7 days); 24 hours/session	Yes	22
Czyz et al. 2012	Blepharoplasty surgery	Pain, oedema and ecchymosis	RCT; 57 subjects; 2 groups	PSWT		9.4×10^{-9}	10^{5}	1000	0.94×10^{-6}	4–10 (over 4–10 days); ≈7 hours/session	No	21
Wilson 1972	Ankle soft tissue injury	Pain, swelling and disability	Non-RCT; 40 subjects; 2 groups	PSWT		975	65	600	38	3 (over 3 days); 60 min/session	Yes	16

Wilson 1974	Ankle soft tissue injury	Pain, swelling and disability	Non-RCT; 40 subjects; 2 groups	CSWT/ PSWT	NR	975	65	600	38	3 (over 3 days); 30/60 min/session	Yes	14
Pasila et al. 1978	Ankle and foot soft tissue injuries	Ankle strength, range of movement, swelling and gait	RCT; 300 subjects; 3 groups	PSWT		NR	NR	NR	38/40	3 (over 3 days); 20 min/session	No	13
Barker et al. 1985	Ankle soft tissue injury	Pain, swelling, range of movement and gait	RCT; 73 subjects; 2 groups	PSWT		NR	65	640	NR	3 (over 3 days); 45 min/session	No	17
McGill 1988	Ankle soft tissue injury	Pain and swelling	RCT; 37 subjects; 2 groups	PSWT		600	400	82	19.6	3 (over 3 days); 15 min/session	No	16
Pennington et al. 1993	Ankle soft tissue injury	Pain and swelling	RCT; 50 subjects; 2 groups	PSWT		NR	NR	NR	NR	1 (over 1 day); 70 min/session	Yes	18
Wright 1973	Lower limb soft tissue injuries	Pain, swelling and 'return to function'	Case series; 40 subjects	PSWT		NR	NR	NR	NR	≤8 (over ≈7 days); NR	Yes	5
Nwuga 1982	Lumbar intervertebral disc prolapse	Lumbar range of movement	Non-RCT; 51 subjects; 2 groups	CSWT	NR					≤18 (over ≈6 weeks); 20 min/session	No	14
Barclay et al. 1983	Hand soft tissue injuries	Pain, swelling and disability	RCT; 230 subjects; 2 groups	PSWT		975	65	600	38	≤14 (over ≈7 days); 30 min/session	Yes	17
Grant et al. 1989	Perineal trauma post childbirth	Pain, oedema, bruising, haemorrhoids and analgesic intake	RCT; 414 subjects; 3 groups	PSWT		NR	65	100	NR	3 (over 2 days); 10 min/session	No	24
Foley-Nolan et al. 1992	Whiplash injuries	Pain, range of movement and analgesic intake	RCT; 40 subjects; 2 groups	PSWT		NR	60	450	NR	84 (over 12 weeks); 8 hours/session	Yes	21
Livesley et al. 1992	Shoulder fracture	Pain, muscle bulk, muscle strength, range of movement and joint function	RCT; 48 subjects; 2 groups	PSWT		300	NR	35	NR	10 (over ≈14 days); 30 min/session	No	20

Buzzard et al. 2003	Calcaneal fracture	Swelling and ankle range of movement	Non-RCT; 20 subjects; 2 groups	PSWT		35	200	26	0.18	10 (over 5 days); 15 min/session	Yes, but not better than ice therapy	17
Rhodes 1981	Oral surgery	Bleeding, healing time, return to function, pain and oedema	Non-RCT; 501 subjects; 2 groups	PSWT		975	65	600/ 400	38/ 25.3	NR adequately; 40 min/session	Yes	8
Goldin et al. 1981	Skin graft wounds	Rate of healing and degree of pain	RCT; 67 subjects; 2 groups	PSWT		975	65	400	25.3	29 (over 7 days); 30 min/session	Yes	12
Nicolle et al. 1982	Blepharoplasty surgery	Oedema and ecchymosis	Case series; 21 subjects	PSWT		NR	100	1000	NR	1 (over I day); 24 hours/session	Yes	12
Bentall and Eckstein 1975	Orchidopexy surgery	Oedema and healing rate	RCT; 100 subjects; 2 groups	PSWT		NR	65	500	NR	12 (over 4 days); 30 min/session	Yes	NA
Arghiropol et al. 1992	Postoperative wound	Healing rate and plasma fibronectin concentration	NA	PSWT		NR/ 975	65	400/ 600	NR/ 38	NA; 45 min/session	Yes	NA
Cameron 1964	Surgical and non-surgical wounds	Rate of healing and hospital stay	Non-RCT; 646 subjects (3 studies with 2 groups each)	PSWT		NR	65	400	NR	8 (over 4 days); 40 min/session	Yes	5
Muirhead et al. 1991	Pre-tibial laceration	Size of wound and healing time	RCT; 129 subjects; 2 groups	PSWT		NR	400	20–46	NR	≤18 (over ≈6 weeks); 10 min/session	No	16
Ma et al. 1997	Pneumothorax	Time to lung re-expansion	RCT; 22 subjects; 2 groups	CSWT	NR					≤13 (over ≈13 days); 25 min/session	Yes	18

RCT – Randomised Controlled Trial; RF – Radiofrequency; CSWT – Continuous Shortwave Therapy; PSWT – Pulsed Shortwave Therapy; PP – Peak power; PD – Pulse duration; PRR – Pulse repetition rate; MP – Mean power; NR – Not reported; NA – Not available to the authors; W – Watts; µs – Microseconds; pps – Pulses per second; min – Minutes.

3.1.1 Studies on pain and inflammation

Studies on acute conditions relating to pain and inflammation were the largest group. Conditions included postoperative pain (nine studies),[124,126,127,130,227,228,235,241,242] ankle injuries (six studies),[125,229,231,234,236,239] fracture pain (two studies),[238,240] hand injuries (one study),[233] acute low back pain (one study),[232] whiplash injuries (one study)[237] and pelvic trauma in women (one study).[131] In addition, there was one case series on soft-tissue injuries in professional footballers.[230]

3.1.1.1 Postoperative pain

Significant reduction in postoperative pain, oedema and erythema was achieved using PSWT on patients who had undergone foot surgery (100 participants in two groups – active or placebo) in the study by Kaplan and Weinstock.[227] PSWT applications were given for 10–15 minutes twice daily to the operative site as well as to the epigastrium. However, only limited reporting (especially dosage and statistics) has been done by the authors when compared with current expected reporting standards, and it is unsure if the two study groups were statistically equal at baseline. Comparable results to this study were also achieved by Aronofsky,[228] who used a similar dose of PSWT on patients who had undergone oral and dental surgical procedures (90 patients in three groups). Two treatment sessions (15 and 10 minutes) were given pre-operatively and/or 10 minutes postoperatively to the surgical site of the participants in the active group(s). This was a methodologically poor-quality trial lacking objective outcome measures, without blinding or randomisation and lacking equivalence between groups at the baseline.

Hutchinson and colleagues[124] reported contrasting results from a similar group of dental surgery patients (82 participants in two groups – active and placebo), who failed to improve their symptoms after PSWT (10 minutes once daily) delivered over the dental surgical sites. It is unclear what dose of PSWT was delivered. Santiesteban and Grant[235] agreed with Kaplan and Weinstock,[227] as two 30-minute sessions of PSWT on the day of surgery significantly reduced NSAIDs intake and hospital stay among patients who underwent foot surgery (50 participants in two groups). It was interesting to note that favourable results were reported despite employing a substantially lower dose of PSWT and number of sessions. This was not a blinded trial and it was unclear if the two groups were equal at baseline. In another study, ‘non-thermal’ PSWT (15 minutes twice daily for two days) failed to improve patients who had undergone inguinal herniorrhaphy.[127] However, it can be argued that an extremely low intensity of treatment (MP of 0.02 W, Table 3.1) with a short intervention period was equivalent to a placebo.[80]

Four RCTs on small wearable type RF generators have been reported recently. Benefit from such therapy in terms of reduced postoperative pain and reduced consumption of pain

medication was shown by two small studies[130,241] on patients who had undergone breast augmentation surgery. PSWT was delivered for 30 minutes 3–6 times per day for the first six postoperative days; and then two times per day until the follow-up visit on day seven In the first study by Heden and Pilla.[130] PSWT was delivered continuously from postoperative day one till day seven in the second study by Rawe and colleagues.[241] In another small study, Rohde and colleagues[126] demonstrated a three-fold drop in the postoperative pain scores after being treated by a wearable PSWT device in 12 patients who underwent breast reduction surgery, compared to 12 placebo-treated patients. The study used a similar device and treatment regimen as Heden and Pilla.[130] The authors also argued that an RF-induced modulation of the wound healing process resulted in a reduction in the interleukin 1-β levels of the wound exudate, which in turn indicated a faster wound resolution. These three studies were of good methodological quality although they were small. The results need to be interpreted with caution until larger studies have been reported.

However, the above benefits were not reproduced when similar wearable device was used in a further study[242] to treat patients who underwent bilateral upper blepharoplasty (57 active and 57 placebos). The participants did not report any difference between the active and placebo in terms of postoperative pain, oedema or ecchymosis in their eyes. However, compared to the placebo the physician-graded erythema was significantly lower in the actively treated eyes. The devices were worn for varying durations postoperatively (active for one eye and placebo for the other), for up to a week. Nonetheless, the participants in this trial also used other treatments such as cold patches where required, which were not controlled or accounted for in the final analysis. The use of PSWT devices varied greatly between participants, and the assessment periods may have differed between groups affecting the validity of data. Besides, it was unclear if the groups were equivalent at the baseline.

Most of the studies in this category have claimed significant benefits from RF therapy. The RF intervention was started either pre-operatively or immediately postoperatively. The studies that reported RF therapy to be not beneficial have generally employed a lower dose and/or duration of treatment (Table 3.1). However, any potential range of ideal doses could not be identified because of the varied nature of dosage parameters used in the studies. The overall methodological quality was problematic for several studies, especially the earlier ones.[124,127,227,228,235] Lack of sufficient statistical power and poor equivalence between the groups at baseline has weakened their overall impact. Also, the majority did not feature a true control group. The epigastric area (over the liver) was treated in some earlier studies, as preceding studies performed on healthy adults[90,175] reported that it increased peripheral circulation. However, this trend disappeared in later years.

3.1.1.2 Acute ankle injuries

Patients (20 active, 20 placebo) who sustained acute ankle inversion injuries experienced a reduction in pain and disability after receiving 60 minutes of PSWT for three consecutive days in an RCT by Wilson.[229] These results were repeated in a further similar study that employed PSWT as well as CSWT, by the same author.[125] Both studies had several methodological limitations. They were neither randomised nor adequately controlled or blinded, did not employ any follow-ups and the statistical reporting was poor. In contrast to their results, a much larger study published by Pasila and colleagues[231] comprising 300 patients with recent ankle and foot injuries failed to demonstrate any significant difference in pain and swelling secondary to PSWT. Two active groups receiving two types of PSWT, and one placebo group were employed. The mean PSWT dose was similar (38 W), but the treatment duration was much shorter (20 minutes daily for three days) in this study compared to that by Wilson.[229] The methodological quality of the study remained equally poor and most of the methodological limitations listed above applied to this study as well. Similarly, no evidence in support of PSWT for acute ankle injuries (45 minutes each for three days) when compared to a placebo was revealed by Barker and colleagues.[234] The study started with 73 participants, but experienced high drop-out at the follow-up, which were not accounted for in the data analysis. Dose parameters for PSWT were not fully reported and neither was there any evidence for the study groups being equal at baseline.

PSWT (three 15-minute sessions) was not found to be beneficial by McGill,[236] who studied patients (37 participants in two groups – active and placebo) with lateral ligament sprain of the ankle. However, the energy delivered was potentially too small to make a realistic impact, since only three short treatments were given. The latest study of this category published by Pennington and colleagues[239] reported that fifty participants who had suffered grade I–II ankle sprain when treated with either PSWT or placebo for one session alone (30 minutes medially and 30 minutes laterally to the ankle joint; 10 minutes to the epigastrium), the PSWT group demonstrated significant reduction in ankle oedema. This study provides little information regarding the benefit of PSWT treatment beyond one day. Also, it was unclear if the groups were equivalent at baseline.

The evidence in this group was ambiguous and none of the studies was of acceptable methodological quality. Except in two studies where the RF intervention started with a delay of 3–4 days after the injury,[231,239] the treatment commenced within 36 hours after the injury in all the other studies. Overall, the methodological shortcomings were several. The doses were varied (Table 3.1) where reported while many studies failed to report any dose-related information. A similar trend to that of the studies on postoperative pain was noted in this group as well, in that the studies that reported no benefit from RF therapy employed a lower dose and/or overall intervention duration.

3.1.1.3 Fracture pain

Two RF studies were found in the fracture pain category. In the first study by Livesley and colleagues[238] PSWT (30 minutes daily for 10 consecutive days) was not found to be beneficial in the management of fracture pain of the neck of humerus. Forty-eight patients (22 active, 26 placebos) were followed-up for up to six months. No significant differences, either for pain or for functional scores were noted at any stage. The study demonstrated good methodological quality but was not devoid of shortcomings. The dosage information was not fully reported; baseline equivalence of the outcome measure data was not established and potentially lacked adequate statistical power.

In the second study, Buzzard and colleagues[240] studied twenty patients with unilateral calcaneal fractures. Either PSWT (15 minutes twice daily for five days) or ice therapy ('Cryocuff' for 20 minutes, six times a day for five days) was applied. Both groups seemed to improve similarly and equally in the daily measurements of swelling and ankle ROM. This study only employed a very low mean dose of PSWT (Table 3.1), which may have been too low to be clinically effective. Moreover, it was neither randomised nor blinded, lacked sufficient statistical power and experienced high participant drop-out rates.

3.1.1.4 Other acute conditions with pain

Wright[230] published a case report on the PSWT management of soft tissue injuries in professional footballers, where daily PSWT repeated for up to a week resulted in a rapid reduction in intra-muscular haematoma. This was not a randomised or controlled study and dose parameters for PSWT were not reported. Fifty-one female patients affected by acute low back pain were treated with either CSWT (20 minutes thrice weekly) or spinal manipulation, for up to six weeks in a clinical trial by Nwuga.[232] This study did not make any objective assessment of pain or outcomes of functional quality of life (QoL). Spinal and pelvic range of movement (ROM) was the main outcome measured. Manipulation was shown to have a greater response compared to CSWT in terms of improving the same. Only female subjects were included in this study making it less generalizable and there were no follow-up assessments.

Women who were recovering from pelvic trauma sustained during childbirth (414 participants) when studied in four groups (PSWT, ultrasound, placebo-PSWT or placebo-ultrasound) by Grant and colleagues,[131] did not reveal any treatment being particularly beneficial. The PSWT treatment was given for 10 minutes daily for three days. This study was large, but lacked objective outcome measures, did not report dosage parameters and the intervention may have been too short. By contrast, in a large trial on 230 patients who had sustained hand injuries, Barclay and colleagues[233] reported marked reduction in pain, swelling and disability in half the number of patients who were treated actively by PSWT (30 minutes twice daily for up to seven days), as against a control group. The patients also used

pain medication, but it is unsure if they were controlled for. The study was not blinded, and it was unclear if the groups were equal at baseline. Similarly, 20 patients who had sustained acute whiplash injuries reported significant improvement in pain compared to a placebo when treated with PSWT (RF generating collar worn for eight hours daily for 12 weeks) in a well-designed study by Foley-Nolan and colleagues.[237] This study was different from the rest of the studies in this group because it employed a low power wearable PSWT device more like the one used in the postoperative studies[126,130,241,242] discussed earlier. The dose parameters were not reported fully.

3.1.2 Studies on tissue healing

Five studies out of the seven from this group were on healing of postoperative wounds.[154,155,243-245] One study each reported bone healing[226] and healing of lacerated lower limb wounds.[129] All studies used devices delivering RF energy at a frequency of 27.12 MHz.

3.1.2.1 Postoperative wound healing

There were four clinical trials[154,155,243,244] and one cohort study[245] examining the effects of SWT on postoperative wound healing. Accelerated rate of bruise resolution in boys who underwent orchidopexy operation was achieved when PSWT was used (20 minutes locally to the operated site; 10 minutes to the epigastrium three times a day for four days) in a double-blinded RCT by Bentall and Eckstein.[154] Full-text for this study was not available for a full review. Accelerated recovery was also achieved in patients who had undergone oral surgery, with daily exposure to PSWT (30 minutes locally and 20 minutes over the liver) by Rhodes[244] in a study with over 500 participants. Although it had a large sample, the study was poor in methodological quality. It was not randomised or blinded, lacked objective outcome measures, there was no statistical analysis of the data and the intervention parameters were not reported adequately.

In another study, Goldin and colleagues[243] treated 29 skin grafted patients using PSWT in an RCT. There was significantly improved healing to their donor sites compared to 38 patients who received a placebo. One 30-minute treatment was given pre-medication to the donor site and then four times daily postoperatively, for seven days. The group sizes varied significantly, and it was unclear if they were equivalent at the baseline. Similar enhanced wound healing was shown in a pilot study of 21 cases of blepharoplasty when treated postoperatively with a wearable PSWT device (worn for 24 hours continuously postoperatively) by Nicolle and Bentall.[245] However, this was not a controlled clinical trial, but only a case series report. Localised (15 minutes) and over the liver (30 minutes) treatment with PSWT increased blood plasma levels of fibronectin in postoperative patients, which correlated well with improvement in wound healing in the study by Arghiropol and colleagues.[155] Full-text was not available for the latter study.

3.1.2.2 Other studies on tissue healing

Favourable results with PSWT in bone and soft tissue injuries was reported in the study by Cameron.[226] The large study had a total of 646 surgical and non-surgical orthopaedic patients benefitting from PSWT (20 minutes over the liver and 20 minutes over the wound, twice daily for four days). The study however lacked in most methodological areas including the design, outcome measures and statistics, and hence the results could not be accepted on face value. By contrast to the above results, Lower limb injuries (pre-tibial lacerations) when treated with PSWT (10 minutes three times a week) in addition to standard wound dressing did not result in accelerated wound healing in the study by Muirhead and colleagues (RCT on 129 participants in two groups).[129] Overall, the reporting in this study was inadequate, including dosage parameters.

3.1.3 Studies on other applications

Only one study was identified in this category. Twenty-two patients with pneumothoraxes of less than 30% volume were studied in a blinded RCT by Ma and colleagues.[246] A daily dose of 25 minutes of CSWT (at an intensity causing 'just perceptible warmth') was given to one of the groups. Another group (control group) was kept under observation with only bed rest. Significantly faster lung re-expansion was achieved in the CSWT group compared to the bed rest group (3–12.5 days and 8–17 days respectively). Although this pilot trial was published several years ago, more studies on this condition have not been reported.

3.1.4 Conclusions

The evidence for RF-based therapy within the referred frequency range in acute clinical conditions is mixed. As the review did not employ a cut-off (Downs and Black) score for the methodological quality, all the identified studies were included. However, the conclusions drawn here were influenced primarily by the results from well-designed studies besides the overall evidence from all the studies.

No studies were reported below the shortwave RF range. Within the SWT, the majority were carried out using PSWT (93%), with CSWT only featuring in three studies. One study employed both devices. Significant benefits of PSWT treatment on postoperative pain was reported by the bulk of the studies in that group. The same cannot be stated about acute ankle injuries as the studies have shown mixed results. As identified, dose-dependency issues were apparent in both these groups. Only a limited number of studies were identified on the effects of RF-based therapy for other acute conditions giving rise to pain.

As identified, the 'postoperative pain' and 'postoperative wound healing' groups potentially overlapped. The allocation of studies was performed based on the main outcome as identified by their author. Based on these results there is reasonable volume and quality of evidence to support the use of PSWT for postoperative pain and postoperative wound

healing. Where reported the dosage ranges were varied. Hence based on the reported studies an ideal PSWT treatment recipe for either the postoperative pain or wound healing condition cannot be recommended. Evidence for any other acute conditions is sparse and conflicting.

3.2 Studies on chronic conditions

As stated in Chapter 2, there were 90 studies that investigated the effects of RF-based therapy on chronic clinical conditions. They are considered in detail in the following sections. The key features of the studies, including dose parameters (where reported) and the Downs and Black scores are given as tables in the respective sections.

3.2.1 Non-shortwave studies

There were eight studies that employed RF at frequencies between 30 kHz – 10 MHz to treat chronic therapy-related clinical conditions. Among these five studies were clinical trials,[247-251] one was a cohort study[194] and the other two were case studies.[252,253] All eight non-shortwave studies investigated the effects of RF on pain and inflammation. OA of the knee joint,[194,249-251] shoulder pain,[253] temporo-mandibular joint (TMJ) pain and dysfunction,[247] tendinopathy[248] and chronic pain conditions[252] were the study areas. A frequency range of 250 kHz – 500 kHz was used in all studies, except Takahashi and colleagues[194] and Nelson and colleagues[251] where 6,000 kHz – 8,000 kHz (6–8 MHz) was the frequency used.

Three studies on OA knee were RCTs. Nelson and colleagues[251] reported that 15 participants when treated with an active 6.8 MHz PEMF device (80 (±9) sessions in 42 days, 15 minutes per session) presented a three-fold significant improvement in the pain scores compared to 19 placebo-treated participants. There were no follow-ups, and pain was the only outcome measured. The benefits of this treatment beyond the immediate post treatment phase and its effects on the functional QoL are therefore unknown. The study also failed to fully report the RF dose parameters.

Taverner and colleagues[250] used 480 kHz transcutaneous pulsed radiofrequency (TPRF) therapy against a placebo on patients awaiting total knee replacement (TKR) (52 participants in two groups: active and placebo). Significant reduction in the pain scores at one and four weeks post treatment was reported by the active group participants compared to the placebo group. Only one session of RF treatment that lasted 10 minutes was delivered in this study. Dosage parameters were not fully reported. While the patients also took pain medications, they were not accounted for in the data analysis. Pain was the only outcome measured; hence its effect on functional QoL is unknown similar to the above study. Besides, it was unclear if the groups were equal at baseline.

Very similar results were obtained by Alcidi and colleagues[249] who tested a similar type of 500 kHz RF as above (five sessions in five days, 20 minutes per session) against TENS (50 Hz, 0.5-millisecond square waves for 20 minutes per session for five days) in patients with OA knee (40 participants in two groups of 20 each). The authors claimed that the RF therapy yielded a greater and longer lasting reduction in pain than the TENS. However, although a 20-minute treatment may suffice for RF, it may be deemed too short for TENS.[254] Moreover, TENS is shown to induce more effective pain relief during treatment as opposed to post-treatment.[255] The study did not undertake a between-group statistical comparison at any time point (baseline, post treatment or one-month post treatment) to be able to claim that one treatment was better than the other.

Twelve patients presenting with OA knee were treated using an 8 MHz RF applicator (three sessions in three weeks, 20 minutes per session) by Takahashi and colleagues[194] in a pilot study. Hyperthermia was induced inside the knee joints and significant pain relief was obtained. The authors used an invasive metallic thermocouple that remained *in situ* for the duration of treatment to record the temperature inside the joint. Therefore, a direct heating of the thermocouple by the RF could not be ruled out. It was unclear whether the researchers had attempted to mediate this effect. This was not a controlled clinical trial; hence the results needed to be interpreted with caution. The authors measured pain and function (WOMAC), but the WOMAC results were left unreported.

Balogh[252] presented a case series of TPRF therapy, which was applied to four patients, three of whom had suffered lumbar intervertebral disc injuries and one patient with multiple injuries secondary to a road traffic accident. Conventional TENS electrodes and a 500 kHz RF generator (10 minutes at 1–5 weekly intervals) were used. Three out of four patients experienced improved pain and function. However, the patient treatment protocols were variable depending on their condition. In another similar study, Taverner and colleagues[253] used RF at 480 kHz (single session of TPRF therapy for up to 12 minutes) to treat shoulder pain. No further details about the condition were reported. A cohort of 13 patients (15 shoulder joints) were studied, two-thirds of which reported pain relief over three months. The dose parameters used were not reported in either study. Both studies being small case series did not provide much insight into the usefulness of such therapy.

Reduction in TMJ pain and improvement in mandibular range of movement (ROM) was reported by Al-Badawi and colleagues[247] in a double-blinded RCT (40 participants in two groups of 20 each). The participants received either 250 kHz pulsed RF (PRF) or a placebo (six sessions in two weeks, 90 seconds per session). The immediate relief of pain and mandibular ROM obtained by 448 kHz CRMRF therapy were significantly better than the placebo, but the groups were not equivalent at the baseline. Dose parameters were not fully reported either.

Costantino and colleagues[248] reported that 448 kHz CRMRF was not significantly better than cryoultrasound therapy or laser CO_2 therapy when used to treat 45 athletes affected by Achilles, patellar or elbow extensor tendinopathy (3 equal groups, each receiving 12 sessions of one of the three EPAs). CRMRF was delivered for 30 minutes, laser for 15 minutes and cryoultrasound for 20 minutes. Intervention duration and dosage parameters were incompletely reported. This study had several significant methodological issues. Despite being a multi-group study, it was not randomised, controlled or blinded. There were no follow-up assessments. At the baseline, it was unclear if the group outcomes were equivalent.

It is obvious from the literature discussed so far, that only a very small number of clinical studies have been published in the non-shortwave RF category. The indication from the studies available is that RF below 10 MHz might deliver appreciable therapeutic benefits. However, there is no clear indication from the previously reported experimental studies as to how RF frequencies below the shortwave band may induce biological effects that may lead to clinical benefits. Moreover, the results of the clinical studies themselves must be weighed against their volume and overall methodological quality, several of which were seriously lacking as described above. Substantially more quality research is warranted in this area given the non-existence of quality evidence in the form of well-designed RCTs. The base frequencies used were different in virtually every study, hence no comparison was possible. As of now it is unclear which RF frequency in this category is most appropriate for therapy should they prove to be genuinely beneficial. Key points from the non-shortwave studies are summarised in Table 3.2.

Table 3.2: Non-shortwave RF studies on chronic conditions

Study	Diagnostic category	Outcomes measured	Study type, sample size and number of groups	Type of RF used	RF dose parameters					Number and duration of sessions	Did RF improve the outcomes significantly?	Downs and Black score (out of 28)
					CRF Power (W)	PRF						
						PP (W)	PD (μs)	PRR (pps)	MP (W)			
Takahashi et al. 2011	OA knee	Pain and function	Cohort; 11 subjects (12 knees); 1 group	PRF; 8 MHz		NR	NR	NR	200	3 (over 3 weeks); 20 min/session	Yes	16
Balogh 2004	Back pain, Multiple injuries	Pain	Case series; 4 subjects	PRF; 0.5 MHz		NR	20,000	2	NR	Numerous; 10 min/session	Yes	9
Taverner et al. 2012	Shoulder pain	Pain	Case series (retrospective audit); 13 subjects (15 shoulders)	PRF; 0.48 MHz		NR	20,000/ 10,000	2/5	NR	Single session; ≤12 min/session	Yes	9
Nelson et al. 2012	OA knee	Pain	RCT; 34 subjects; 2 groups	PRF; 6.8 MHz		NR	7000	1	NR	≤89 (over 42 days); 15 min/session	Yes	25
Taverner et al. 2010	OA knee	Pain	RCT; 52 subjects; 2 groups	PRF; 0.48 MHz		NR	20,000	2	NR	Single session; 10 min/session	Yes	20
Alcidi et al. 2007	OA knee	Pain and function	RCT; 42 subjects; 2 groups	CRF; 0.5 MHz	≤30					5 (over 5 days); 20 min/session	Yes	17
Al-Badawi et al. 2004	TMJ pain and dysfunction	Pain and TMJ function	RCT; 40 subjects; 2 groups	PRF; 0.25 MHz		NR	NR	600	NR	6 (over 2 weeks); 90 sec/session	Yes	21
Costantino et al. 2005	Tendinopathy	Pain	Non-RCT; 45 subjects; 3 groups	CRF; 0.48 MHz	NR					12 (NR); 30 min/session	Yes	15

RCT – Randomised Controlled Trial; OA – Osteoarthritis; TMJ – Temporo-mandibular Joint; RF – Radiofrequency; CRF – Continuous Radiofrequency; PRF – Pulsed Radiofrequency; PP – Peak power; PD – Pulse duration; PRR – Pulse repetition rate; MP – Mean power; NR – Not reported; NA – Not available to the authors; W – Watts; μs – Microseconds; pps – Pulses per second; min – Minutes.

3.2.2 Shortwave studies

Eighty-two clinical studies related to chronic therapy-related clinical conditions were identified within the shortwave frequency range of 10 – 30 MHz. The base shortwave frequency of 27.12 MHz either in continuous (CSWT) or in pulsed (PSWT) form was used in all the studies. Fifty-nine studies were related to conditions on pain and inflammation, 16 studies to tissue healing and the remaining seven studies to other less reported conditions such as joint stiffness.

3.2.2.1 Studies on pain and inflammation

Nearly half of the 59 studies (28 studies) reported the effects of SWT on arthritis, mainly OA of the knee joint.[55,256-282] Except one cohort experimental study,[257] all were multi-group clinical trials. Eight clinical trials[156,283-289] and a cohort study[290] were on chronic low back pain (LBP). One clinical trial[291] and five case studies[292-296] involved various gynaecological conditions giving rise to pelvic pain.

In addition, Chronic neck disorders (three clinical trials),[132,297,298] carpal tunnel syndrome (two clinical trials),[158,299] plantar fasciitis (one clinical trial[133] and one case study[300]), chronic shoulder problems (one clinical trial[301] and one case study[302]), one clinical trial each on TMJ pain,[303] trigger point pain[304] and myofascial pain[305] and one case study each on Herpes Zoster pain,[306] heel neuroma,[307] avascular necrosis of the femoral head,[308] and multiple cases of pain[53] were also identified.

Arthritis

Studies on arthritis formed the single largest group. They have been published as early as the 1950's. A varied group of 62 patients affected by either rheumatoid arthritis (RA of hands or knees) or OA knee were studied by Hamilton and colleagues.[256] They reported improved outcomes of walking and stair climbing among the participants who were treated with CSWT (12 sessions in 4 weeks, 20 minutes per session). CSWT exposure (single session for 20 minutes) was shown to improve circulation to the knee joints of people affected by RA if the condition was quiescent, but counterproductive if RA was active in an experimental study by Harris.[257] CSWT (18 sessions in 6 weeks, 20 minutes per session) gained better long-term improvement over placebo tablets and placebo injections among patients with OA knee (38 participants in three groups) in the study by Wright.[258] Till the early 1990's, several more studies were published where neither CSWT nor PSWT were found to be significantly better than other treatments for OA.[55,259-265] The majority of those studies were based on CSWT. Results were mixed, but generally favoured the use of CSWT for OA knee. However, all these early studies were affected by significant methodological limitations such as improper randomisation, lack of appropriate statistical analysis, lack of validated outcome measures and inequivalent groups at baseline. The reporting remained poor in almost all studies.

More recently, Klaber Moffett and colleagues[266] found no significant benefit with PSWT (nine PSWT sessions in three weeks, 15 minutes per session) for self-reported pain and QoL measures of 92 participants affected by hip and knee OA in a well-designed RCT. However, the study may not have attained sufficient statistical power. Two more very similar clinical trials,[268,269] that employed four different PSWT doses (six and nine sessions respectively in two weeks, 20 minutes per session) reported that there were no significant benefits from PSWT. Of this the study by Callaghan and colleagues[268] was very small and statistically underpowered. Also, it was unclear if the study groups were equivalent at the baseline. The second study by Laufer and colleagues[269] also had similar limitations despite being a larger trial. Their method was non-randomised, and the possibility of a type II error was confirmed by their post-hoc analysis.

PSWT (10 sessions in two weeks, 15 minutes per session) was combined with ultrasound therapy and progressive resistance exercises in the study by Tuzun and colleagues 40 participants in two groups).[267] Pain and function was improved by both low and high doses. However, it cannot be ascertained from this study whether the benefits were due to the addition of PSWT since both groups improved equally. It may be assumed that either both doses of PSWT were equally beneficial or else they had no impact at all. In another study, Jan and colleagues[270] demonstrated lower pain and knee joint synovial thickness in CSWT-treated group (30 sessions in 8 weeks, 20 minutes per session) compared to a control group irrespective of their NSAID intake. The study had a modest sample (36 participants in three groups) but did not use a randomised design. Moreover, the groups were not equal at the baseline in terms of pain levels, and the use of pain medication was not monitored or controlled for.

Later studies compared the effects of SWT to spa, ultrasound, ice or exercise therapies,[271-273,277] none of which suggested added benefit from either CSWT[271-273] or from PSWT.[277] Similar methodological issues that were noticed in the previously discussed trials were present in these studies too, as only the RCT conducted by Rattanachaiyanont and Kuptniratsaikul[277] employed a well-designed methodology. However, even they included only female participants. Another contentious issue with this study was that the mean PSWT power dosage used (3.2 W) was potentially too low to be of benefit in a chronic condition such as OA knee.

Recently, Cetin and colleagues[274] reported that CSWT (24 sessions in 8 weeks, 15 minutes per session) reduces pain and improves function among women with OA knee (100 patients in 5 groups) when used with hot packs and isokinetic exercises. Confounding factors such as medication intake was not controlled for. Also, there was 15% drop-out of participants, which was not considered in the data analysis. Akyol and colleagues[278] contradicted the above findings in another similar study (40 patients in 2 groups) with CSWT (12 sessions in

four weeks, 20 minutes per session) and isokinetic exercises. Both studies only applied to women of menopausal age group.

Among the recent PSWT studies, Ovanessian and colleagues[276] reported that PSWT delivered at a mean power (MP) of 14.5 W (9 sessions in 3 weeks, either 19 minutes or 38 minutes per session) produced significantly better outcomes compared to a control group. The study suggested that increasing the treatment duration did not commensurately increase the rate of improvement of symptoms. This was a small pilot study with 36 participants in three groups and no follow-ups. Agreeing to Ovanessian and colleagues, Fukuda and colleagues published two well-designed RCTs[275,279] on the effects of PSWT on pain and function in women affected by OA knee. PSWT at a MP of 14.5 W (9 sessions in 3 weeks, either 19 or 38 minutes per session) were tested. Both studies suggested that PSWT improved the clinical outcomes regardless of the treatment durations they used.

Atamaz and colleagues[280] reported another well-designed multi-centre RCT (203 patients in 6 groups) recently in which TENS, interferential therapy, PSWT and their three placebo versions were employed alongside exercises and advice in all six groups (15 sessions in three weeks, 20 minutes per session). All groups including the placebos improved their pain scores significantly and the only difference between the groups was that there was reduced paracetamol intake in the active groups at the end of the intervention, with no difference between the active groups. Longer term results are not known, as there were no follow-up assessments. Like the Rattanachaiyanont and Kuptniratsaikul[277] study, the mean active PSWT power dose in this study was only 3.2 W, which was potentially too low to be effective.

Most recently, Boyaci and colleagues[282] compared CSWT (10 sessions in two weeks, 20 minutes per session) with ultrasound and ketoprofen phonophoresis in OA knee (101 female participants in three groups). Self-reported pain and function improved in all three groups significantly, but the group results were not significantly different from each other. In a second smaller pilot study (24 participants in two groups of 12 each) by Teslim and colleagues,[281] both CSWT and PSWT (eight sessions in four weeks, 20 minutes per session in both groups) improved the knee ROM and pain, but the CSWT results were significantly better than PSWT. Follow-up assessments were absent in both studies and neither did they report the dose parameters. The absence of a control group was a further limitation of both studies.

While many of the more recently published studies have supported the use of SWT (mainly PSWT) for treating OA knee, the earlier studies mostly gave conflicting results and were also affected by methodological issues. Reporting of the full dosage parameters has been an issue with many studies. Where reported the treatment power and overall duration of intervention varied greatly, but the rationale for such a selection was not reported. The

number of intervention weeks varied from single to several weeks in most studies (average of 3–6 weeks). No CSWT studies have reported their actual doses employed. Overall, based on the outcomes of the more recent studies that supported the application of PSWT for OA knee, there is moderate evidence to support the use of PSWT in OA knee. The intervention parameters reported in those studies suggest that a mean dose at or above 14.5 W, 8–12 sessions over 4–6 weeks, and 15–20 minutes per session may be considered as an effective intervention. Additional information on the RF-based management of OA knee can be obtained from systematic reviews that are already published.[137,139,309,310] These reviews also include some of the studies covered in this thesis. Key points from all the shortwave studies on OA knee are summarised in Table 3.3.

Table 3.3: Shortwave studies on OA knee

Study	Diagnostic category	Outcomes measured	Study type, sample size and number of groups	Type of RF used	RF dose parameters					Number and duration of sessions	Did RF improve the outcomes significantly?	Downs and Black score (out of 28)
					CSWT Power (W)	PSWT						
						PP (W)	PD (μs)	PRR (pps)	MP (W)			
Hamilton et al. 1959	RA hands/knee; OA knee	ROM and function	Crossover RCT; 131 subjects; 4 groups	CSWT	NR					12 (over 4 weeks); 20 min/session	Yes	16
Harris 1961	RA knee	Local circulation (Radio-Sodium clearance)	Experimental; 16 subjects; 2 groups	CSWT	NR					Single session; 20 min/session	Yes/No	8
Wright 1964	OA knee	Pain, tenderness, walking time and analgesic intake	RCT; 38 subjects (59 joints); 3 groups	CSWT	NR					18 (over 6 weeks); 20 min/session	Yes	13
Valtonen and Alaranta 1971	OA knee/hip	Level of improvement	RCT; 160 subjects; 2 groups	CSWT	NR					13–14 (over 5 weeks); 15–20 min/session	Yes	10
Clarke et al. 1974	OA knee	Pain, stiffness, tenderness and swelling	RCT; 48 subjects; 3 groups	CSWT	NR					9 (over 3 weeks); NR	No	18
Bansil and Joshi 1975	OA knee	Pain and function	RCT; 60 subjects (100 joints); 2 groups	CSWT	NR					NR; 20 min/session	No	12
Chamberlain et al. 1982	OA knee	Pain, function, ROM, maximum weight lift and endurance	RCT; 42 subjects; 2 groups	CSWT	NR					12 (over 4 weeks; NR	Yes	17
Quirk et al. 1985	OA knee	Pain, function, ROM, exercise endurance and knee girth	RCT; 38 subjects; 3 groups	CSWT	NR					12 (over 4 weeks); 20 min/session	Yes	17
Svarcova et al. 1988	OA knee/hip	Pain and 'therapeutic effect'	Non-RCT; 180 subjects; 3 groups	PSWT		700	NR	NR	NR	10 (over 3 weeks); 4 min/session	Yes	15
Jan and Lai 1991	OA knee	Function and muscle torque	RCT; 61 subjects (94 joints); 4 groups	CSWT	NR					24–69 (over 6–18 weeks); 20 min/session	Yes	15

Sewell et al. 1991 (Abstract only)	RA knee	Pain, swelling and function	RCT; 81 subjects; 2 groups	PSWT		NR	65	200 (1:3)	NR	8 (over 4 weeks); 10 min/session	No	NA
Klaber Moffett et al. 1996	OA knee/hip	Pain and function	RCT; 92 subjects; 3 groups	PSWT		NR	NR	82	23	9 (over 3 weeks); 15 min/session	No	19
Tuzun et al. 2003	OA knee	Pain, function, ROM and muscle strength	RCT; 40 subjects; 2 groups	PSWT		1000/ 600	400	20/ 110	8/ 26.4	10 (over 2 weeks); 15 min/session	Yes	15
Callaghan et al. 2005	OA knee	Pain, timed walk, ROM and muscle strength	RCT; 27 subjects; 3 groups	PSWT		125	200/ 400	400	10/20	6 (over 2 weeks); 20 min/session	No	22
Laufer et al. 2005	OA knee	Pain, function, timed walk and stair use	Non-RCT; 103 subjects; 3 groups	PSWT		200	82/ 300	110/ 300	1.8/1 8	9 (over 3 weeks); 20 min/session	No	19
Jan et al. 2006	OA knee	Pain and synovial sac thickness	Non-RCT; 30 subjects (44 joints); 3 groups	CSWT	NR					30 (over ≤8 weeks); 20 min/session	Yes	17
Cantarini et al. 2007	OA knee	Pain, function, QoL and analgesic intake	RCT; 74 subjects; 3 groups	CSWT	NR					10 (over 3 weeks); 15 min/session	No	20
Manhal et al. 2007	OA knee	Pain, deformity and muscle wasting	RCT; 24 subjects; 2 groups	CSWT	NR					6–10 (over 2 weeks); ≤20 min/session	Yes	8
Silva et al. 2007	OA knee	Pain, function, ROM and muscle strength	RCT; 25 subjects; 3 groups	CSWT	NR					10 (over 5 weeks); 20 min/session	No	16
Cetin et al. 2008	OA knee	Pain, function and muscle strength	RCT; 100 subjects (200 joints); 5 groups	CSWT	NR					24 (over 8 weeks); 15 min/session	Yes	20
Fukuda et al. 2008	OA knee	Pain, function and ROM	RCT; 84 subjects; 4 groups	PSWT		250	400	145	14.5	9 (over 3 weeks); 19–38 min/session	Yes	21
Ovanessian et al. 2008	OA knee	Pain, function and ROM	RCT; 42 subjects; 3 groups	PSWT		250	400	145	14.5	9 (over 3 weeks); 19–38 min/session	Yes	17

Rattanachaiyanont and Kuptniratsaikul 2008	OA knee	Pain, function, timed walk and stair use	RCT; 113 subjects; 2 groups	PSWT		300	NR	NR	3.2	9 (over 3 weeks); 20 min/session	No	24
Akyol et al. 2010	OA knee	Pain, function, QoL and timed walk	RCT; 40 subjects (80 joints); 2 groups	CSWT	NR					12 (over 4 weeks); 20 min/session	No	21
Fukuda et al. 2011	OA knee	Pain, function and QoL	RCT; 121 subjects; 4 groups	PSWT		250	400	145	14.5	9 (over 3 weeks); 19–38 min/session	Yes	25
Atamaz et al. 2012	OA knee	Pain, function and ROM	RCT; 203 subjects; 6 groups	PSWT		300	NR	NR	3.2	15 (over 3 weeks); 20 min/session	Yes	26
Teslim et al. 2013	OA knee	Pain and ROM	RCT; 24 subjects; 2 groups	CSWT/ PSWT	NR	NR	NR	NR	NR	8 (over 4 weeks); 20 min/session	Yes	17
Boyaci et al. 2013	OA knee	Pain, function and timed walk	RCT; 101 subjects (202 joints); 3 groups	CSWT	NR					10 (over 2 weeks); 20 min/session	Yes	23

RCT – Randomised Controlled Trial; OA – Osteoarthritis; RA – Rheumatoid Arthritis; ROM – Range of Movement; QoL – Quality of Life; RF – Radiofrequency; CSWT – Continuous Shortwave Therapy; PSWT – Pulsed Shortwave Therapy; PP – Peak power; PD – Pulse duration; PRR – Pulse repetition rate; MP – Mean power; NR – Not reported; NA – Not available to the authors; W – Watts; μs – Microseconds; pps – Pulses per second; min – Minutes.

Low back pain

Two large multi-group trials by Gibson and colleagues[285] (12 CSWT sessions in four weeks, session duration not reported) and Sweetman and colleagues[287] (six CSWT sessions in two weeks, 20 minutes per session) reported that CSWT was not particularly beneficial over the comparator treatments (exercises, traction, osteopathy or placebo-CSWT). In the first study, the use of medication was not controlled, and the authors failed to report the intervention parameters. In the second, the intervention only lasted two weeks. Both studies did not demonstrate sufficient equivalence between the groups at baseline.

Conversely, the effects of both pulsed and continuous SWT were significant in relation to pain relief in two other small clinical trials by Davies and colleagues[284] (CSWT dose parameters not reported) and Wagstaff and colleagues[288] (six PSWT sessions in three weeks, 15 minutes per session). The outcome was unaffected by adding an exercise regime to the intervention or using different shortwave pulse patterns. Both studies did not demonstrate sufficient equivalence between the groups at baseline. The intervention parameters were not reported in the first study. The study by Wagstaff and colleagues[288] had several additional methodological issues. The authors did not control for medication intake. All three treatment groups employed SWT and exercises; hence it was difficult to determine the effect of SWT alone.

Both CSWT and PSWT (10 sessions of 20 minutes each) were reported to effectively reduce LBP although the effects of PSWT were greater in the study by Kerem and Yigiter.[286] They studied 60 participants in three groups (CSWT and two different doses of PSWT). This was not a randomised or blinded study. Like the Wagstaff and colleagues[288] study, all three treatment groups employed SWT and exercises; hence it was difficult to determine the effect of SWT alone. Similarly, CSWT (18 sessions in 6 weeks, 15 minutes per session) significantly improved chronic LBP in three studies published by Shakoor and colleagues.[156,283,290] It was further supported by Kim and colleagues,[289] who reported in their study on 11 patients with LBP that CSWT (single session of treatment, duration not reported) significantly complement manual therapy (nerve mobilisation) when compared to manual therapy alone.

The number of SWT studies on LBP was much smaller compared to that for OA knee. CSWT was the favoured method of treatment in most studies. Similar methodological shortcomings as in the OA knee studies were apparent in this group as described above. Likewise, no commonalities could be drawn on dosing or any dose-related information owing to the lack of information supplied and the inconsistency where such information was supplied. The average duration of intervention was 3–5 weeks in most studies (ranged between single sessions to six weeks), based on the studies that have reported beneficial

effects of SWT. Except for two, all studies reported the intervention to be beneficial for the management of LBP; hence there exists some evidence in favour despite all the methodological shortcomings within the literature.

Pelvic pain

The effect of SWT on pelvic conditions were studied as early as 1938, when Waters[296] published positive responses to CSWT (up to 36 sessions delivered) from 120 patients in their case study. Subsequently, 50 cases of pelvic sepsis treated by CSWT (12–16 sessions in 4–6 weeks, 30 minutes per session) to obtain intra-vaginal hyperthermia was reported by Burgess[293] as case studies. Cases of chronic inflammation due to pelvic sepsis benefitted from the RF treatment. Later studies included gynaecology patient studies by Punnonen and colleagues[295] (10–15 PSWT sessions on alternate days) and case studies on pelvic inflammatory disease (PID) by Balogun and Okonofua[292] (9 CSWT sessions in 3–4 weeks, 25–60 minutes per session) and Lamina and Hanif[294] (15 CSWT sessions in 30 days, 30 minutes per session). All the above studies were supportive of the use of RF to treat pelvic pain in women. Only one of the six studies in this category was an RCT.[291] Lamina and colleagues studied 32 participants (in three groups) with pelvic inflammatory disease. CSWT (15 sessions in 30 days, 20 minutes per session) showed greater benefit over analgesics and a control condition in reducing pain. However, the groups were not shown to be equivalent at the baseline.

Neck pain

Three well-designed RCTs were identified, examining the effects of PSWT on chronic neck pain, although two studies were based on the same data.[297,298] PSWT therapy gave better outcomes of pain and neck ROM compared to a placebo in the study by Foley-Nolan and colleagues.[132] PSWT generating soft cervical collar was worn for eight hours daily for six weeks. This was a small study (20 participants in two groups) without any long follow-up assessments. The RF device used in this study was similar to those wearable devices used on the acute postoperative patients described in the previous chapter. Although the MP dose of such devices is extremely low, a significant amount of energy will still be delivered since it is worn for several hours during the day.

In a more recent and larger RCT 350 patients (three groups – manual therapy, PSWT and control (advice and exercise)) were studied over 32 weeks (8 PSWT sessions in 6 weeks, 15–20 minutes per session) by Dziedzic and colleagues.[297] The treatment dosage was not fixed for the whole sample. The finding was that the addition of PSWT to ‘advice and exercise’ did not provide a greater outcome than the other two. However, this study involved 55 different therapists to deliver the intervention, potentially raising reliability concerns. Lewis

and colleagues[298] later evaluated the economic outcomes of the above study and concluded that PSWT was unlikely to be the most cost-effective intervention among the three.

Other conditions with pain and inflammation

Brook and colleagues[133] demonstrated a significant reduction of morning pain in 70 patients affected by plantar fasciitis (42 active, 28 placebos) after using a wearable type low power PSWT device during the night (did not specify the duration) for seven days. The study did not recruit the anticipated number of participants (70 instead of the expected 140). Michel[300] supported this in their case study with six patients. Their intervention duration was significantly longer with the wearable device (over 200 sessions in 13 – 15 weeks, 30 minutes twice daily) although dose parameters were not reported.

Chronic shoulder pain is another clinical area where studies have been identified. PSWT (10 minutes to the shoulder and 10 minutes to the liver) gave 'impressive clinical results' (in author's own words) according to Ginsberg[302] in his multiple case study (94 patients affected by shoulder bursitis with calcification). The study completely lacked any objective reporting; hence no inference could be made regarding the efficacy of PSWT. In another clinical trial,[301] CSWT (10 sessions in 2 weeks, 20 minutes per session) produced significant improvement among 40 cases of shoulder adhesive capsulitis. However, the effects were less pronounced when compared to manual therapy (Cyriax approach). Shortwave dose parameters were not reported and the duration of intervention at two weeks may potentially have been too short for a chronic condition such as the adhesive capsulitis.

Mild and moderate carpal tunnel syndromes (CTS) were reported to improve with both CSWT and PSWT (15 sessions in 3 weeks, 20 minutes per session) (CSWT was reported to be more effective) in two recently published studies.[158,299] Pain, hand function and the electrophysiological measurements improved significantly in the active groups when compared to the placebo groups. The dosage parameters were not reported in either study. The full-text was unavailable for one of the studies.[158]

Among other less reported conditions, Gray and colleagues[303] compared CSWT, PSWT, laser and ultrasound (12 sessions in 4 weeks; CSWT 10 minutes per session, PSWT 20 minutes per session) in a clinical trial on 176 patients with TMJ pain. All groups reported similar and significant improvement. TMJ-related myofascial pain was also shown to improve markedly by CSWT in another trial[305] (120 patients in three groups – drug therapy, CSWT and ultrasound; 14 sessions of CSWT in 2 weeks, 20 minutes per session), although the effects were less pronounced compared to ultrasound. Both studies had significant methodological flaws including a lack of standardised objective outcome measures and poor reporting.

A single treatment of CSWT (20 minutes) was found to have a greater effect than a similar single treatment with moist heat for reducing tenderness from trigger points in another small study.[304] This single-session experimental study does not provide much information about the potential prolonged effect of CSWT on this condition. Case studies where SWT was found to be effective in the management of pain arising from other conditions included studies on Herpes Zoster[306] (daily CSWT sessions of 20 minutes each), heel neuroma[307] (6–12 PSWT sessions in 3–4 weeks, 10–15 minutes per session), and avascular necrosis of the femoral head[308] (PSWT for varying durations). As above, these reports do not provide much information to the reader.

Key points from the all SWT studies on pain and inflammation (except arthritis) are summarised in Table 3.4. The effects of SWT on various chronic conditions giving rise to pain and inflammation were reviewed in this section. Except for OA knee and LBP, sufficient numbers of studies have not been reported. As already stated, there is moderate evidence to support the use of PSWT in OA knee and some evidence exists for the use of CSWT for LBP. The evidence for other conditions is sparse and conflicting.

Table 3.4: Shortwave studies on pain and inflammation (except arthritis)

Study	Diagnostic category	Outcomes measured	Study type, sample size and number of groups	Type of RF used	RF dose parameters					Number and duration of sessions	Did RF improve the outcomes significantly?	Downs and Black score (out of 28)
					CSWT Power (W)	PSWT						
						PP (W)	PD (μs)	PRR (pps)	MP (W)			
Ahmed et al. 2009	LBP	Pain, tenderness and analgesic intake	RCT; 97 subjects; 2 groups	CSWT	NR					18 (over 6 weeks); 15 min/session	Yes	17
Davies et al. 1979	LBP	Pain and flexion ROM	RCT; 43 subjects; 3 groups	CSWT	NR					NR (over 4 weeks); NR	Yes	17
Gibson et al. 1985	LBP	Pain and flexion ROM	RCT; 109 subjects; 3 groups	CSWT	NR					12 (over 6 weeks); NR	No	18
Kerem and Yigiter 2002	LBP	Pain, ROM and muscle strength	Non-RCT (?); 60 subjects; 3 groups	CSWT/ PSWT	NR	300/ 600	4000	200/ 46	240/ 110	10 (NR); 20 min/session	Yes	17
Shakoor et al. 2008	LBP	Pain	RCT; 102 subjects; 2 groups	CSWT	NA					NA	Yes	NA
Sweetman et al. 1993	LBP	Clinical outcome	RCT; 400 subjects; 4 groups	CSWT	NR					6 (over 2 weeks); 20 min/session	No	20
Wagstaff et al. 1986	LBP	Pain	RCT; 23 subjects; 3 groups	CSWT/ PSWT	NR	300/ 700	400	200/ 82	23.4/ 23.2	6 (over 3 weeks); 15 min/session	Yes	14
Kim et al. 2012	LBP	Pain, function and knee extensor strength	RCT; 22 subjects; 2 groups	CSWT	50					Single session; NR	Yes	17
Shakoor et al. 2010	LBP	Pain and tenderness	Cohort study; 50 subjects; 1 group	CSWT	NR					18 (over 6 weeks); 15 min/session	Yes	14
Lamina et al. 2011	PID	Pain and inflammation	RCT; 32 subjects; 3 groups	CSWT	≈8.27					15 (over 4 weeks); 20 min/session	Yes	19
Balogun and Okonofua 1988	PID	Pain	Case study; 1 subject	CSWT	NR					9 (over 3 weeks); 25–60 min/session	Yes	7

Burgess 1950	Mixed cases of pelvic sepsis	Pain and treatment outcome	Case series; 50 subjects	CSWT	NR					12–16 (over ≤6 weeks); 30 min/session	Yes	4
Lamina and Hanif 2008	PID	Pain	Case series; 3 subjects	CSWT	NR					15 (over 4 weeks); 30 min/session	Yes	9
Punnonen et al. 1980	Mixed gynaecology and obstetrics cases	Pain and treatment outcome	Case series; 71 subjects	PSWT		300	NR	62	NR	10–15 (over 3–4 weeks); 30 min/session	Yes	6
Waters 1938	Mixed gynaecology and obstetrics cases	Pain and treatment outcome	Case series; 120 subjects	CSWT	NR					≤36 (over ≤4 weeks); ≈15 min/session	Yes	6
Dziedzic et al. 2005	Non-specific neck pain	Pain and function	RCT; 350 subjects; 3 groups	PSWT		NR	NR	NR	≈7.4	8 (over 6 weeks); 20 min/session	Yes	22
Foley-Nolan et al. 1990	Neck pain	Pain and ROM	RCT; 20 subjects; 2 groups	PSWT		NR	60	450	0.001 5/cm^2	48 (over 6 weeks); 8 hours/session	Yes	19
Lewis et al. 2007	Non-specific neck pain	Cost effectiveness	RCT; 350 subjects; 3 groups	PSWT		NR	NR	NR	≈7.4	8 (over 6 weeks); 20 min/session	Yes, but not cost effective	22
Brook et al. 2012	Plantar fasciitis	Morning pain	RCT; 70 subjects; 2 groups	PSWT		98 x 10^{-4}	100	1000	98 x 10^{-5}	7 (over 1 week); NR	Yes	24
Michel 2012	Plantar fasciitis	Pain and tenderness	Case series; 6 subjects	PSWT		NR	NR	NR	NR	≤215 (over 13–15 weeks); 30 min/session	Yes	7
Guler-Uysal and Kozanoglu 2004	Adhesive capsulitis shoulder	Recovery rate, pain and ROM	RCT; 40 subjects; 2 groups	CSWT	NR					10 (over 2 weeks); 20 min/session	Yes	20
Ginsberg 1961	Calcified bursitis shoulder	Calcium absorption rate	Case series; 94 subjects	PSWT		1025/ NR	65	600/ 400	40/ NR	NR; 20 min/session	Yes	7
Gray et al. 1994	TMJ pain and dysfunction	Pain, 'clinical signs' and mandibular ROM	RCT; 176 subjects; 5 groups	CSWT/ PSWT	NR	NR	60	100	NR	12 (over 4 weeks); 10/20 min/session	Yes	15

McCray and Patton 1984	Trigger points	Pain	RCT; 19 subjects; 2 groups	PSWT		NR	NR	NR	NR	Single session; 20 min/session	Yes	14
Talaat et al. 1986	Myofascial pain syndrome	Pain, tenderness, TMJ noises and ROM	RCT; 120 subjects; 3 groups	CSWT		NR	NR	NR	NR	14 (over 2 weeks); 20 min/session	Yes	10
Allberry et al. 1972	Herpes zoster pain	Pain	Case series; 97 subjects	CSWT		NR	NR	NR	NR	NR; 20 min/session	Yes	7
Shandles et al. 2002	Heel neuroma	Pain	Case series; 317 subjects	PSWT		975/ NR	65	600/ 400	38/ NR	≈6–9 (over ≈3 weeks); 20–30 min/session	Yes	4
Oke et al. 2011	AVN femoral head	Pain and ROM	Case series; 4 subjects	PSWT		200	400	400	32	≈72 (over 4 months); 20 min/session	Yes	7
Taylor 1936	Abscess, neuralgia, neuritis	Pain	Case series; 3 subjects	CSWT		NR	NR	NR	NR	NR; NR	Yes	4
Boyaci et al. 2014	Carpal tunnel syndrome	Pain, function and nerve conduction	RCT; 30 subjects (55 joints); 3 groups	CSWT/ PSWT	NR	NR	400	82	NR	15 (over 3 weeks); 20 min/session	Yes	24
Incebiyik et al. 2014	Carpal tunnel syndrome	Pain and function	RCT; 31 subjects (58 joints); 2 groups	CSWT	NA					15 (over 3 weeks); NA	Yes	NA

RCT – Randomised Controlled Trial; LBP – Low Back Pain; PID – Pelvic Inflammatory Disease; AVN – Avascular Necrosis; TMJ – Temporo-mandibular Joint; ROM – Range of Movement; RF – Radiofrequency; CSWT – Continuous Shortwave Therapy; PSWT – Pulsed Shortwave Therapy; PP – Peak power; PD – Pulse duration; PRR – Pulse repetition rate; MP – Mean power; NR – Not reported; NA – Not available to the authors; W – Watts; µs – Microseconds; pps – Pulses per second; min – Minutes.

3.2.2.2 Studies on tissue healing

The majority among the 16 studies (14 studies (88%)) identified in this category examined the effect of shortwave on chronic wounds or chronic ulcers.[123,128,311-322] The remaining two studies examined bone healing.[157,323] Radiofrequency at 27.12 MHz in the pulsed mode (PSWT) was used in all studies. Nine were case studies[128,315-322] and one cohort study.[311] Four clinical trials were also reported.[123,312-314]

Itoh and colleagues[311] reported faster healing when PSWT (30 minutes twice daily) was used in addition to conventional wound dressing to treat a group of 22 patients with pressure ulcers. On average, stage II ulcers unhealed after 3–12 weeks of conventional dressing alone healed in 2.33 weeks with PSWT and stage III ulcers unhealed after 8–168 weeks healed in 8.85 weeks. This was not a controlled study and neither did it undertake any statistical analysis.

Comorosan and colleagues[312] in their clinical trial treated elderly patients with pressure ulcers (30 participants in three groups) with PSWT (30 minutes twice daily locally, 20 minutes once daily to the liver) and reported that the PSWT group improved faster (Stage II ulcers healed in 3.28 weeks and Stage III ulcers healed in 4.87 weeks on average) compared to the poor or no improvement in placebo and control groups. This trial had numerous methodological limitations including absence of valid outcome measures and absence of statistical analysis.

Improved methods were employed by Salzberg and colleagues[313] and Kloth and colleagues[314] in their studies although the sample was small in the latter. In the first study the healing of stage II and stage III pressure ulcers in spinal cord injured patients were significantly accelerated by a 12-week PSWT treatment programme (intervention parameters not reported).[313] Significantly higher healing rate was obtained with four weeks of PSWT (20 sessions, 30 minutes per session) when compared to a placebo in the second study.[314] In another well-designed study, Seaborne and colleagues[123] conducted a well-controlled double-blinded RCT on 20 non-ambulatory male patients in a small clinical trial. The participants were treated for four weeks with four different PSWT pulse and field protocols (the study had four groups, each acting as its own control) (20 sessions, 20 minutes per session). While all groups improved significantly, there were no significant differences between the groups, which implied that there was no dose-response relationship in this case. All three studies were potentially statistically underpowered and there were issues with poor baseline equivalence between their study groups.

Among the other studies, accelerated bone repair (as against standard treatment) with externally applied PSWT in 16 cases of non-union of fractures (case study) and in 45 patients with post-traumatic algoneurodystrophies were reported by Sharp[323] and Comorosan and colleagues (full-text not available).[157] Diabetic foot ulcers,[128,315,319] chronic

pressure ulcers,[316,322] chronic lower extremity wounds,[317,320] and venous/microvascular stasis ulcers[318,321] were the conditions reported in the case studies. The case studies are not being explained here in detail. Their key details and outcome are given in Table 3.5.

Well-designed and adequately controlled studies on tissue healing were low in number. While there is a pressing need for further quality research, the existing studies suggested the potential benefits of PSWT in wound healing. Similar methodological limitations and dosing and reporting issues as discussed previously alongside the other groups of studies were also relevant to this segment. Key points from all the SWT studies on tissue healing are summarised in Table 3.5.

Table 3.5: Shortwave studies on tissue healing

Study	Diagnostic category	Outcomes measured	Study type, sample size and number of groups	Type of RF used	RF dose parameters					Number and duration of sessions	Did RF improve the outcomes significantly?	Downs and Black score (out of 28)
					CSWT Power (W)	PSWT						
						PP (W)	PD (μs)	PRR (pps)	MP (W)			
Itoh et al. 1991	Pressure ulcers	Ulcer size and healing rate	Cohort; 20 subjects (22 ulcers); 1 group	PSWT		975	65	600	38	≤308 (over ≤22 weeks); 30 min/session	Yes	13
Comorosan et al. 1993	Pressure ulcers	Ulcer size and healing rate	RCT; 30 subjects; 3 groups	PSWT		975/ NR	65	600/ 400	38/ NR	≤112 (over ≤8 weeks); 30/20 min/session	Yes	15
Salzberg et al. 1995	Pressure ulcers	Ulcer size and healing rate	RCT; 30 subjects; 2 groups	PSWT		NR	NR	NR	NR	NR (over ≤12 weeks); NR	Yes	20
Seaborne et al. 1996	Pressure ulcers	Ulcer size	RCT; 20 subjects; 4 groups	PSWT		700	400	110/ 20	30.8/ 5.6	20 (over 2 weeks); 20 min/session	Yes	23
Kloth et al. 1999	Pressure ulcers	Ulcer size	RCT; 10 subjects; 2 groups	PSWT		NR	65	600	NR	20 (over 4 weeks); 30 min/session	yes	20
Larsen and Overstreet 2008	Diabetic foot ulcers	Ulcer size and healing rate	Case series; 2 subjects	PSWT		NR	42	1000	NR	NR (over 16–17 weeks); NR	Yes	9
Porreca and Giordano-Jablon 2008	Pressure ulcers	Ulcer size	Case study; 1 subject	PSWT		NR	42	1000	NR	60–420 (1–7 months); 30 min/session	Yes	7
Frykberg et al. 2009	Pressure, diabetic and venous ulcers	Ulcer size	Case series; 4 subjects	PSWT		NR	42	1000	NR	120–240 (over 2–4 months); 30 min/session	Yes	9
Fletcher 2011	Venous ulcer	Pain and ulcer size	Case study; 1 subject	PSWT		NR	42	1000	NR	≈150 (over 6 weeks); 30 min/session	Yes	7
Frykberg et al. 2011	Diabetic foot ulcers	Ulcer size	Case study; 1 subject	PSWT		NR	42	1000	NR	≈200 (over 14 weeks); 30 min/session	Yes	7

Frykberg et al. 2011	Pressure, diabetic and venous ulcers	Ulcer size	Cohort (retrospective audit); 113 subjects; 1 group	PSWT		NR	42	1000	NR	56 (over 4 weeks); 30 min/session	Yes	14
Maier 2011	Cutaneous ulcers of the ankle	Ulcer size	Case series; 2 subjects	PSWT		NR	42	1000	NR	42–392 (over 3–28 weeks); 30 min/session	Yes	8
Conner-Kerr and Isenberg 2012	Pressure ulcers	Ulcer size and healing rate	Cohort (retrospective audit); 89 subjects; 1 group	PSWT		NR	42	1000	NR	56 (over 4 weeks); 30 min/session	Yes	14
Rawe and Vlahovic 2011	Diabetic foot ulcers and venous ulcer	Ulcer size and pain	Case series; 4 subjects	PSWT		NR	NR	1000	NR	21–42 (over 3–6 weeks); 6–8 hours/session	Yes	9
Sharp and Lightwood 1983	Fracture non/delayed union	Healing rate	Case series; 16 subjects	PSWT		NR	NR	NR	NR	NR (over 11–54 weeks); NR	Yes	6
Comorosan et al. 1991	Post-traumatic Algoneurodystr-ophies	NA	Cohort; 45 subjects	PSWT		NA	NA	NA	NA	NA; NA	Yes	NA

RCT – Randomised Controlled Trial; RF – Radiofrequency; CSWT – Continuous Shortwave Therapy; PSWT – Pulsed Shortwave Therapy; PP – Peak power; PD – Pulse duration; PRR – Pulse repetition rate; MP – Mean power; NR – Not reported; NA – Not available to the authors; W – Watts; µs – Microseconds; pps – Pulses per second; min – Minutes.

3.2.2.3 Studies on other applications

It is evident from the results and discussions so far that most of the research surrounding the use of RF in therapy-related clinical practice is centred on conditions of pain and inflammation and tissue healing. A small number of studies investigated other unrelated conditions, for example post-traumatic/post-surgical stiffness and ROM,[196,197,324-326] and vascular disorders.[327,328]

Potential therapeutic benefit of PSWT on 'intermittent claudication' were reported by Hedenius and colleagues in 1966.[327] Eighteen patients treated with PSWT (372 individual sessions in 62 weeks, 20 minutes per session) had their skin temperature and walking tolerance significantly improved compared those who did not receive PSWT. This was also supported by Santoro and colleagues[328] in their study (10 participants) on patients affected by peripheral vascular disease (PVD), when treated by CSWT (20 sessions in 4 weeks, 30 minutes per session). While the first one was a non-randomised multi-group study, the second study only featured one group with no comparator treatments.

Clinical effectiveness of PSWT for improving ankle joint ROM[197] (8–13 sessions in 5 weeks, 20 minutes per session), elbow joint ROM[196,324] (4–9 sessions in 2–3 weeks, 20 minutes per session) and necrotising fasciitis[326] (12–15 sessions in 6 weeks, 20 minutes per session to each body segment treated); and CSWT (daily sessions for 2 weeks, 20 minutes per session) for post-operative ROM in the knee joint[325] were demonstrated by Draper and colleagues in their case studies. They combined RF treatment with manual therapy and/or joint mobilisations to obtain the best results. PSWT was applied safely over areas with metal implants. The authors suggested that proper technique and caution will enable such safe delivery of a thermal modality.[324] Treatments at 38–48 W of RF energy were used in all studies with the intervention period lasting for 2–6 weeks. The above studies only provided limited information as they were not clinical trials. Full multi-group clinical trials with appropriate methodology need to be carried out before any conclusions can be drawn. Key points from all the SWT studies included in this category are summarised in Table 3.6.

Table 3.6: Shortwave studies on other applications

Study	Diagnostic category	Outcomes measured	Study type, sample size and number of groups	Type of RF used	RF dose parameters					Number and duration of sessions	Did RF improve the outcomes significantly?	Downs and Black score (out of 28)
					CSWT	PSWT						
					Power (W)	PP (W)	PD (µs)	PRR (pps)	MP (W)			
Draper et al. 2004	Post-traumatic (fracture) stiffness (elbow)	ROM	Case study; 1 subject	PSWT		150	400	800	48	6 (over 2 weeks); 20 min/session	Yes	11
Seiger and Draper 2006	Post-traumatic (fracture) stiffness (ankle)	ROM	Case series; 4 subjects	PSWT		150	400	800	48	8–13 (over 3–5 weeks); 20 min/session	Yes	12
Draper and VanPatten 2010	Post-surgical stiffness (knee)	ROM	Case study; 1 subject	CSWT	35					6 (over 2 weeks); 20 min/session	Yes	11
Johnson and Draper 2010	Fibrosis and adhesions post breast cancer	ROM	Case study; 1 subject	PSWT		150	400	800	48	12–15 (over 6 weeks); 20 min/session	Yes	11
Draper 2014	Post-traumatic/ Post-surgical stiffness (elbow)	ROM	Case series; 6 subjects	PSWT		150	400	800	48	4–6 (over 2 weeks); 20 min/session	Yes	12
Hedenius et al. 1966	Intermittent claudication	Toe skin temperature, walking tolerance, oscillography and calf circumference	Non-RCT; 58 subjects; 5 groups	PSWT		975	65	600	38	372 (over 62 weeks); 20 min/session	Yes	14
Santoro et al. 1994	Arterial peripheral vascular disease	Doppler pressure, Laser Doppler Flowmetry, transcutaneous partial pressure of oxygen and thermistor thermography	Cohort; 10 subjects; 1 group	PSWT		NR	95	7000/ 700	NR	20 (over 4 weeks); 30 (20+10) min/session	Yes	12

RCT – Randomised Controlled Trial; ROM – Range of Movement; RF – Radiofrequency; CSWT – Continuous Shortwave Therapy; PSWT – Pulsed Shortwave Therapy; PP – Peak power; PD – Pulse duration; PRR – Pulse repetition rate; MP – Mean power; NR – Not reported; NA – Not available to the authors; W – Watts; µs – Microseconds; pps – Pulses per second; min – Minutes.

3.2.3 Conclusions

The evidence for RF-based therapy within the referred frequency range in chronic clinical conditions is mixed, and some of the general conclusions that were drawn within the acute category are relevant to the chronic section as well. As the review did not employ a cut-off (Downs and Black) score for the methodological quality, all the identified literature was included. However, the conclusions drawn here are influenced primarily by the results from well-designed studies besides the overall evidence from the respective cohort (like the acute studies). A clear association could not be found between the quality scores obtained by the studies and their reported clinical outcome. Even though some studies that scored highly (> 20) on the Downs and Black scale supported the use of RF, some others have disagreed. Similar trend was noted among the studies that scored low (< 20) on the scale.

Most of the identified studies were in the shortwave frequency range. Within the SWT, the majority were carried out using PSWT. Although several of the earlier studies gave conflicting reports about SWT management of OA, a majority of well-designed recent studies have supported its use in the treatment of OA; mainly in its pulsed form (PSWT). Hence, it is concluded that overall there is moderate evidence to support the use of PSWT for OA knee. Based on the available evidence, for OA knee, a mean PSWT dose at or above 14.5 W, 8–12 sessions over 4–6 weeks, and 15–20 minutes per session may be considered as an effective intervention. Some evidence is also available favouring the use of CSWT to treat chronic LBP. However, recommendations on CSWT dosage for the treatment of LBP cannot be given based on the available evidence, as the dosage parameters were not adequately reported. Only a limited number of studies were identified on the effects of RF-based therapy for other chronic conditions giving rise to pain.

Some evidence, although weak, also exists for the use of PSWT to promote the healing of chronic wounds. Most of the studies identified in this category were case studies. Well-designed and adequately controlled studies on tissue healing were low in number. While there is a pressing need for further quality research, the existing studies suggested the potential benefits of PSWT in wound healing. Like LBP, dosage recommendations cannot be made owing to the lack of reporting and the considerable variations in durations of intervention among the studies.

It is evident from the review that most of the research surrounding the use of RF in therapy-related clinical practice was centred on conditions of pain and inflammation and tissue healing. A small number of studies investigated other conditions such as tissue extensibility and ROM. Like most of the studies on tissue healing, all the identified studies in this area were case studies. They recommended that PSWT may be useful for improving ROM in

conditions like post-traumatic stiffness. Proper clinical trials are yet to be carried out in this area; hence no recommendations can be made.

Only a very small number of clinical studies have been published in the non-shortwave RF category. The indication from the studies available is that RF below 10 MHz might deliver appreciable therapeutic benefits. However, there is no clear indication from the experimental studies as to what may be their underpinning mechanism of action. It is anticipated that at frequencies less than 1 MHz such EPAs may be able to induce both thermal and nonthermal mechanisms of action in the tissues. Substantially more quality research is warranted in this area given the non-existence of quality evidence in the form of well-designed RCTs. The base frequencies used were different in virtually every study, hence no comparison was achievable.

The overall quality of the studies should be considered while interpreting the evidence reported here. Reporting has been poor overall, although the trend seemed to improve in the newer studies (reporting of dose-related information continued to be a problem). Lack of robustness in the methodology (e.g. grouping issues and several other issues mentioned in the discussion) also followed a similar trend as reporting. In this review recommendations have been made where possible depending on the level of information available. However, dosage parameters for the RF used and their criteria for selection have been either unclear or left unreported, making recommendations problematic. The same is true for the statistical information given in the reports. Where participant drop-outs were high, they were not accounted for in the final analysis in most studies (no intention-to-treat analysis) as would be expected from a more recent publication.

3.3 Section II summary

Radiofrequency is a multifaceted entity in the wider clinical world. The literature pertaining to the clinical applications of RF is extensive. Since most of that literature was outwith the primary remit of this project, only those studies that were directly relevant to therapy-related clinical practice were included here. RF-based EPAs have long been used in therapy practice. Over the years, the RF frequency ranges employed in such EPAs have narrowed owing to various reasons identified in the previous sections. Recent research suggested that in contemporary practice the use of RF-based EPAs is largely limited to the frequency range of 30 kHz – 30 MHz. The literature pertaining to this frequency band is much smaller compared to the wider clinical literature relating to RF as stated above. Only 120 clinical studies (published in English) concerning the use of RF-based treatment in therapy-related clinical practice were identified from a comprehensive literature search within the above frequency range. Several studies that were relevant to this research project but conducted on non-clinical samples/populations such as laboratory animals, tissue models (*in vitro*

studies) or asymptomatic humans (healthy-subject studies) have also been discussed briefly.

All 120 clinical studies have been reviewed in detail in chapter 3. The studies belonged to either a smaller 'acute conditions' (30 studies; 25%) subgroup or a larger 'chronic conditions' (90 studies; 75%) subgroup. Both groups contained studies that employed various methodological approaches ranging from case studies to multi-group clinical trials. They also contained similar application categories – mainly the studies on pain and inflammation and the studies on tissue healing. A comparison and contrast of the main results of the reviews from both the acute and chronic subgroups are given in Table 3.7.

Table 3.7: Key review findings from the acute and chronic subgroups of RF studies

Acute conditions	Chronic conditions
▪ Limited research, majority on PSWT ▪ No studies on the non-shortwave RF range ▪ Good evidence for post-operative pain and post-operative wound healing ▪ Sparse and conflicting evidence for other acute conditions ▪ Inadequate methodological quality ▪ Poor overall reporting	▪ Wider research, both PSWT and CSWT studies ▪ Very limited number of studies on the non-shortwave RF range ▪ Moderate evidence for OA knee ▪ Some evidence for LBP and wound healing ▪ Sparse and conflicting evidence for other chronic conditions ▪ Inadequate methodological quality ▪ Poor overall reporting

Together, for the acute and chronic conditions, notable evidence only exists for chronic OA knee, acute postoperative pain and acute postoperative wound healing. Some evidence also exists for chronic LBP and healing of chronic wounds. None of the other clinical areas where studies were identified has sufficient evidence to support the use of RF-based therapy. The clinical areas of research, methodological shortcomings of the studies, and issues with reporting remained common for both acute and chronic subgroups. In both categories, a clear association could not be found between the quality scores (Downs and Black) obtained by the studies and their reported clinical outcome. Several studies considered here were affected by significant methodological issues as identified in the relevant sections, which appeared to be common to both acute and chronic categories.

RF-based EPAs have been used in therapy practice for almost a century. Yet, research in this area continues to be minimal, warranting substantially more work. The non-shortwave RF band is particularly less well investigated since only eight out of the 120 studies in this review employed RF frequencies other than the commonly employed frequency of 27.12 MHz. It was non-existent in the acute category with zero studies identified. This is clearly

surprising since EPAs employing RF frequencies below shortwave are already in clinical use in many countries for decades. This observation is also true for non-clinical studies investigating the theory underpinning the potential modes and mechanisms of RF action in tissues.

SECTION III: PHYSIOLOGICAL EFFECTS OF 448 kHz CRMRF-BASED THERAPY ON ASYMPTOMATIC ADULTS – A LABORATORY-BASED INVESTIGATION

4 Chapter 4 – Materials and methods, measurement principles and pilot experiments.

4.1 Introduction

The previous two sections provided a detailed account on the fundamental principles of RF-tissue interaction and the literature on the effects of RF-based therapy. It also outlined the rationale, aims and objectives of this research project. It is clear from the existing literature that there is a lack of research to show how specific RF frequencies below the shortwave frequency band interact with the human body, while there are reasonably good levels of such research available on the higher frequencies (shortwaves and microwaves, microwaves not covered here). It is reasonable to state (based on the literature that was published in English) that EPAs based on RFs below shortwave have become commercially available and embedded into clinical practice without extensive underpinning evidence. Besides the lack of clinical studies, no *in vivo* human or animal studies were identified investigating the physiological effects of 448 kHz CRMRF, which is the frequency of RF being investigated in this project. This is true also for all other RF frequencies below shortwaves.

The purpose of this chapter is primarily to outline all physiological measurement techniques that were relevant to the work carried out in this research project, explain the principles of measurement and report all pilot experiments that were carried out. To avoid repetition in the following chapters, reference will be made to the contents of this chapter where relevant while describing the methodology. The chapter will also describe the procedures adopted to process the resultant data. It will explain the measures relating to superficial, deep and systemic physiological responses. All measures adopted in this project were non-invasive and those that reflect the changes to body's thermoregulatory/thermophysiological system when subjected to exogenous EMF. Numerous researchers have used such or similar measures in related RF research.[77-81,85,87,95,96,105,175,178-180,187,191,329] Numerous pilot studies were conducted as part of this project to ascertain the reliability of the involved methods (equipment and techniques) in comparison with other similar methods, where multiple methods were available for use; and to ascertain the intra-rater reliability where the techniques were complex.

4.2 The RF treatment devices

4.2.1 The CRMRF device

The CRMRF treatment was administered using 'Indiba Activ 902' device (Indiba S. A., Barcelona, Spain) (Figure 4.1). It was a brand-new factory calibrated machine pretested to

ensure reliability and accuracy of output. The peak power of the device is 200 W (or 450 Volt-Ampere (VA)). It delivers RF energy in two modes: Capacitive (CAP) and Resistive (RES), which are delivered using different types of electrodes. RF is generated at 448 kHz in a continuous wave form in either mode. The intensity of the energy delivery is given as percentage output. The theory underpinning the CAP mode function is similar to the capacitive method of SWT. Likewise, the RES mode is similar to the inductive method of SWT. These methods of SWT are well-documented.[18] The mechanism of RF-tissue interaction is already covered in detail in the previous sections.

The two main differences between the CRMRF and SWT are:

1) The operating frequency – SWT is delivered mainly at 27.12 MHz while CRMRF is delivered at 448 kHz.
2) In CRMRF the energy is applied via a contact method using a coupling medium unlike in SWT where the transmission is over an air gap.

The CAP electrode is coated with a polyamide material that acts as a dielectric medium. This medium insulates its metallic body from the skin surface, thereby forming a capacitor with the treated tissues. The RES electrode is uncoated. Energy delivery to the body is enabled using a conductive cream (coupling medium) (Figure 4.1), since the frequency of the RF is not high enough to be able to conduct through air. The device offers different sizes of round metallic treatment electrodes for both modes of treatment (Figure 4.1). The size is chosen according to the size of the body area being treated. The return electrode is metallic and is either flat or cylindrically shaped. The machine can be operated from a close distance using a remote control that has start/stop and intensity up/down functions. In the research environment, a monitoring device can be attached to the machine to transfer the operating data wirelessly using computer-based monitoring software.

The device used in this project was modified by the manufacturer to meet the requirements of blinded and randomised laboratory testing, and the appropriate monitoring of the energy delivery. However, the fundamental functions and the working of the device remained identical to a commercially available device except for the following modifications.

1) An additional setting allowing the therapist to choose treatment programmes from 0 – 99, half of which were active treatment programmes and half placebo.
2) The CAP mode display would normally show the energy delivery units in Volt-Ampere; however, the current device displayed this information in Watts to enable identical energy monitoring for both CAP and RES modes.

Figure 4.1: The ‘Indiba Activ 902’ device, electrodes and conductive cream

Electrodes measuring of 65 mm in diameter were used as treatment electrodes and a flexible rectangular metallic electrode measuring 200 x 260 mm was used as return electrode throughout the current project. A conductive cream that was supplied by the device manufacturer was used as a coupling medium between the electrode and the skin. The machine displays the RF intensity and the energy output while the treatment is being delivered, which is also mapped by the computer-based monitoring software.

More details are discussed in the pilot study section of this chapter.

4.2.2 The PSWT device

PSWT was delivered using ‘Bosch Ultramed’ machine (Robert Bosch GmbH, Germany) (Figure 4.2) that operates at the base shortwave frequency of 27.12 MHz. The Bosch Ultramed is a therapeutic apparatus that can deliver shortwave in both continuous and pulsed modes. In the pulsed mode, the device can deliver pulses that are fixed at 400 µs in duration (pulse duration; PD), repeating at a rate (pulse repetition rate; PRR) of 15–200 Hz enabling the operator to vary the output. The peak power (PP) can be varied from 100 to 1000 Watts (W). The desired mean power (MP) output can be obtained by manipulating the various pulse parameters. The device was fully tested and calibrated prior to the commencement of the study.

Figure 4.2: The Bosch Ultramed SWT device

4.3 Selection of physiological parameters to investigate

The RF physiological studies published so far (including animal studies) have focussed predominantly on the thermophysiological effects such as changes to tissue temperature, blood flow, nerve conduction and tissue extensibility. These studies were mainly conducted either using pulsed or using continuous SWT devices. Since similar research is non-existent among the lower frequency non-shortwave RF (including the 448 kHz CRMRF), a series of laboratory-based studies were designed to investigate the effect of CRMRF on the physiological parameters in an asymptomatic sample. The chapters that follow in this section will address the various physiological responses of CRMRF under different experimental conditions and doses. A comparison of the effects of CRMRF with those obtained with a comparable dose of PSWT will also be undertaken later in the section (chapter 6).

4.4 Selection of a body area to treat

The literature shows various body segments being exposed to RF-based treatment and to the measurement of physiological responses. They included the lower limb[80,81,83,89,90,95,105] in many studies and the upper limb[77-79,85] in some other studies. The studies often followed key anatomical landmarks (such as a specific joint or a muscle group), which can be related directly to clinical conditions. In other words, if the use of an RF-based EPA is shown to be feasible on a body segment and if the effects are present in terms of physiological parameters such as blood flow or nerve conduction, then its clinical application pertaining to a condition specific to that body segment potentially becomes more feasible.

One of the main aims of this project was to investigate the clinical effect of CRMRF in a relevant musculoskeletal condition. The choice of a condition must be based on its prevalence, impact of the condition on patients' health-related QoL, its resistance to existing conservative treatment methods (recalcitrance), potential response to RF-based treatment and the feasibility of a clinical evaluation in terms of availability of participants for the study. The literature review has shown that OA of the knee joint is the single largest clinical area investigated by the existing RF studies and showed some of the best available evidence. The condition is still regarded as one of the most pressing chronic public health issues affecting the functional QoL of people.[330-334] Hence, OA of the knee was regarded as the most appropriate condition to be investigated for the clinical effects of CRMRF treatment and be compared to existing forms of RF treatment such as PSWT. Hence, in the laboratory-based physiological investigation the knee region was chosen as the body area to be treated and assessments to be undertaken.

4.5 Superficial physiological measurements

Skin temperature (SKT), Skin blood flow (SBF) and nerve conduction velocity (NCV) were the localised superficial outcome measurements obtained. They are explained in detail below alongside the various measurement systems used to obtain them.

4.5.1 Skin temperature

The SKT is an important physiological parameter that can reflect on the presence of disease and injury. It can also characterise the body's interaction with the environment and plays a fundamental role in thermoregulation. Hence monitoring of SKT is important for both clinical and non-clinical settings.[335-337] Since RF is used in therapy predominantly for its thermal effects, it is prudent to use SKT as a key outcome. SKT should be distinguished from core temperature, which in simple terms is the temperature of the inside of the body. While the normal SKT varies depending on the body area, metabolic level and the environment, the core temperature reflects the temperature in the hypothalamus and undergoes rhythmical variations through the day; however, under normal circumstances the core temperature is maintained within a narrow band of 36 – 38 ^{o}C.[336,338-342] Although core temperature will be monitored in this study (mentioned later), the main focus is on the local SKT changes in response to localised therapeutic application of non-invasive RF.

There is extensive literature on various methods of SKT measurements. Broadly, there are contact (conductive) and contactless (non-conductive) methods of skin temperature measurement. There are a wide variety of these devices available. Three of the most popular types of devices employed in research and clinical practice are thermocouples, thermistors and telemetry sensors (e.g. iButtons).[343-345] Wireless sensors are also available, which have been validated against thermocouples and thermistors.[337,346]

The contactless devices are normally the quick response IR surface thermometers that are used by many researchers,[347-352] or IR thermography.[353-359] Similar to the contact conductive devices, the IR thermometers provide a 'spot' measurement, which is the average temperature of the small surface area where it is measuring.[336] Some IR thermometers require skin contact to enable measurement, but the majority of them do not. Usually there is a manufacturer instruction as to how far from the skin the device can be held (e.g. 50 mm) while a reading is taken. There are devices that allow a greater distance and hence a greater measurement area; however, this often will affect the accuracy.[360]

Instant response thermistors are usually employed for real-time temperature monitoring, enabling up to thousands of readings to be taken every second via computer-based monitoring software (e.g. Biopac system (Figure 4.4)). They are highly temperature sensitive and accurate within the human physiological range.[336,344] Although there is a disadvantage in being a wired device and that they are much more expensive (the encoders), thermistors are

a valid and reliable method of skin temperature measurement used in both clinical practice and research.[80,192,350,352,361,362]

4.5.2 Skin blood flow

The measure of SBF can be a good indicator of perfusion in the superficial tissue structures. It responds to both internal and external factors such as rest, physical activity, hormones, heat, cold and a range of chemical and mechanical stimuli. The physiology of SBF and the effects of heat and cold on SBF are well documented.[8,254,341,342,363-368] Besides SKT, the changes in SBF can be used as an important outcome measure to understand the physiological effects of RF since tissue effects of RF are thought to be predominantly thermal and the changes in SBF being predominantly a thermophysiological response.[1,21,22] It has been used extensively as an outcome measure in previous research with RF in the shortwave frequency range.[77,80,85,86,192]

Over the years, numerous studies on the methods (invasive or non-invasive)[369-389] and their innovations and refinements[382,390-403] have been reported in order to achieve accurate measurement of SBF. Describing all those techniques in detail is beyond the scope of this thesis. Two of the most popular and robust non-invasive measurement techniques that are widely used in clinical research are Photoplethysmography (PPG)[369,379,389,390,392,404-413] and Laser Doppler Flowmetry (LDF).[371,374,383,400,414-418] Both are valid and reliable techniques to make spot measurements of SBF and several comparative studies between the two are also available,[375,406,409,419-421] the consensus of which is that both techniques can be used effectively for SBF monitoring. Both LDF and PPG were available for use in this research project. However, the LDF probe sustained mechanical damage and could not be repaired or replaced in time for use. PPG was hence used as the measure of SBF in all the studies of this project (Figure 4.4).

LDF measures the microcirculatory blood flow using either a fibre optic probe (laser Doppler perfusion monitoring, LDPM) or an imaging system (laser Doppler perfusion imaging, LDPI). The technique infers the blood perfusion rate by analysing the Doppler frequency shift from the scattered monochromatic laser light reflected by the moving RBCs.[374,414,416,422] PPG, which was first described by Hertzman[386,423,424] in 1937, detects the changes in blood volume in the microvascular bed of tissues. It utilises a light emitting diode (LED) to emit light into the tissues. While this light gets absorbed and scattered in the tissues, a small amount of this scattered light is received by a photodetector plate placed adjacent to the LED source. Variations in this photodetector signal relates to the changes in blood flow.[379,382,389,404,405,411] Besides being used in research, PPG has widespread clinical applications providing valuable information about the circulatory system. The technology is utilised in several

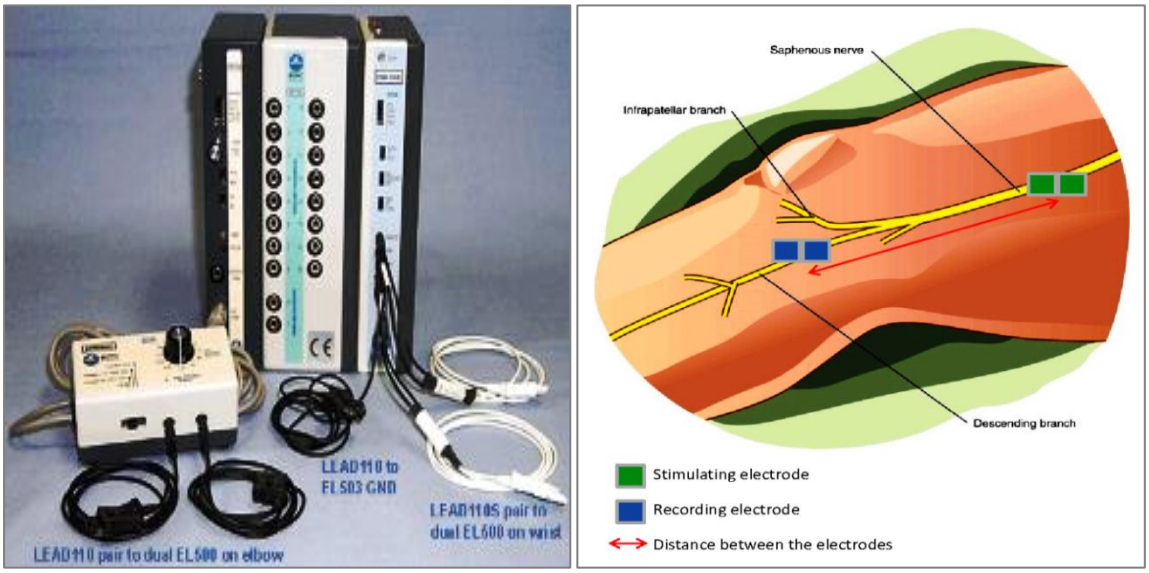
commercially available systems such as pulse oximeters, vascular diagnostics and certain BP monitoring devices.[369,411]

4.5.3 Nerve conduction velocity

Unlike SKT and SBF, RF of any frequency is not known to influence NCV greatly. Literature in this area has been limited, with only few studies that showed mixed results.[78,191,192] However, as stated the existing literature is solely based on SWT with no information available on any potential effects of CRMRF on nerve conduction. In fact, the literature is completely lacking for any RF frequencies below the shortwave frequency band.

In simple terms, NCV is the speed with which an electrical impulse (action potential) travels along a nerve fibre either orthodromically or antidromically in a sensory, motor or mixed nerve. In clinical practice, it is used as a diagnostic measure of the pathophysiology of a nerve. During the test, the nerve is stimulated at one point using mild short electrical impulses that are applied to the skin using an attached surface electrode patch (stimulating electrode). The nerve response to this impulse is recorded at a suitable distance along the same nerve using another attached surface electrode patch (recording electrode). The NCV is then calculated from the distance between the stimulating and recording electrodes and the time taken by the impulse to reach the recording electrode (Figure 4.3).[425-430]

Figure 4.3: Representative image showing NCV measurement and device setup



The velocity of conduction varies from nerve to nerve and from person to person. In general, the larger the diameter of the nerve fibre and higher the degree of myelination (myelin sheath forms an ‘insulation’ around the nerve fibre), the faster the nerve conduction is. A normally functioning nerve with undamaged fibre and intact myelination will transmit the impulses more effectively than an injured nerve.[431-434] This is like a large and properly

insulated electrical cable being able to transmit a strong electric signal consistently than a thin wire with no proper insulation.

Several devices exist that can measure NCV; however, they all consist of similar components. There will be a stimulator to deliver the impulse, a recording unit to capture the nerve response and an amplifier to magnify the recorded signal. This system is connected through stimulating and recording electrodes along with their lead wires. A ground electrode is also used to reduce stimulation artefacts, noise and interferences. The amplifier utilises high or low pass filters to keep unnecessary signals (noise) out. NCV can also be recorded using needle electrodes; however, in the current project only non-invasive methodologies were employed hence standard square ECG twin electrodes were used. A separate pilot study was undertaken (explained later in this chapter) to identify the most suitable ECG electrode for this purpose by testing many commercially available brands.

4.5.4 The skin physiological measurement devices

4.5.4.1 The Biopac system

Biopac MP150 (Biopac Systems, CA) (Figure 4.4) physiological measurement system was used in the main study (study described in chapter 6) to record all three outcome measures described above (SKT, SBF and NCV). The existing Biopac MP100 that was successfully used in an earlier PhD project[192] and whose findings have also been published,[80] was upgraded to MP150 for the current project incorporating the latest modules, transducers and the latest version of the computer-based software. Biopac systems are used world over in contemporary research, in similar or unrelated subject areas.[435-442] It is an acquisition system that can collect, analyse, store and retrieve data. There are 16 input/output channels and a maximum sampling rate of up to 200 K samples/second. The technical specifications of the unit are further detailed in Appendix 4.1.

The local SKT was recorded using the SKT100C amplifier module and the TSD202A thermistor transducer. SBF was recorded using the PPG100C photoplethysmogram (PPG) amplifier module and the TSD200 PPG transducer. Nerve conduction velocity was measured using the STM100C stimulator (STM) and EMG100C electromyography (EMG) amplifier modules used in combination. The cited accuracy of the MP150 system was ±0.003% of full scale range.

The TSD202A (together with the SKT100C module) used to record SKT employs a fast response thermistor with a response time of 0.6 seconds. It is appropriate for measuring skin temperature in small areas, and for use in locations where temperature varies rapidly. The TSD200 PPG transducer (together with the PPG100C module) consists of a matched infrared emitter and photo diode, which transmits the changes in blood density (caused by blood pressure changes), at specific body locations. When the TSD200 is attached to the

skin, the infrared light is modulated by blood pulsing through the underlying tissues. The modulated, reflected light results in small changes in the resistance of the photo resistor, which yields a proportional change in the voltage output. The peak measurement recorded by the device indicates the point of maximal blood density at the respective location. The blood flow values are obtained in arbitrary units rather than absolute values.

Figure 4.4: The Biopac MP150 system, modules, and PPG (top right) and SKT (bottom right) probes

4.5.4.2 The FlexComp Infiniti system

The FlexComp Infiniti (SA7550) (Thought Technology Ltd., Montreal, Canada) (Figure 4.5) is a 10-channel multi-modality device (encoder) for real-time computerized psychophysiology, biofeedback and data acquisition. It is a portable unit that can render a wide range of objective physiological measures in clinical practice and research. In this project, the device was used to obtain SKT and SBF from the participants of the clinical trial (final stage). The device has been used in research in other subject areas[443-445]

Figure 4.5: The FlexComp Infiniti device, and PPG and SKT probes

To study the relative change in SBF, a Heart Rate/Blood Volume Pulse (HR/BVP) Sensor (P/N: SA9308M), which is the same as a PPG sensor was used. Default sampling settings with a minimum of 256 samples per second was employed. The SKT was recorded using the Skin Temperature Sensor (P/N: SA9310M). It can perform real-time temperature measurement between 10 ^{o}C – 45 ^{o}C. This thermistor converts changes in temperature to changes in an electrical signal, which is mapped by the encoder and the software. The underpinning principles of both these probes are similar to that of the Biopac probes.

4.5.4.3 Hand-held IR surface thermometer

A hand-held contactless IR skin surface thermometer (Thermofocus 01500A3) (Tecnimed Srl, Varese, Italy) (Figure 4.6) was used for skin surface temperature measurement where the Biopac system was not used (Chapter 5). It had a measurement accuracy of ±0.3 ^{o}C between 20.0–42.5 ^{o}C, with an improved accuracy of ±0.2 ^{o}C between 36.0–39.0 ^{o}C. This was an inexpensive device suitable for use in both clinical and research settings.

Figure 4.6: The Thermofocus IR thermometer

4.6 Deep physiological measurements

Deep blood flow and tissue extensibility were the measures obtained from deeper tissues. They both are explained in detail below along with the ultrasound devices that were used to measure them.

4.6.1 Deep blood flow

Blood flow to the deeper tissues (two centimetres or more from the skin) was monitored using Doppler ultrasound measurements that provided information on the velocity, volume and intensity of blood flow. Even though the function of blood flow has been a subject of science since centuries, quantitative methods to study deep blood flow in man have not been available until the beginning of last century. Addition of advanced instruments such as Doppler ultrasound to the battery of measurement tools enabled objective recording of the blood flow in larger blood vessels inside the body without interfering with the process of circulation.[446] The power Doppler imaging is relatively new when compared to colour Doppler and displays blood flow with significantly improved sensitivity than the conventional colour Doppler imaging.[447] The colour Doppler is most effectively used when examining

whole vessel flow and power Doppler for tissue perfusion or microcirculation. Further technological advancements in ultrasound imaging in the past few decades have made the technique more accurate, without the need of being invasive or needing to administer intravascular contrast agents.

4.6.2 Tissue extensibility

The indices of tissue extensibility (measurements of 'hard', 'intermediate' and 'soft' tissues) were obtained using Sonoelastography. Sonoelastography provides an estimation of tissue elasticity (extensibility) by analysing the degree of distortion in tissues secondary to the application of an external force. This dynamic technique employs ultrasound and is comparatively new. In this technique, the relative extensibility of the tissues is displayed as a colour overlap on the standard grey (B-Mode) image.[448,449] Although used mainly for the imaging of tumours, it is proposed to be a promising tool in determining the elastic properties of human tendons and skeletal muscles.[448]

4.6.3 Ultrasound scanning devices

An 'Esaote MyLab70 XVG' (Esaote S.p.A, Genoa, Italy) (Figure 4.7) ultrasound scanner was used alongside a linear array probe 'LA523' that supports a frequency range of 4–13 MHz (Esaote S.p.A, Genoa, Italy) to collect the deep blood flow and Elastography data in the main laboratory study (Chapter 6). Since this device was not portable, another portable device 'Esaote MyLab 25' (Esaote S.p.A, Genoa, Italy) was used in the clinical trial phase (Chapter 9) to ensure safe and easy transportation from and to the trial site. The LA523 probe was compatible with both scanning devices.

Figure 4.7: The Esaote ultrasound scanning devices and probe

4.7 Other outcome measures

Core temperature, blood pressure and pulse rate were the other outcomes monitored alongside the main outcome measures described in the above sections. There is no evidence in the existing literature to suggest that localised application of any frequency of RF will impact on systemic parameters such as core temperature, blood pressure or pulse rate. There is also no indication that the application of CRMRF to local tissues may induce any changes to the same. However, monitoring these systemic physiological parameters would enable a better understanding of the extent of effects of the local therapeutic application of CRMRF.

An infra-red (IR) tympanic thermometer (Braun ThermoScan IRT 4520, Braun GmbH, Kronberg, Germany) was used for core temperature measurement. It had a measurement accuracy of ±0.2 ^{o}C between 35.5–42.0 ^{o}C and ±0.3 ^{o}C outside of this range. Blood pressure (BP) and pulse rate (PR) were monitored using a digital upper arm BP monitor (Omron M2, Omron Healthcare Europe B.V., Hoofddorp, Netherlands).

4.8 Other devices used in the project

During the experiments three other devices in addition to the outcome measure devices were used to collect the anthropometric data, room temperature and humidity and to assist with the method of treatment delivery (Chapter 5). A body composition monitor (Omron BF508, Omron Healthcare Europe B.V., Hoofddorp, Netherlands) was used to obtain the weight, body fat percentage, visceral fat and the body mass index (BMI) measurements of the participants. The room temperature and humidity were monitored using an electronic thermohygrometer (RS 212-124, RS Components Pte Ltd., Singapore). An electronic metronome (Seiko Corporation, Japan) and a computer-based timer were used to aid the experimental procedure described in chapter 5.

4.9 Processing of physiological data

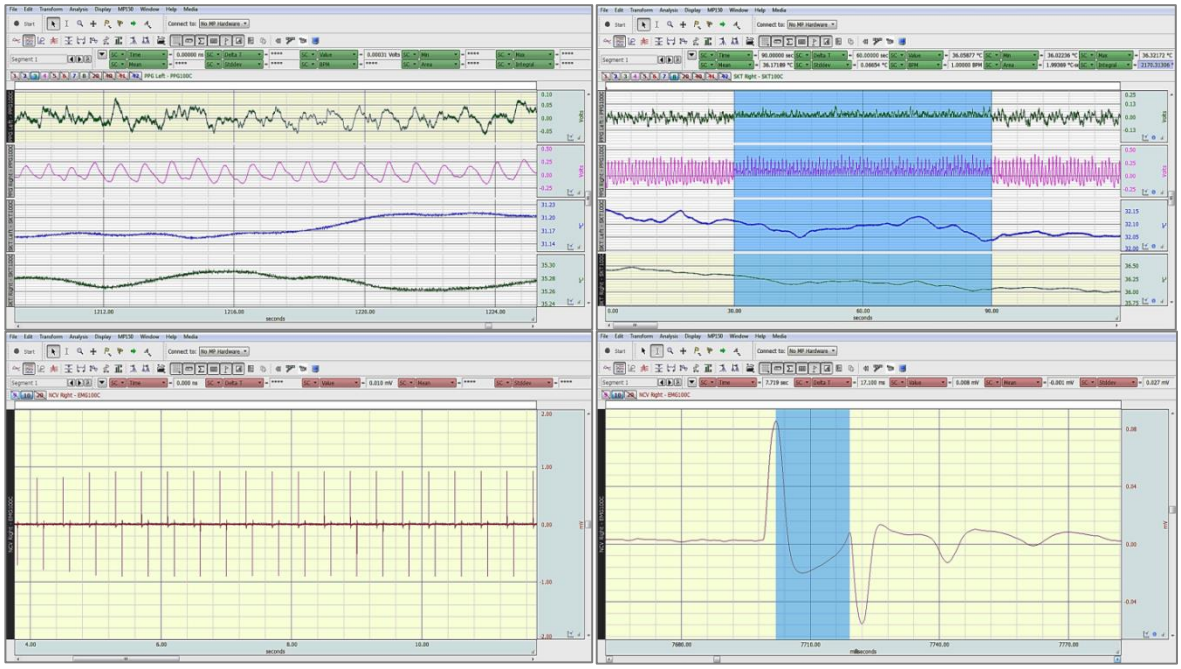
This section will explain how the raw physiological data obtained from the Biopac, FlexComp Infiniti and ultrasound devices were processed to obtain the corresponding numerical data to be analysed statistically.

4.9.1 Processing of Biopac data

The Biopac data provides actual values for SKT and NCV, but for SBF the PPG module reports the data in Volts from which the relative change in SBF can be inferred. For both SKT and PPG, 60 seconds worth recordings were processed to obtain each of the three measurements (pre-treatment, post treatment and follow-up). The Biopac ‘AcqKnowledge’ software allowed the processing and required calculations to be made on each data stream.

Before obtaining the measurement values the data streams were subjected to the ‘Comb Band Stop’ and ‘Low Pass’ digital filters to exclude the unwanted signal noise. For SKT the mean value over the selected 60 seconds was taken. For PPG, the area under the curve was obtained by first reversing the negative cycles and then using the ‘integral’ function of the software. For NCV after applying the above digital filters the area of one action potential was magnified and the area between two peak responses (external stimulus and subsequently the nerve response) was marked. This denoted the time lag (ΔT) between the peaks of the stimulus and the nerve response, which is essentially the nerve conduction time. The distance between the stimulating and recording electrodes is already known. From this time and distance, NCV can be calculated. Figure 4.8 shows the raw and processed data streams of SKT, PPG and NCV obtained during an experimental session from one of the participants.

Figure 4.8: Raw (left) and processed (right) Biopac data. SKT & PPG (top), NCV (bottom)



4.9.2 Processing of ultrasound data

The ultrasound images were computationally analysed using MATLAB (MathWorks, Massachusetts) to process the colour image data into numerical data. The MATLAB algorithms were written by Dr Anthony Herbland (Educational Technologist & Senior Lecturer, School of Health and Social Work, University of Hertfordshire) after the idea was discussed and conceived among the researcher (BK), the supervisor (TW) and Dr Herbland.

For every image frame the MATLAB algorithms generated two types of data: the total number of coloured pixels (pixel count) in the ‘region of interest’ (ROI) indicating the volume information, and the total colour intensity value based on the intensity value for all the colour

pixels in the ROI. The intensity value in turn was calculated based on the linear property of the green colour component in the colour and power Doppler scales. The green colour decimal value range varied linearly from 0 to 232 for the colour Doppler scale and from 0 to 241for the power Doppler scale.

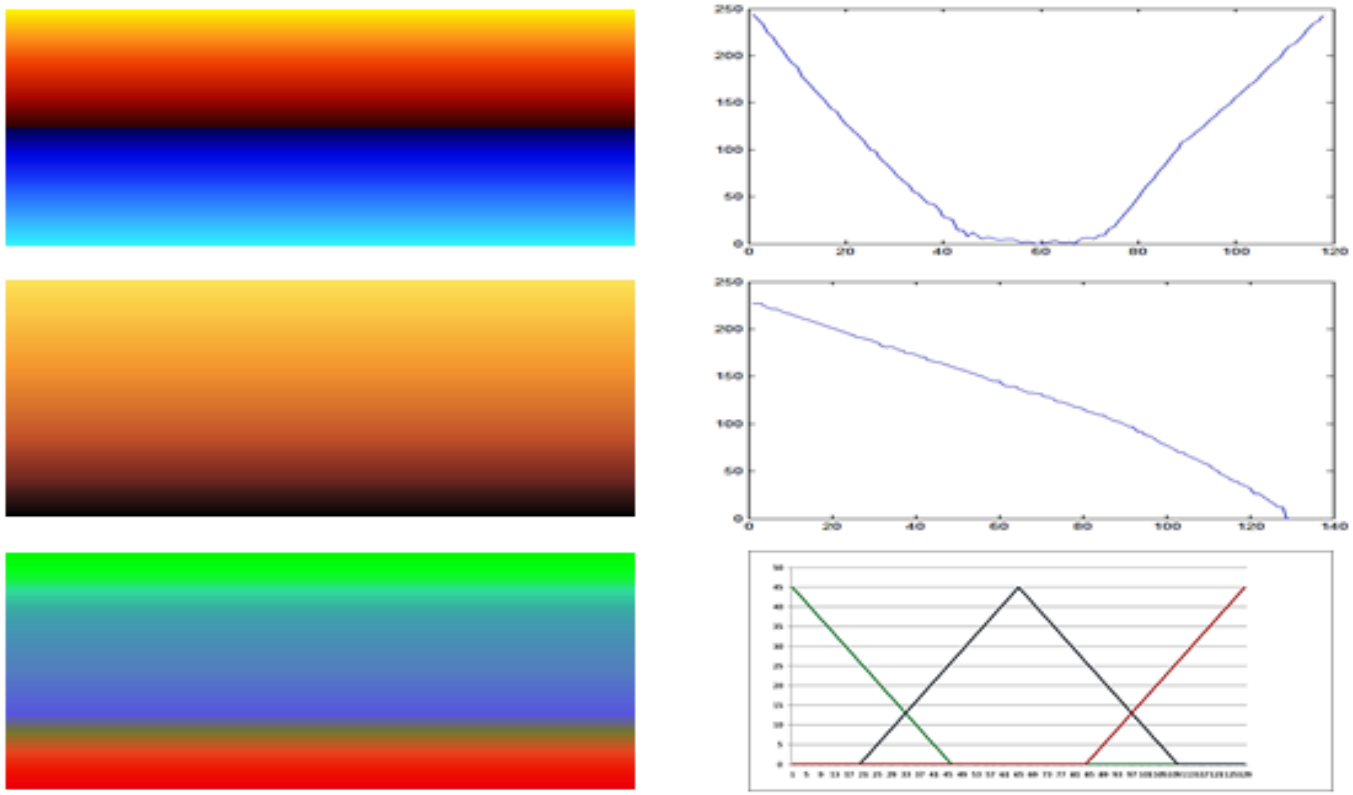
In all results, the pixel count was expressed as ‘kilo pixels’ (total number of pixels divided by 1000) and the ‘colour intensity index’ as the mean colour index per pixel by dividing the total colour score of a frame by the total number of pixels in that frame. For colour Doppler, the ‘colour intensity index’ scores (total green colour intensity divided by pixel count as described above) indicated the relative velocity of the flow of blood. For power Doppler, both ‘pixel count’ and ‘colour intensity index’ were taken in to account separately. The total number of pixels (pixel count) represented the overall ‘blood flow volume’ and the colour intensity index (calculated as in colour Doppler) represented ‘blood flow intensity’. Higher the count and/or index, higher were the flow of blood.

The degree of tissue compliance (level of ‘hard/soft’ ness) in Sonoelastography was analysed differently to the Doppler data in that all three colour components red, blue and green were analysed as described above, for the hard, intermediate and soft tissue types respectively.

The MATLAB analysis of the machine colour scales for the colour and power Doppler and Elastography is further illustrated in (Figure 4.9). The algorithms used for the processing of the ultrasound images obtained from the MyLab 70 device (laboratory study) are given in Appendices 4.2, 4.3 & 4.4. Appendices 4.5 & 4.6 show the algorithms used for analysing the ultrasound images obtained using the MyLab 25 portable device (clinical study).

Figure 4.9: The MATLAB analysis of the ultrasound machine colour scales

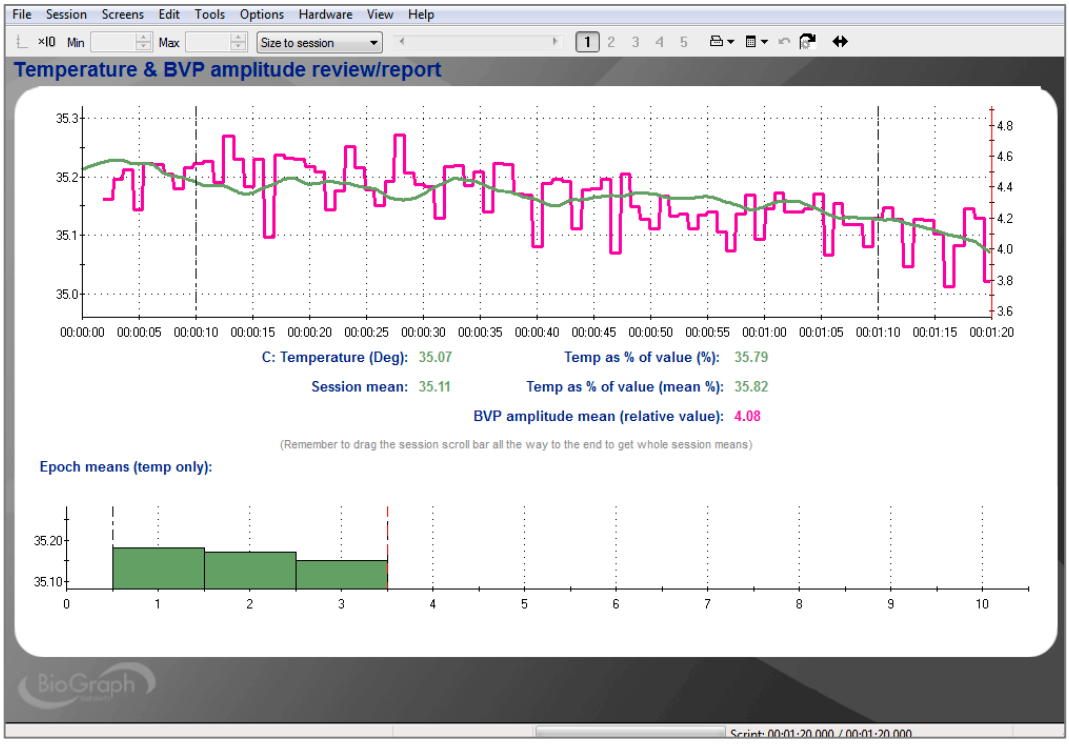
Images (left) and graphs (right) showing the analysis of colour Doppler (top), power Doppler (middle) and Elastography (bottom) colour scales. For colour and power Doppler, a linear relation was identified between the intensity of colour on the scale and the amount of 'green' component (as plotted) of the corresponding RGB (red, green and blue) spectrum. Red and blue components did not follow this linear relation and were hence not used for the analysis of either colour or power Doppler. The x-axis shows the 'pixels' from the top to the bottom of the scale on the left and the y-axis shows the corresponding value of 'green' from the RGB scores. For Elastography, which was divided into 'hard', 'intermediate' and 'soft' categories, all three colour components (red, blue and green respectively) were analysed and used for interpretation as shown in the graph.



4.9.3 Processing of FlexComp Infiniti data

The FlexComp Infiniti measurement unit was used as the portable alternative to Biopac to measure SBF and SKT in real-time on the participants of the clinical trial. The device works with the BioGraph Infiniti software system that was used to obtain the session reports from each of the recording made using the FlexComp Infiniti hardware. Like Biopac the SKT was given in degree Celsius as actual values whereas the PPG report was shown as the amplitude mean (relative value) of the blood volume pulse (BVP). The software showed session means (mean of 120 seconds of data) by default. Figure 4.10 shows an example of a session report obtained from one of the participants in the clinical trial.

Figure 4.10: Sample data report from the BioGraph Infiniti software



4.10 Methodological considerations and pilot experiments

This section will discuss a series of methodological aspects relating to the conduct of the study through all primary pilot laboratory experiments performed as part of this project, some of which were simple desktop experiments while others were studies involving human participants (asymptomatic volunteers).

The aims of the pilot studies were:

1) To establish key issues regarding the CRMRF treatment device.

2) To calibrate the equipment where necessary.

3) To study the potential signal interference between devices.

4) To identify and address issues with probe attachment.
5) To identify and address the sources of signal noise.
6) To analyse signal baselining time.
7) To determine Biopac sampling rate.
8) To establish the agreement between various SKT measurement devices.
9) To identify suitable NCV electrodes for signal stability.
10) To study the effect of CRMRF on NCV electrodes attached to the skin.
11) To establish the test retest reliability of ultrasound measurement techniques.

4.10.1 The CRMRF device: familiarisation, operating principles and identifying the key issues (addressed aim 1)

Extensive practice sessions and testing of the CRMRF device was undertaken to fully understand the operating principles and identify the key issues.

4.10.1.1 Machine parameters

Among the various machine parameters, the output intensity settings on the device were dissimilar on either mode of treatment. While the RES mode allowed more incremental dosages reaching up to 100%, the CAP mode allowed only a smaller number of dosage selections until 100% power was reached. In addition, the increments were not linear in either mode. From the study point of view this meant that a direct dosage comparison between the two modes will be problematic. The treatment electrodes were available in a variety of sizes for either mode. Considering the size of the treatment area (knee), 65 mm treatment electrodes were considered the most appropriate to ensure uniform field distribution. Since the treatment was set to be delivered to the participant while he/she was positioned in supine, the ideal position for the return plate electrode was under the calf muscle. Like SWT (in the capacitor field method) the distance between the active and return electrodes had to be adequate to ensure a uniform field density in the tissues, by preventing field accumulation closer to the junction between the electrodes.

4.10.1.2 The coupling medium

A manufacturer supplied conductive cream was used for energy delivery. It was found that this cream was sensitive to heat when the treatment was delivered, commensurate with the level of dose. As the cream temperature increased, its viscosity reduced resulting in the cream flowing out of the skin. To compensate, it was decided that sufficient quantity of cream should be added at the starting point of treatment itself to prevent drying. After testing

it was decided that 20 ml of cream was sufficient for either mode. The return plate electrode was also decided to be coated with 20 ml of cream to ensure consistency.

4.10.1.3 Provision for blinding

As stated before, the device supplied for this research study was modified by the manufacturer to add the provision for blinding. An additional item was integrated into the set-up menu that allowed the selection of any treatment programme from 0 – 99. At random, half of these settings represented active treatment with normal energy delivery and the other half represented a placebo with zero energy delivery. After testing these settings, it was clear to the researcher that despite the provisions for blinding, the therapist will not be able to be blinded since skin heating and cream issues discussed above will be present. Hence, it was decided to only use the settings ‘zero’ (represented active) and ‘one’ (represented placebo) for the study. However, the participant who is unaware of the potential sensations that might arise from the RF delivery would remain blinded to what level of doses he/she may be receiving. Also, it was decided that at the end of each randomised study involving active and placebo versions a concealment checking would be undertaken to find out the extent of blinding achieved. This can be achieved by asking the participant if they could recollect and identify the sessions they received.

4.10.1.4 Treatment duration and sequence

The manufacturer had recommended to use CAP mode first for five minutes followed by RES modes for 10 minutes in sequence and to end the treatment session with a second five-minute CAP application. Thus, a total 20 minutes per treatment session was recommended by the manufacturer. However, this recommendation was not based on evidence-based reasoning. Moreover, sessions lasting 15 minutes (5 min CAP + 10 min RES) were sufficient commensurate with current practice in the UK. Hence, a CAP-RES sequence was employed instead of a CAP-RES-CAP sequence.

4.10.1.5 Issues with application techniques

The treatment had to be delivered with the electrode exerting mild to moderate pressure on the skin and by moving constantly in uniform circles to avoid undue accumulation of energy and adverse heat build-up. The ideal speed was identified to be one cycle per second. It was decided that a metronome should be used in the lab study to ensure consistency of this technique. The researcher had to at the same time prevent the loss of coupling medium by not letting it flow out of the zone (cream issue discussed above). As the treatment doses were incrementally raised the recipients felt heat sensation on the skin, which increased commensurately with the dose. It was hence decided that the recipient had to be tested and cleared for any lack of skin thermal perception prior to receiving treatment.

4.10.2 Calibration of equipment (addressed aim 2)

The CRMRF treatment device was new and factory calibrated. No periodic user calibration was recommended by the manufacturer. The PSWT device was certified as serviced and calibrated for accuracy of output prior to its use in the study by a licenced engineer who visited the site. Out of the main outcome measure devices, the Thermofocus hand-held thermometer was factory pre-set to run its own periodic self-calibration while in idle mode. The FlexComp Infiniti portable unit was newly supplied and did not require user calibration. The Biopac MP150 main unit and key modules used in this study were new and factory calibrated. Repeat user calibration was not recommended *per se*; however, the manufacturer suggested that accuracy of output may be tested by assessing the noise levels and ensuring that the baseline signal has no voltage drift. Calibration/accuracy testing of the Biopac modules is explained below. The accuracy testing of the modules was done on a weekly basis while the data was being collected.

4.10.2.1 Calibrating the SKT biopotential amplifiers

The fast response TSD202A thermistor transducer can be calibrated while setting the channel up for measurement. The user was only required to choose between Degree Celsius (^{o}C) and Degree Fahrenheit (^{o}F) in the channel setup. Once the desired measurement unit, gain level, sampling rate and channel number were chosen no further modifications were required. All temperature measurements in this study were done in the absolute (^{o}C) readings. The physical controls on the amplifier module can be used to change the gains and filters where required. The module has the available gain settings of 0.5, 1, 2 and 5 ^{o}F/V. The gain setting used in this study was 5 ^{o}F/V and the module auto scaled the measurement settings accordingly.

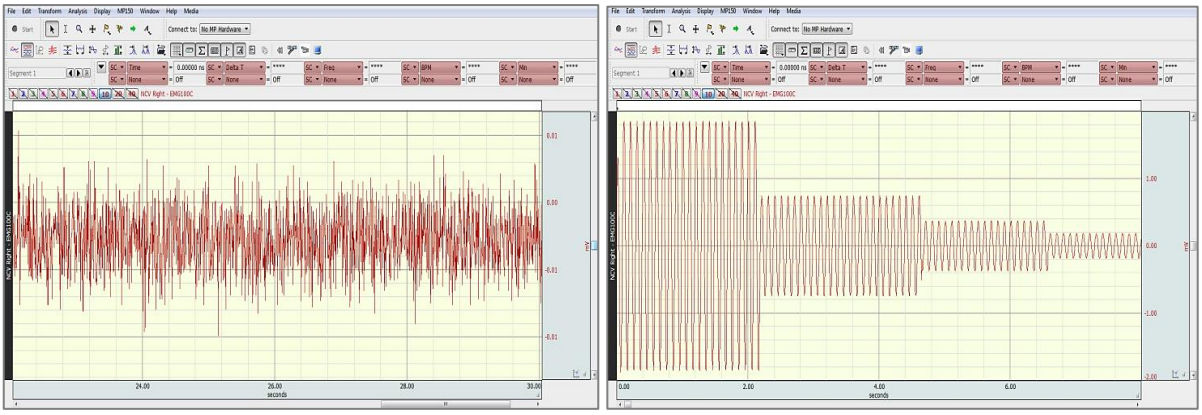
4.10.2.2 Calibrating the PPG biopotential amplifiers

The PPG100C photoplethysmogram (PPG) amplifier module and the TSD200 PPG transducer do not require user calibration according to the manufacturer. When turned on without connecting the transducer, the amplifier module shows the baseline signal constituting only the noise in Volts. When testing for accuracy, if the scaling of this signal shows either a positive or a negative drift from zero Volts, it can be brought back to zero by manipulating the zero-adjustment screw at the top front of the module. The PPG modules used in this study were new and unused; hence they were not displaying any voltage drift from zero. The module has gain settings of 10, 20, 50 and 100. A gain level of 100 was used in the study by default.

4.10.2.3 Calibrating the EMG biopotential amplifiers

The EMG100C is factory set and does not require user calibration according to the manufacturer. However, to confirm the accuracy of the device, they recommended using the CBLCAL, which is a special output cable that can diminish the recorded signal into a known stimulus and re-route it into the amplifier, to be amplified by the selected gain setting. The accuracy of the EMG was tested at all the gain settings on the module (500, 1000, 2000 and 5000). The gain setting of 5000 was used in this study for all NCV measurements. The step by step procedure, as detailed in the Biopac hardware guide (Appendix 4.7) was followed for calibrating the module at the required gain levels (Figure 4.11).

Figure 4.11: EMG module calibration output data obtained using CBLCAL (Left – before calibration; Right – after calibration at gains 5000, 2000, 1000 & 500 (left to right))



4.10.2.4 Calibration of the stimulator

The STM100C is a single-channel stimulator amplifier that is designed for use in stimulus response and testing and in biofeedback procedures. The device is factory calibrated and any user calibration is not advised by the manufacturer.

4.10.3 Investigating signal interference (addressed aim 3)

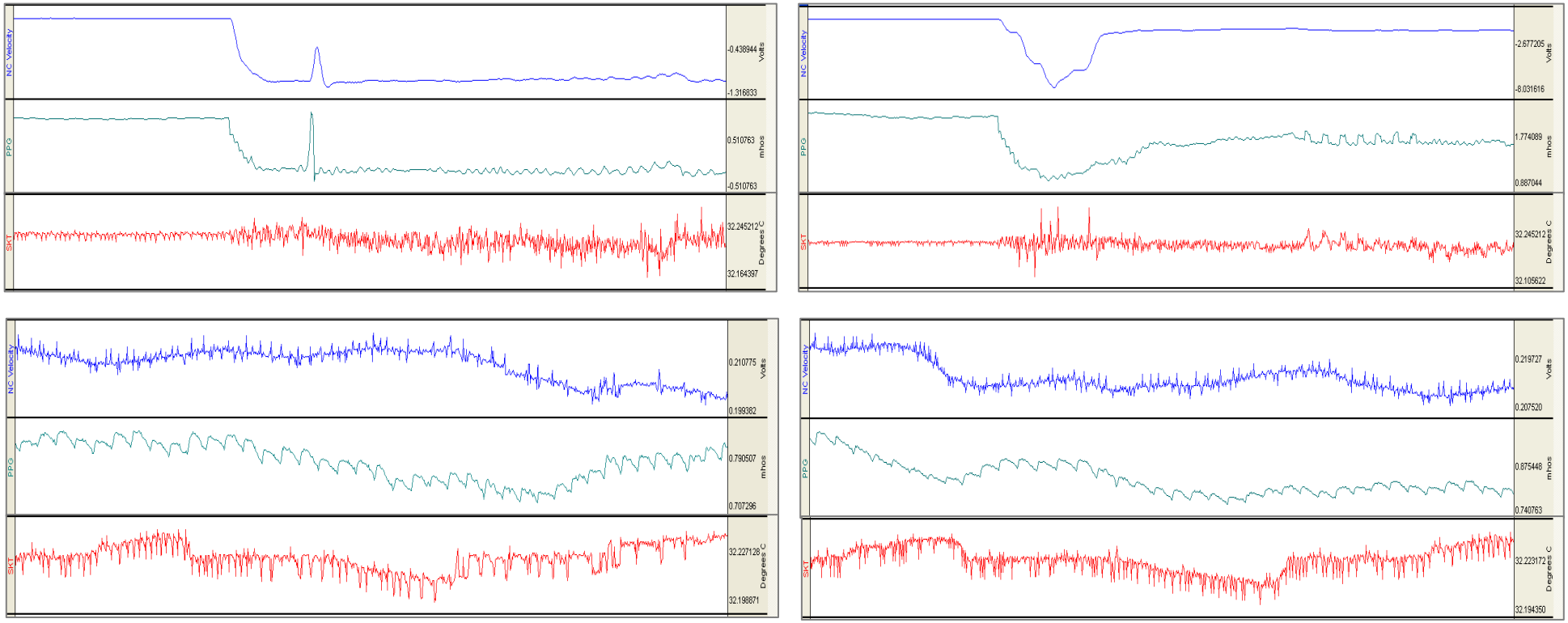
The administration of RF energy involves electric (E) and magnetic (M) field emission, which could potentially extend several meters beyond the perimeter of the device,[18,450-452] and could potentially affect the functioning of other electronic devices around it. Hence, establishing the safe working distance between the RF device and the data acquisition system and a safe working environment for the participants is imperative. Pilot experiments were conducted on one participant to explore the effect of both CAP and RES modes of CRMRF on the Biopac data streams while they were both functional. The study was approved by the Health and Human Sciences Ethics Committee with Delegated Authority (HHSECDA) of the University of Hertfordshire (Protocol number: HSK/PG/UH/00015) (Appendix 4.8). Similar work, extensively investigating the effect of PSWT fields on Biopac data streams has been previously undertaken within the same research group[192] and were

hence not duplicated in this project. Unlike in the previous PSWT study,[192] in this study the Biopac unit was not recording data while RF was being delivered. The measurements were obtained only before and after treatment. So, ensuring the purity of data streams by avoiding RF interference was not the primary concern. However, the safety of the measurement probes and avoidance of skin irritation at the site of probe attachment on the participant needed to be ensured in the presence of RF fields, by identifying the optimum distance between devices.

4.10.3.1 Effect of the distance between CRMRF device and Biopac unit

To determine the safe yet practicable positions of the treatment and measurement units in relation to each other the SKT, PPG and EMG electrodes were attached to the lower medial thigh of the participant and the Biopac was set to run at the default setting. Signals were recorded at three distances (2 m, 1.5 m & 1 m) between the two units, while both the CAP and RES modes of the CRMRF device were turned on. At 1 m, considerable noise was observed in the data stream when the CAP/RES modes were turned on. At 1.5 m, the noise in the signal was very minimal, whereas there was no noise when the devices operated from a distance of 2 m (Figure 4.12). However, 2 m distance between the devices was not deemed practicable for the experiment due to the cables being stretched. Therefore, a distance of over 1.5 m was chosen for this study.

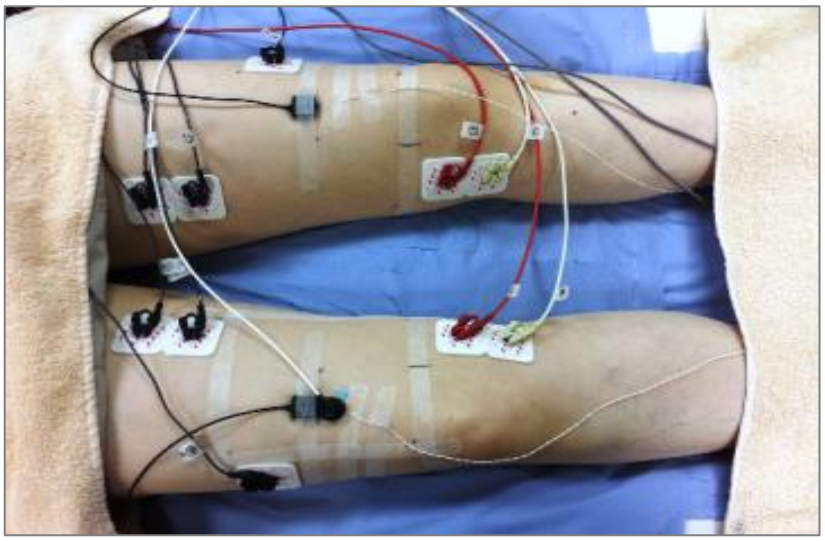
Figure 4.12: Effect of the distance from CRMRF device on the Biopac data streams. Top left – Units switched on when one metre apart. Top right – Units switched on and off when one metre apart. Bottom left – Units switched on when one and half metres apart. Bottom right – Units switched on when two metres apart.



4.10.4 Issues surrounding probe attachment and signal noise (addressed aims 4 & 5)

Before attaching the probes, the skin was prepared by cleaning the area with two types of wipes; firstly with 'Clinell© Universal Sanitising Wipes' and secondly with 'Clinell© Alcoholic 2% Chlorhexidine Wipes'. This process cleaned the skin off any dirt and greasy material thus enabling better conductivity. It was decided not to shave the hair off as it would cause considerable skin irritation. However, it was challenging to properly attach the probes on male participants who had hairy legs. Probes were positioned at the medial aspect of the lower one fourth of the right thigh (Figure 4.13).

Figure 4.13: Biopac probe attachments used in the study



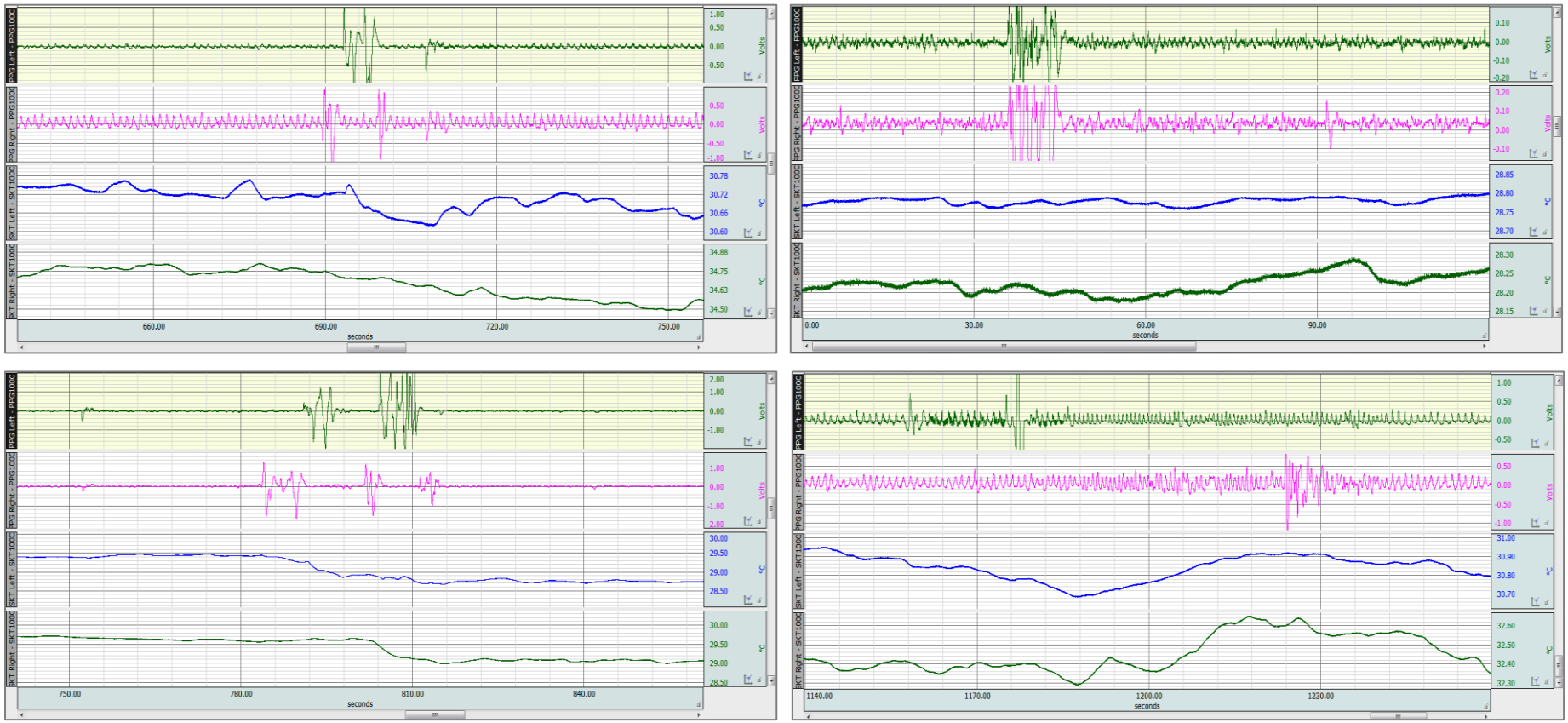
The SKT and PPG probes were attached without touching each other, to the middle of the upper half of the square that was boundary marked using Micropore© tape. The points of attachment were identified using a tape measure from the inner end of the square and were clearly marked using pen markers to ensure repeatability during re-attachment. The NCV electrodes were placed proximally and distally to the marked square region where the RF was delivered. With the average size of the square expected to be around 11 cm based on assumption, the inner distance between the NCV electrodes would be around 15 cm. Hence the distance from the middle of one set of twin electrodes (stimulating electrodes) to the other (recording electrodes) was 22 cm. It was decided based on this observation that 22 cm will be taken as the NCV measurement length for all participants for all sessions. After treatment with CRMRF it initially took three minutes for the process of clearing the skin and re-attaching the probes. With practice, the researcher could do this in two minutes. A two-minute delay was considered reasonable and was taken as standard across the study.

The SKT probes did not have any attachment leads on them. Hence, either an adhesive tape or a Velcro© strap needed to be used to attach them firmly to the skin. Given the probes were small; the much larger straps were not identified as appropriate. The probes changed position and orientation when attached using Velcro© straps, unless they were tied very tight to the skin. Making the attachment too tight would make the participant uncomfortable and affect the blood flow data. Micropore© tape measuring 13 mm in width was found to be the most suitable method for attaching the SKT probe, with zero movement of the probe in relation to the skin. On the contrary, the PPG probes were too big to be attached with the Micropore© tape. Moreover, the PPG data stream was noisy with no firm skin contact when attached with Micropore© tape. Securing the probe around the leg solely using a Velcro© strap resolved these issues. The NCV electrodes were self-adhesive and did not require additional securing once attached to the skin.

The potential effects of external sources of noise on the data stream were investigated using simulated conditions that were likely to occur during the experiment. They included movements (participant's body, probe or cable), pressure on the probes/electrode and cables touching each other. Electromagnetic interference from mobile phone or other smart devices was avoided by default, by turning all such devices off during the experiment. However, conditions like movement and cables crossing each other may be unavoidable during an experiment. Once the researcher could successfully identify and distinguish the noise from real physiological change, the data can be processed accurately.

To investigate the noise, the probes and electrodes were attached to a participant as it would be the case in the real experiment. The modules were set to run while the above mentioned potentially noise generating conditions were applied. The variations happening to the signal in response were observed (Figure 4.14). While all data streams were susceptible to noise, PPG produced the largest artefacts. In addition, even slight limb movements, including any muscle contractions significantly affected the PPG data stream by introducing large spikes of noise. Although these were easily distinguishable from real data and could be excluded during the analysis, the important point identified from the pilot was that the participant must be resting still, fully relaxed by trying to avoid any voluntary muscle contraction.

Figure 4.14: Sources of signal noise. Top left – Cable movement. Top right – Participant limb movement. Bottom left – Pressure on the probe. Bottom right – Cables crossing each other



4.10.5 Baselining of the data streams and electrode acclimatisation (addressed aims 6 & 10)

The stabilisation times for the different Biopac data streams (except NCV) were assessed by running a simple experiment. The device was setup to run in capture mode one hour before the start, which was taken as standard for all experimental sessions. The probes were attached to the skin of the participant and then the data capture was restarted. Prior to attachment the probes remained at room temperature. The data streams were observed to assess the time taken for them to stabilise (reach the baseline level). The PPG signal was quick to stabilise, within seconds. Although the manufacturers had claimed that the SKT probes were fast-response thermistors, it took approximately two minutes for them to stabilise and reach the participant's baseline SKT level. It was decided that this two-minute period should be accounted for when SKT is recorded in the main studies.

After testing, it was decided that the NCV electrodes need not be removed from the skin, if their connecting leads are detached. The participant reported skin irritation from under the electrodes while delivering RF treatment if the leads were left connected. However, once the leads were detached, the skin irritation disappeared. Hence, the NCV electrodes remained on the skin and did not need any acclimatisation time. The intensity of the STM stimulus applied was chosen at a level that did not cause any discomfort to the participant, but at the same time strong enough to elicit an adequate nerve response. There was no evidence from the pilot study of any difference in NCV between a weaker stimulus and a stronger stimulus.

4.10.6 Sampling rate for the Biopac system (addressed aim 7)

The sampling rate for the Biopac system was chosen to be 200 Hz although the system was capable of recording at significantly higher rates. Considerable work was carried out in the previous project by Al-Mandeel (2004)[192] comparing the sample rates 200 Hz and 500 Hz. Pilot experiments were carried out using PPG, the results of which showed no difference between the signals obtained using 200 Hz and 500 Hz.

4.10.7 Validation of temperature readings using different measurement techniques (addressed aim 8)

To establish the reliability and repeatability of the temperature measurements obtained in this study, a desktop experiment was conducted using two measurement devices and a temperature source (heated thermode from TSA II Neurosensory Analyser). The neurosensory analyser is a device used for quantitative sensory testing by inducing mechanical stimuli such as heat. The thermode can generate and sustain pre-set temperatures with good accuracy.

4.10.7.1 Methods

Using the TAS II thermode as a source of constant temperature (stable within 0.1 ^{o}C), a comparative study was conducted between the readings of Thermofocus hand-held IR thermometer and the Biopac SKT100C module and TSD202A thermistor transducer. The thermode was set at five different temperatures that were arbitrarily chosen – 26, 29, 32, 35 and 38 ^{o}C. It was anticipated that these temperatures would fairly reflect the range of SKTs that were likely to be obtained from the study.

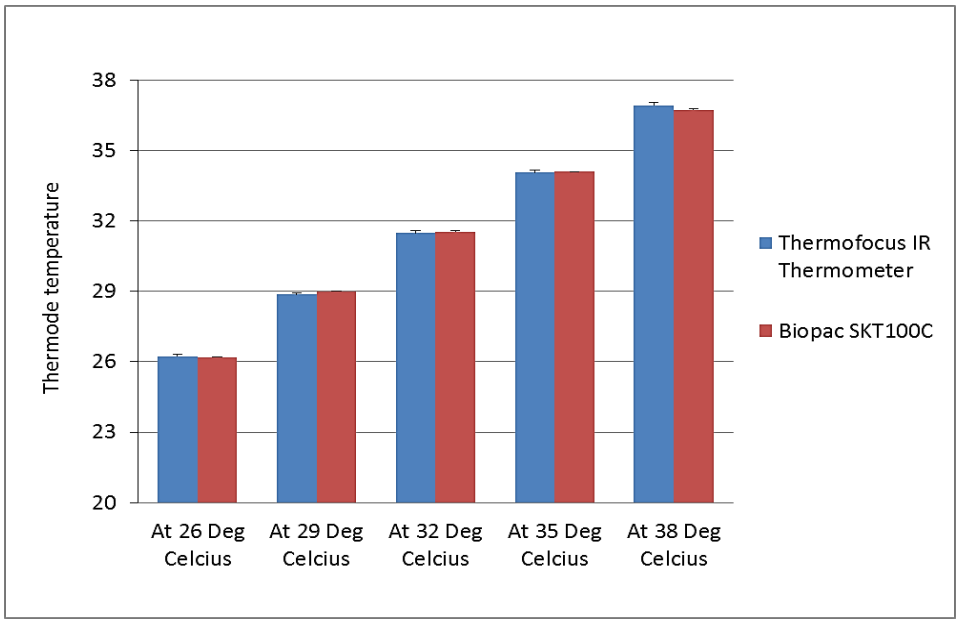
The Biopac thermistor was attached to the thermode surface using Micropore© tape after applying sufficient quantity of an inert conductive material (supplied by the TSA II manufacturer) around the probe. The inert material ensured that the surface area between the thermode and the probe was large enough to maintain good contact. Without this material, the point of contact is small, given that the probe is round and the thermode surface flat. The probe was attached towards the corner of the surface of the thermode so that there was adequate space left on the surface for measurement using the hand-held thermometer. The room temperature at the time of the experiment was 24 ^{o}C and the humidity 34%.

The experiment started at the lowest temperature level of 26 ^{o}C. The thermode temperature reached the set level within seconds, as displayed on the TAS II software. The Biopac was set to run continuously for 20 minutes at each temperature, but the Thermofocus was used once every two minutes for a total of 20 minutes, giving 10 readings at each temperature level. When analysing, the corresponding two-minute data points were retrieved from the Biopac data stream. A reliability analysis was then performed on the data using SPSS (Version 20, IBM SPSS Statistics) to obtain the Intraclass Correlation Coefficient (ICC) (3,1).[453]

4.10.7.2 Results and conclusion

The raw temperature data is shown in (Appendix 4.9). The mean (SD) temperature values obtained from the 10 readings in relation to the thermode are plotted in Figure 4.15. The projected reliability between the temperature readings (ICC (3,1)) was 0.989, with 95% CI (0.965, 0.995). The result indicated that there is perfect agreement between the measures,[454] meaning either of the two devices (Thermofocus or Biopac) could be reliably used for spot SKT measurement within the tested range. It appears from the results that at higher temperatures there was no agreement between the thermode temperature and the two thermometers. It is possible that the thermode temperature might not have reached the set levels due to a calibration issue with that device although the researcher was unable to confirm this.

Figure 4.15: The mean (SD) temperatures obtained from Biopac SKT100C and Thermofocus IR thermometer in relation to pre-set thermode temperatures



4.10.8 Electrode stability tests for NCV (addressed aim 9)

A simple desktop experiment was carried out to identify the best electrodes for use in the NCV measurement. The electrodes, when attached face-to-face and connected to the EMG module, a zero Volts reading should be obtained if both the module and electrodes are working properly. The EMG module had already been tested for accuracy (discussed earlier in the chapter). Some electrodes might have a permanent offset from zero depending on their quality and conductive property of the electrodes. For this study five commercially available medical recording electrodes were obtained through local purchase. The details of the brands are not being identified.

4.10.8.1 Methods

The Biopac unit with the EMG module were set up to run for one hour prior to this study, as standard. Two electrodes each were taken from every brand. Each pair was stuck face-to-face ensuring correct approximation of the gel and metallic conductors. The data acquisition was paused momentarily. The two EMG leads were then connected to either side of the electrodes. The acquisition was then re-started to observe the following.

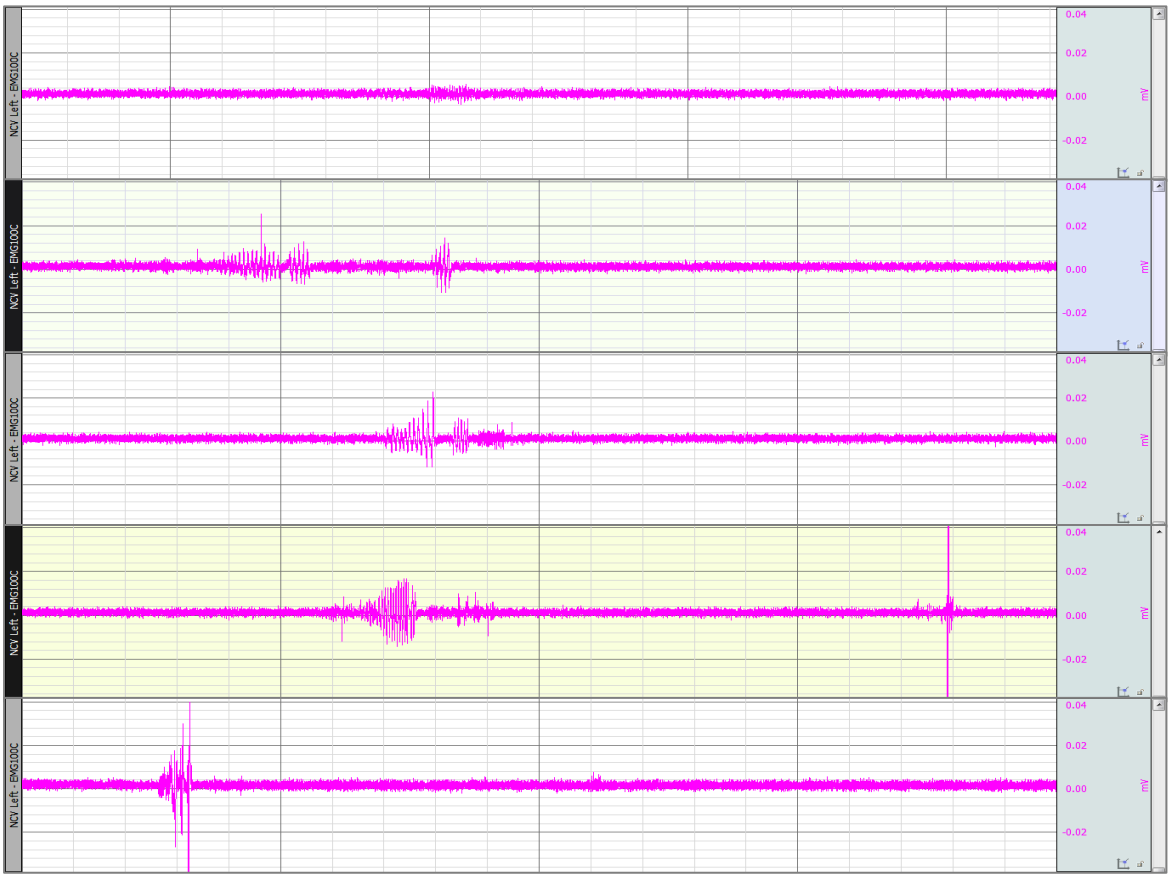
1) Time taken for stabilisation of the data stream.
2) Time taken for zeroing of the data stream.
3) The signal response to direct pressure applied on the electrodes.
4) The signal response while the cables were moved.
5) Noise during the CAP and RES modes of CRMRF.

To assess the above, a total of 45 minutes' worth data was recorded from each electrode pair exposing them through the above conditions in order. The room temperature at the time of the experiment was 24 ^{o}C and the humidity was 34%.

4.10.8.2 Results and conclusion

The individual response to each pair of electrodes is not being reported here. No statistical analysis of any parameters was performed. The quality of the data streams was assessed by visual examination. Figure 4.16 shows a comparison between the tested electrodes. After assessing all five brands of electrodes, it was concluded that 3M™ Red Dot™ was the most stable and least noisy electrode brand. 3M™ Red Dot™ was hence used for NCV measurement in all studies.

Figure 4.16: ECG electrode brands compared based on response to external noise. 3M™ Red Dot™ is given at the top.



4.10.9 Intra-rater reliability of ultrasound measurements (addressed aim 11)

Ultrasound imaging is a specific skill that requires considerable training and practice. The researcher received essential training from a subject expert in musculoskeletal ultrasonography (Mr John Leddy) and received further help and guidance from colleagues at the University of Hertfordshire who were qualified in ultrasonography. Several hours of self-practice was also undertaken to gain sufficient confidence in the imaging technique.

Subsequently, the test retest reliability of the researcher for both the Doppler and Elastography measurements was investigated.

4.10.9.1 Methods

The reliability study was conducted in the same research lab prior to the commencement of the main laboratory study (Chapter 6). The same Ultrasound scanner and probe that was used in the main lab study were used. Similar scanning procedure that would be employed in the main physiological study was employed.

Twelve asymptomatic adult volunteers from among the members of the University of Hertfordshire took part in the study. Each participant attended the physiotherapy research laboratory once, in a session that lasted about one hour. An informed consent was signed prior to the study (Appendix 4.10). Anthropometric data was collected prior to the assessment using the body composition monitor described earlier in this chapter. The study was approved by the Health and Human Sciences Ethics Committee with Delegated Authority (HHSECDA) of the University of Hertfordshire (Protocol number: cHSK/PG/UH/00143) (Appendix 4.11).

4.10.9.2 Procedure

On the day of the study the participants were asked to attend the sessions by avoiding food, beverages and strenuous exercises within one hour before the start. This was to ensure that their physiological condition remained stable during the sessions.[80,455,456] The participants positioned themselves in supine fully supported with pillows on the couch, as would be the case in the main study. Medial aspect of the lower one fourth of the right thigh was marked with tape in a square shape. Twenty-minute acclimatisation time was allowed in the lying position prior to the start, during which the participants rested.

For each participant, two measurements were performed with an interval of 30 minutes in between. This interval was chosen based on the approximate anticipated interval between the pre-and post ultrasound measurements in the main study. Blood flow was identified by manoeuvring the ultrasound probe over the lower anteromedial aspect of the quadriceps femoris muscle. Once the most prominent pulsatile (arterial) flow was identified, skin markings were used to establish the accuracy of probe placement and ensure repeatability. For Sonoelastography measurements, a fixed position was adopted for all participants with minimal probe manoeuvring. The probe was placed parallel to the longitudinal axis of thigh, perpendicular to the skin in the middle lower part of the marked area. Minimal probe pressure and liberal amount of conductive gel were used to avoid any undue compression of the tissues. For all participants, the machine settings remained the same for both pre-treatment and post treatment measurements. Recordings were performed in the following order.

1st Colour Doppler for velocity of flow

2nd Power Doppler for volume and intensity of flow

3rd Elastography for the compliance of tissues

Up to five seconds of data clips were recorded with colour Doppler, power Doppler and Sonoelastography during each of the two measurements.

4.10.9.3 Statistical analysis

The ultrasound image data was processed to numerical data by using MATLAB analysis as described earlier. The agreement between the two sets of numerical data was tested by performing a reliability analysis using SPSS (Version 20, IBM SPSS Statistics) to obtain the Intraclass Correlation Coefficient (ICC) (3,1).[453]

4.10.9.4 Results and conclusion

The full data set obtained from the 12 participants is given in Appendix 4.12. The ICC values are given in Table 4.1. The results indicate substantial to perfect levels of agreement between the two measured scores,[454] and hence intrarater reliability has been established.

Table 4.1: Level of agreement between the two sets of deep blood flow measurements

Parameter	ICC value for single measures	Confidence interval		*p* value
		Lower	Upper	
Blood flow velocity	0.611	0.087	0.870	0.013
Blood flow volume	0.987	0.955	0.996	< 0.001
Blood flow intensity	0.818	0.483	0.944	< 0.001
Hardness volume	0.985	0.950	0.996	< 0.001
Hardness intensity	0.974	0.913	0.993	< 0.001
Intermediate volume	0.957	0.858	0.987	< 0.001
Intermediate intensity	0.960	0.866	0.988	< 0.001
Softmess volume	0.998	0.993	0.999	< 0.001
Softness intensity	0.996	0.987	0.999	< 0.001

4.11 Conclusions

This chapter addressed the measurement principles, methodological aspects and key issues relating to the laboratory-based investigation of the physiological effects of CRMRF therapy. The pilot experiments helped to identify the appropriate methods and confirmed the robustness of the involved techniques. The next two chapters will describe the two studies undertaken on asymptomatic participants to investigate the physiological effects of CRMRF therapy.

5 Chapter 5 – Basic considerations on CRMRF therapy: Skin thermal onset, thermal decay and thermal retention responses to the CAP and RES modes – a randomised crossover study

5.1 Introduction

The key to gauging the optimum therapeutic efficacy of a thermal modality such as CRMRF is to have a clear understanding of its levels of thermal activity in tissues. For RF-based EPAs it is important to understand their thermal profile in tissues, since induced hyperthermia is believed to be their main tissue response. The CRMRF has two modes of applications: CAP and RES, both of which are proposed to have dissimilar methods of action, and hence dissimilar thermal profiles. In clinical practice, the CAP and RES modes are used in combination to induce tissue hyperthermia, but without an up-to-date understanding of the optimum therapeutic design to enable an evidence-based treatment delivery. Clinicians often employ their own preferred methods of treatment based on experience or 'best guess' or on anecdotal evidence provided by the device manufacturers. In this study, the thermal responses to either modes of CRMRF therapy were investigated in a controlled laboratory-based experiment to enable a better understanding of their thermal effects.

5.2 Physiological effects of heat

The main physiological effect of CRMRF is believed to be tissue hyperthermia. It is hence important to briefly discuss the physiological benefits of the application of heat treatment from a physiotherapy perspective. There is a rich amount of literature on the physiological effects of heat on living tissues. Heat can affect the superficial and deep tissues, both at cellular and at systemic levels. Most cellular activity can be accelerated and/or increased by a modest rise in temperature (mild hyperthermia), and the local blood flow in the tissues can be enhanced by heat-induced vasodilatation.[254,341,457,458] Depending on the level of temperature rise heat can also change the properties of connective tissues. It can increase the extensibility of tendon and ligaments, and to some extent reduce the tone and spasm of muscles.[195,254,341,457,459,460]

Heat therapy is often used in clinical practice as a mode of relieving pain and inflammation and thereby enhancing tissue healing.[8,18,457] Changes arising in tissues from an increase in the blood flow, oxygen uptake and chemical reaction rates are believed to be the physiological mechanisms underpinning the effects of heat on pain and tissue repair.[8,461] An increase in tissue temperature by about 1 ^{o}C will help to therapeutically relieve mild

inflammation whereas an increase of 2–3 ^{o}C will lead to a reduction in pain and muscle spasm. A higher increase in the range of 3–4 ^{o}C can alter tissue extensibility.[457,462] A temperature rise to this extent can only be termed ‘mild hyperthermia’, which is notably different to tissue hyperthermia induced by techniques such as RF ablation/coagulation used in the treatment of pain[463-465] or in the treatment of cancer.[466-468]

5.3 Key aims

The main aims of this study were:

1) To identify the point of onset of heating, the point of optimum heating, and the point of onset of heat discomfort with the application of either mode of CRMRF therapy.
2) To record the baseline skin temperature, to record the immediate post treatment skin temperature and to periodically record the subsequent post treatment decline in skin temperature (thermal decay process) at the treated area.

These aims would enable the researcher to identify and establish the 'thermal banding' of the energy delivered by CRMRF therapy, the time taken to attain each of those three time points and the corresponding ‘CRMRF power dose’. It was anticipated that such information would enable a comparison between the effects of CAP and RES mode effects and ultimately provide a better understanding about the differences between a low dose (minimally thermal dose) application and a high dose (moderately thermal dose) application of CRMRF energy.

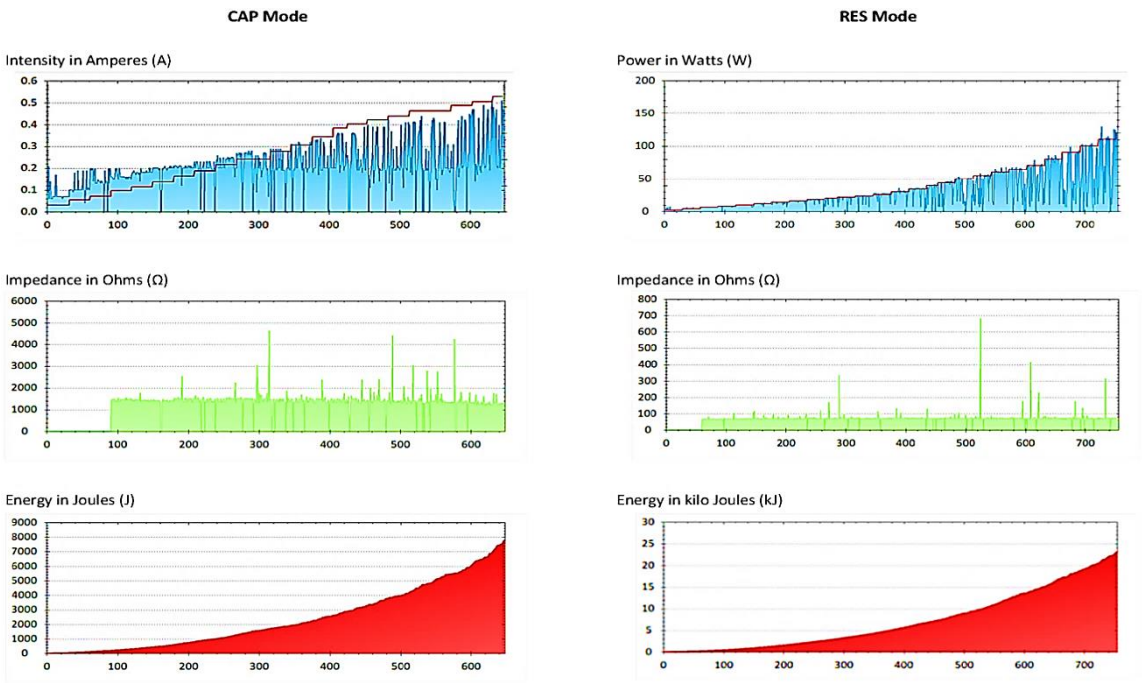
5.4 Materials and methods

5.4.1 Apparatus

5.4.1.1 CRMRF treatment device

The CRMRF treatment was administered with an ‘Indiba Activ 902’ device (Indiba S. A., Barcelona, Spain), which has been described in chapter 4. The machine displays the RF intensity and the energy output while the treatment is being delivered, which is also mapped by computer-based monitoring software (Figure 5.1).

Figure 5.1: Sample CRMRF machine output data (exported using the monitoring software)



5.4.1.2 Skin temperature measurement

A hand-held contactless infra-red (IR) skin surface thermometer (Thermofocus 01500A3) was used for skin surface temperature measurement (chapter 4). Although the main segment of the lab study (chapter 6) used the Biopac system for SKT measurement, it was unavailable for the current experiment. The Biopac kit was being upgraded and the new SKT modules and thermistors were being awaited. Besides, since concomitant SBF measurement (using Biopac PPG) was not present in this study, real-time SKT measurement was deemed not necessary. Numerous studies have suggested that hand-held thermometers (contact or contactless) are a valid, reliable and convenient method of recording the skin temperature.[347-352] It has been suggested that the IR thermometer has an equal or greater level of responsiveness and reliability when compared to traditional thermistors.[350,352] Studies have also used these devices on different segments of the body such as hand,[348,351] knee,[347] ankle[349,352] and multiple sites.[350]

5.4.1.3 Other devices

An infra-red tympanic thermometer (Braun ThermoScan IRT 4520) was used for core temperature measurement. Anthropometric measures were taken using a body composition monitor (Omron BF508). An electronic metronome (Seiko) and a computer-based timer were used to aid the experimental procedure. The room temperature and humidity were monitored using an electronic thermohygrometer (RS 212-124).

5.4.2 Sample and groups

A cohort of 15 asymptomatic (self-reported) adults were randomly selected from among the staff and students (around 27,000) of the University of Hertfordshire. Recruitment emails were sent out university-wide along with the participant information sheet (Appendix 5.1). Screening for inclusion was performed consecutively, with the first 15 eligible volunteers being recruited (eligibility criteria explained below). An informed consent (Appendix 5.2) was signed by all participants prior to the study. The study was approved by the Health and Human Sciences Ethics Committee with Delegated Authority (HHSECDA) of the University of Hertfordshire (Protocol number: HSK/PG/UH/00015) (Appendix 5.3).

There were two experimental groups: CAP and RES. All participants attended two study sessions each, one session representing each group in a random order. Thus all 15 participants represented both study groups (crossover design). The order of attendance to the sessions was randomised by concealment and blinded from the participant. A computer-generated randomisation chart (IBM SPSS Statistics, Version 20) was used for this purpose (Appendix 5.4).

5.4.3 Pretesting and pilot work

Extensive pilot work in the form of pretesting was carried out prior to the commencement of the study to establish the following. Potential confounding factors, measurement issues and apparatus testing have already been explained in the previous chapter.

1) To ascertain the time taken to stabilise the baseline SKT.

2) To design and test an appropriate workable experimental protocol specific to the study.

It was established in pretesting that a minimum of 48 hours is needed between the sessions to ensure that no residual effects from the first session were present at the time of the second. This is also evidenced in the literature with other RF research.[80,458] It was also identified that similar times (± one hour) of the day has to be chosen for either session for each participant in order to minimise core temperature variations as also suggested in the literature.[80,341] It required a minimum of 20 minutes for the baseline SKT in the measurement area to stabilise. A minimum of 90 minutes was required to complete one session of the experiment. It was clear from the pilot experiments that after RF application was stopped once the participant reported the onset of heat discomfort, the skin temperature may not return to baseline levels within 45 minutes in all participants. However, it was not practically feasible to continue the experiment beyond the 90-minute mark to continue the monitoring of temperature decay owing to time constraints on the part of the participants. Anterior aspect of the lower end of thigh just above the patella was identified as the appropriate site for treatment delivery and the measurement of skin temperature.

5.4.4 Experimental procedure

Participants were asked to attend the sessions by avoiding food, beverages and strenuous exercises within one hour before the start. This was to ensure that their physiological condition remained stable during the sessions.[80,455,456] An eligibility questionnaire was used to screen the participants (Appendix 5.5). This questionnaire included questions relating to any recent injury or illness and accepted contraindications to RF therapy (pregnancy, malignancy, metal or electronic implants in the body).

Subsequently, using test tubes filled with water at approximately three different temperatures (±0.5 ^{o}C): 45 ^{o}C (warm), 35 ^{o}C (neutral) and 25 ^{o}C (cold), the participants' 'skin thermal sensitivity' was tested. It was important to ensure that all participants had the full ability to distinguish between hot and cold to remain safe by avoiding excessive heating and potential burn injuries during the treatment. It was decided that any potential participant who failed to make this distinction will be excluded from the study. Once this screening was completed, demographic and anthropometric data were collected.

The participants positioned themselves in supine on a treatment plinth and were fully supported with pillows. The length of thigh was measured from the anterior superior iliac spine (ASIS) to the base of the patella. The leg was measured from the head of fibula to the lateral malleolus. The area covering the lower one-fourth of the anterior aspect of right thigh was marked with tapes as a square (established in the pilot). Skin temperature was recorded from the middle of the square area on the treated leg as well as the corresponding area of the untreated leg. This was repeated every two minutes until stabilised. The stabilised temperature was considered the baseline temperature. The untreated left leg was considered as a control. The core (tympanic) temperature was also monitored at the same time.

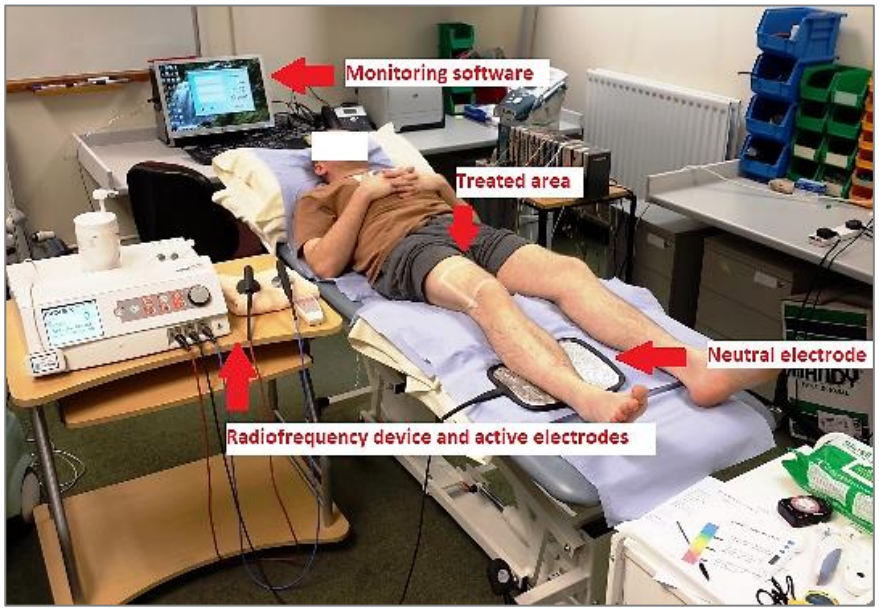
The return electrode was positioned one-fourth way down the length of the leg under the calf muscle belly. The CRMRF treatment was applied within the marked square area using the active electrode and 20 ml of conductive cream. The return plate also had 20 ml of cream smeared over it. For either mode of treatment, the intensity of delivery started at the minimum permitted level on the device and was raised by one level every 30 seconds (30 s timer was set running on the computer). Treatment was given in circular movements, one per second. This process was guided by the electronic metronome.

During treatment, the participants reported clearly and promptly at three time points: Firstly, at the onset of heating of the skin (thermal onset), secondly, when the heat builds up to a moderate (yet comfortable) level (definite thermal sensation), and thirdly, at the point when the heat starts to cause discomfort (onset of thermal discomfort). The three time points and the corresponding CRMRF intensity were noted. The treatment was promptly stopped once

the ‘onset of thermal discomfort’ was reached. At the beginning of the treatment session, these time points were explained to the participants showing a picture of an imaginary heat map (Appendix 5.6).

Once the treatment stopped, the skin was wiped clean of all remaining cream. After clearing the skin, the temperature measurement was repeated from both sides (post treatment (peak) temperature) from the same spot used for the baseline measurement. The core temperature was also recorded now. Repeated measurements of the skin temperature were done every 30 seconds from the treated leg and every five minutes from the control leg. This was continued for 45 minutes or till the skin temperature on the treated leg returned to baseline. Core temperature, room temperature and humidity measurements were only repeated at the end of the experiment. All data were entered a participant data collection form (Appendix 5.7). The lab experimental setup is shown in Figure 5.2.

Figure 5.2: Laboratory setup used for the experiment



5.5 Electrode temperature testing

After the main study, a second brief desktop experiment was conducted to map the temperature of the treatment electrodes at various stages in response to set treatment intensities of the CRMRF energy. For this experiment three incremental intensity levels (arbitrary) along with a fourth intensity level (mean peak power reached during each mode of the main experiment) were chosen (Table 5.3 (given in the results section)). This experiment was conducted on one of the participants from the main study. This participant had received a peak power dose (the dose at the point of thermal discomfort) higher than the group mean dose that was used in this desktop experiment, during both CAP and RES sessions, hence there was no risk of an excessive level of CRMRF being delivered. The treatment procedure

was similar to the main experiment except that the participant did not have to report the three time points. Instead, when the required pre-set intensity levels were reached the treatment delivery was paused to measure the electrode temperature.

5.6 Data analysis

Data processing was done using Microsoft Office Excel (Version 2010, Microsoft Corporation). The statistical analysis of the processed data was performed with IBM SPSS Statistics (Version 20) for Windows. The group data were compared using either a two-way (intervention and time) repeated measures analysis of variance (ANOVA) model at three time points (baseline, post treatment and 45-minute follow-up) or using Friedman's two-way ANOVA by ranks, depending on the distribution of data (Shapiro-Wilk). The statistical significance was set at $p \leq 0.05$ (0.8P, 95%CI).

5.7 Results

Both modes of the CRMRF treatment were well tolerated, with no accounts of any undesirable incidents that might have resulted directly or indirectly from the treatment, including potential concerns due to overheating or any other delayed tissue reactions. All 15 participants completed both their treatment sessions and assessments as anticipated. The participants' demographic and the mean (SD) anthropometric data are reported in Table 5.1.

Table 5.1: Demographic and the mean (SD) anthropometric data from 15 participants

Number	Demographic data			Mean (±SD) anthropometric data				
	Mean (±SD) age (years)	Gender: Males	Gender: Females	Height (m)	Weight (kg)	Body fat (%)	Visceral fat	BMI
15	45.1 (11.6)	6	9	1.7 -0.1	73.1 (13.1)	32.3 -8.3	7.6 -3.4	25.6 -3.8

SD – standard deviation; kg – kilogram; m – metre; BMI – body mass index

The mean (SD) as well as individual skin thermal responses obtained from all 15 participants in both CAP and RES modes of CRMRF therapy are shown in Figures 5.3 (a–b), 5.4 (a–b) and 5.5 (a–b). The baseline, post treatment and 45-minute follow-up mean (SD) skin temperatures obtained for the CAP mode were 30.9 (±1.1) ^{o}C, 34.3 (±1.6) ^{o}C and 31.5 (±1.4) ^{o}C respectively, and for the RES mode were 31.1 (±1.0) ^{o}C, 35.0 (±1.2) ^{o}C and 33.2 (±1.4) ^{o}C respectively.

The mean (SD) time needed, energy delivered, and the peak power reached to attain each thermal stage are shown in Table 5.2. The individual data for the mean (SD) values reported in Table 5.2 are shown in Figures 5.6 (a–c).

The baseline skin temperatures of both groups were identical, with no significant differences between the two. Overall, the thermal response patterns produced by the CAP and RES modes differed significantly ($F(1, 14) = 16.639$, $p = 0.001$). However, the peak skin temperatures obtained from both modes were not significantly different. The (group) mean increase in temperature (ΔT) from baseline to peak was 11.1% in CAP mode, and 12.7% in RES mode.

Table 5.2: The mean (SD) time, energy and peak power reached at each of the three thermal stages for the 15 participants

Stage	CAP Mode			RES Mode		
	Mean (±SD) time (s)	Mean (±SD) energy (J)	Mean (±SD) peak power (W)	Mean (±SD) time (s)	Mean (±SD) energy (J)	Mean (±SD) peak power (W)
Thermal onset	159.1 (55.2)	664.7 (405.2)	6.1 (2.3)	285.5 (109.9)	3417.3 (2299.9)	21.3 (9.6)
Definite thermal	261.5 (56.9)	1635.1 (635.3)	13.2 (3.5)	463.9 (116.2)	8867.6 (4531.4)	42.5 (16.9)
Thermal discomfort	399.7 (70.2)	4764.0 (1467.6)	32.4 (11.8)	656.0 (64.4)	19137.5 (5087)	81.5 (20.1)

SD – standard deviation; J – joules; W – watts; s – seconds

A significant retention of the gained temperature (at the 45-minute follow-up), when compared to their respective baseline, was noted in both CAP and RES modes (CAP: $F(1, 14) = 8.690$, $p = 0.011$; RES: $F(1, 14) = 70.321$, $p < 0.001$). Nonetheless, the rate of this temperature retention was significantly higher for the RES mode compared to the CAP mode (53.6% and 17.5% respectively) ($F(1, 14) = 36.173$, $p < 0.001$).

The actual power of the obtained ANOVA results reported above was confirmed to be 1.0 in a post-hoc power analysis using G*Power (Version 3.1). The results of the second desktop experiment that mapped the temperature changes in the two CAP and RES electrodes used for the main study in response to varying treatment doses are reported in Table 5.3.

The untreated control side temperature and the core (tympanic) temperature did not show any meaningful variation at any time point in either group. The mean (SD) room temperature was 24.0 (±0.8) ^{o}C for the CAP mode and 23.9 (±1.2) ^{o}C for the RES mode. Both these values were within the thermoneutral zone of humans.

Table 5.3: The active electrode temperature at various times and intensity of application during localised CRMRF treatment

CAP Mode Temperature (°C)				RES Mode Temperature (°C)			
Intensity in percentage (device PP is 450 VA)	At three minutes	At six minutes	At nine minutes	Intensity in percentage (device PP is 200 W)	At three minutes	At six minutes	At nine minutes
19	30.2	31.4	31.7	11	27.9	28.1	28.6
31	31	32.5	33.2	22	29.4	30.3	30.7
40	33.4	34.3*	36.2*	32	30.9	30.9*	32.8*
67#	35.7**	XX	XX	40#	32.8**	XX	XX

PP – peak power; VA – volt-ampere; W – watts; °C – degree Celsius; XX – not measured due to thermal discomfort to the participant.

# denotes the mean peak power obtained from 15 participants during the CAP and RES modes of the main experiment.

* Moderate heating reported by the participant.

** High heating reported by the participant.

Figure 5.3a: CAP and RES mode mean skin thermal responses to localised CRMRF treatment. The data shown (baseline, post treatment and 45-minute follow-up) are from 15 participants.

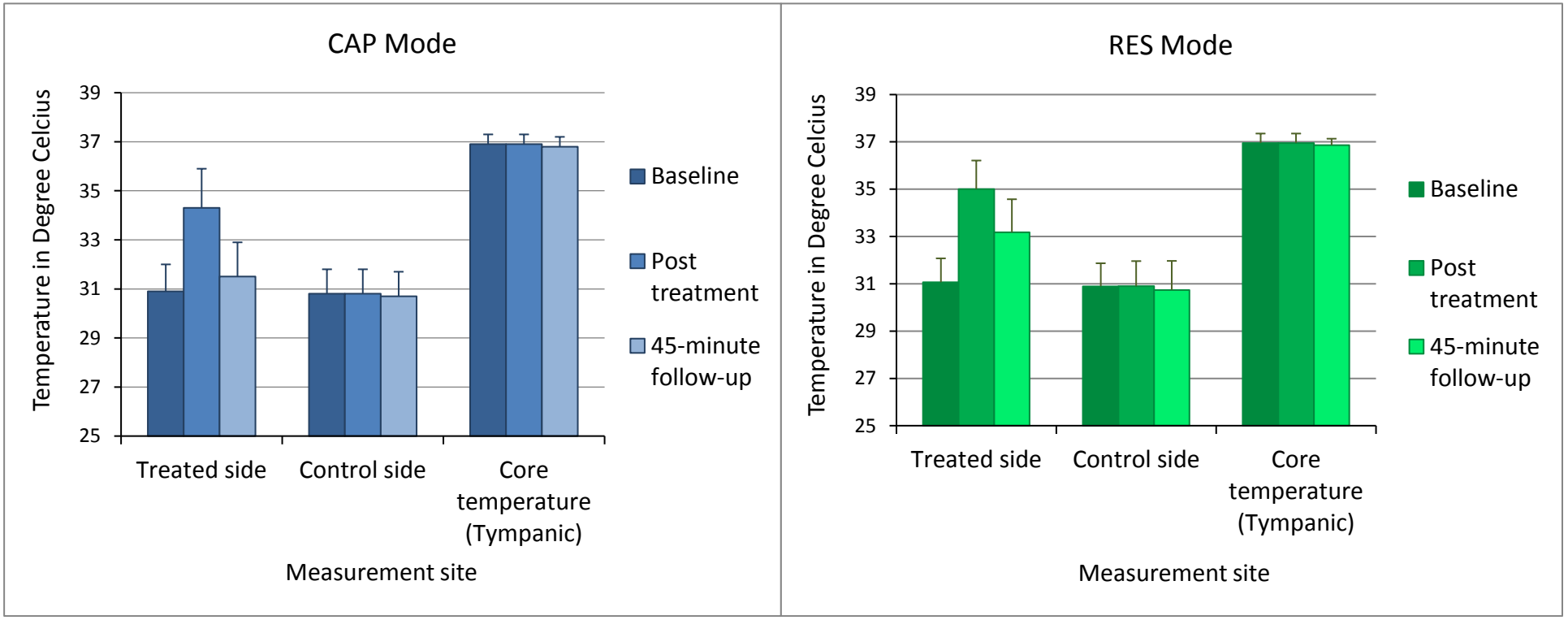


Figure 5.3b: CAP and RES mode individual skin thermal responses to localised CRMRF treatment (treated side). The data shown (baseline, post treatment and 45-minute follow-up) are from 15 participants.

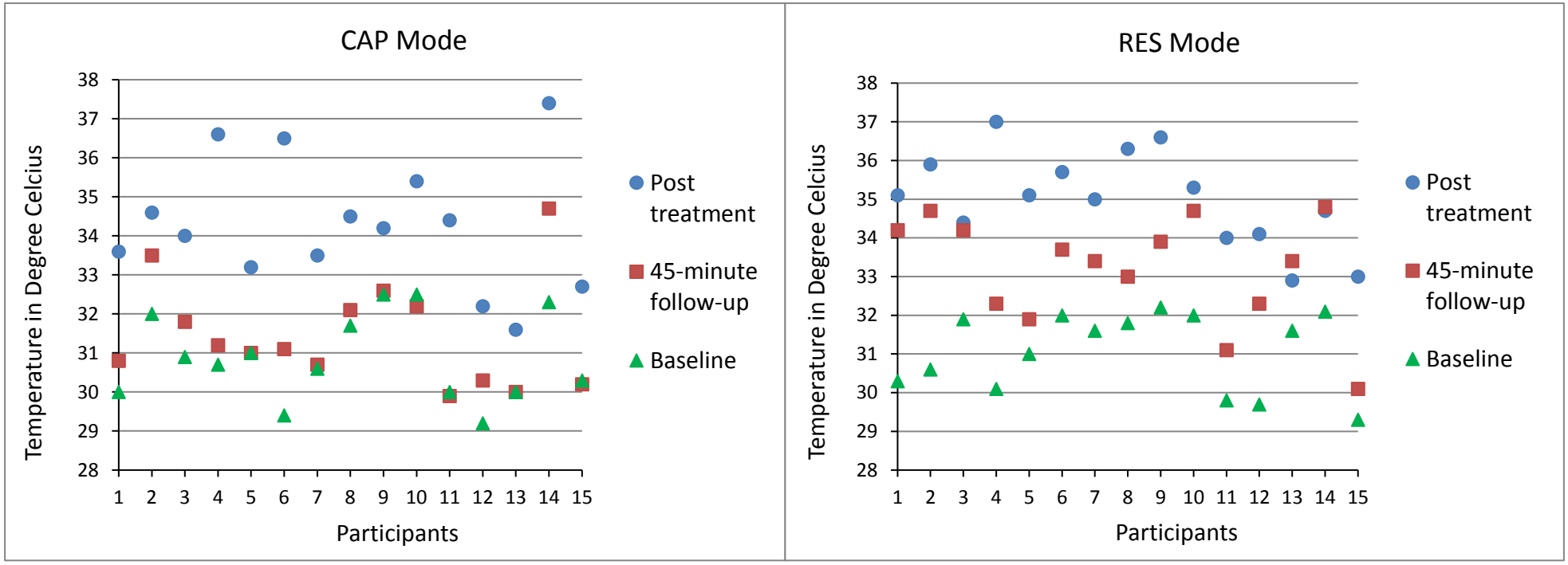


Figure 5.4a: CAP and RES mode mean skin thermal changes after localised CRMRF treatment (treated side). The data shown (thermal build-up, thermal decay and thermal retention) are the changes in relation to the baseline from 15 participants.

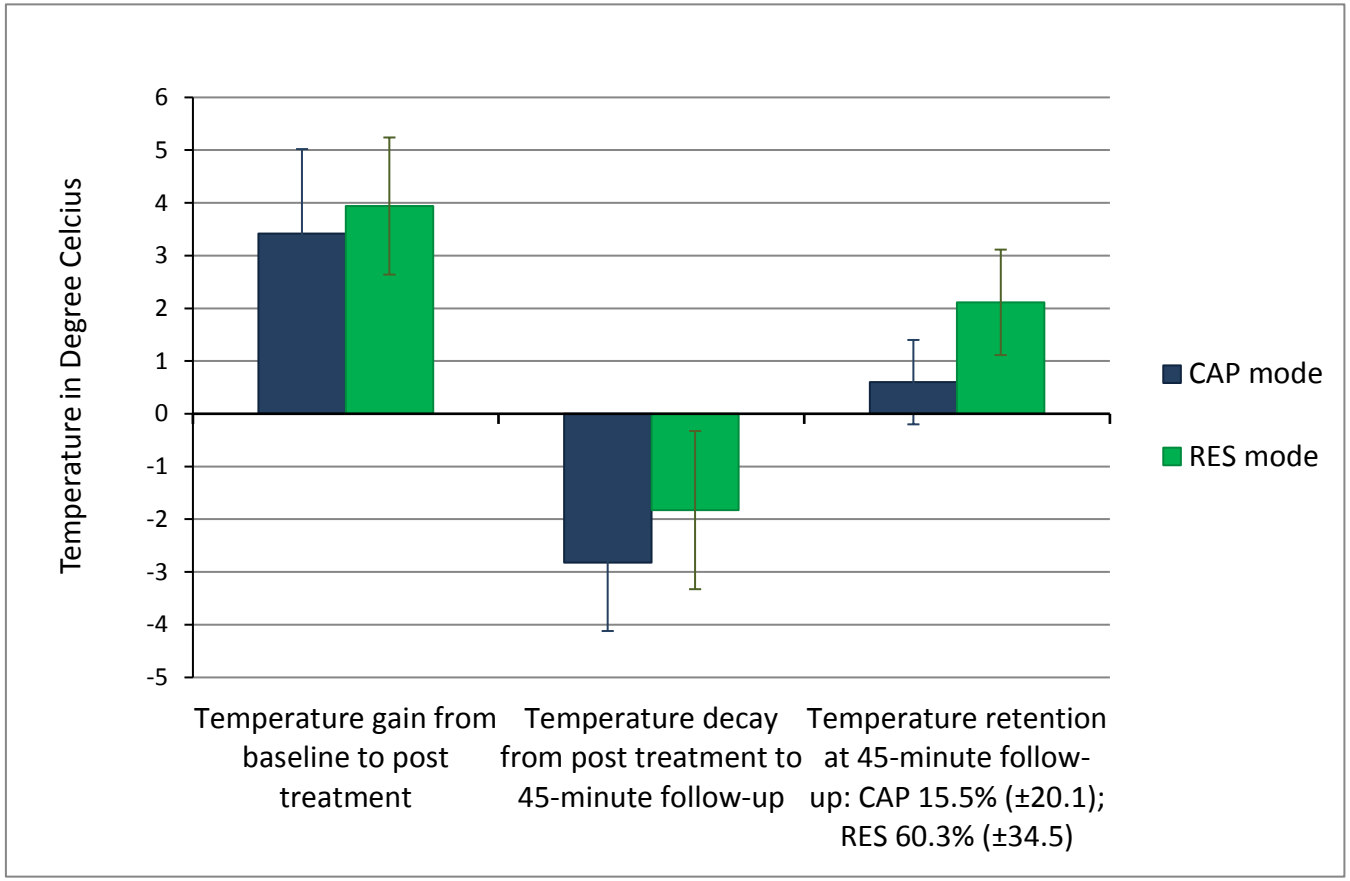


Figure 5.4b: CAP and RES mode individual skin thermal changes after localised CRMRF treatment (treated side). The data shown (thermal build-up, thermal decay and thermal retention) are the changes in relation to the baseline from 15 participants.

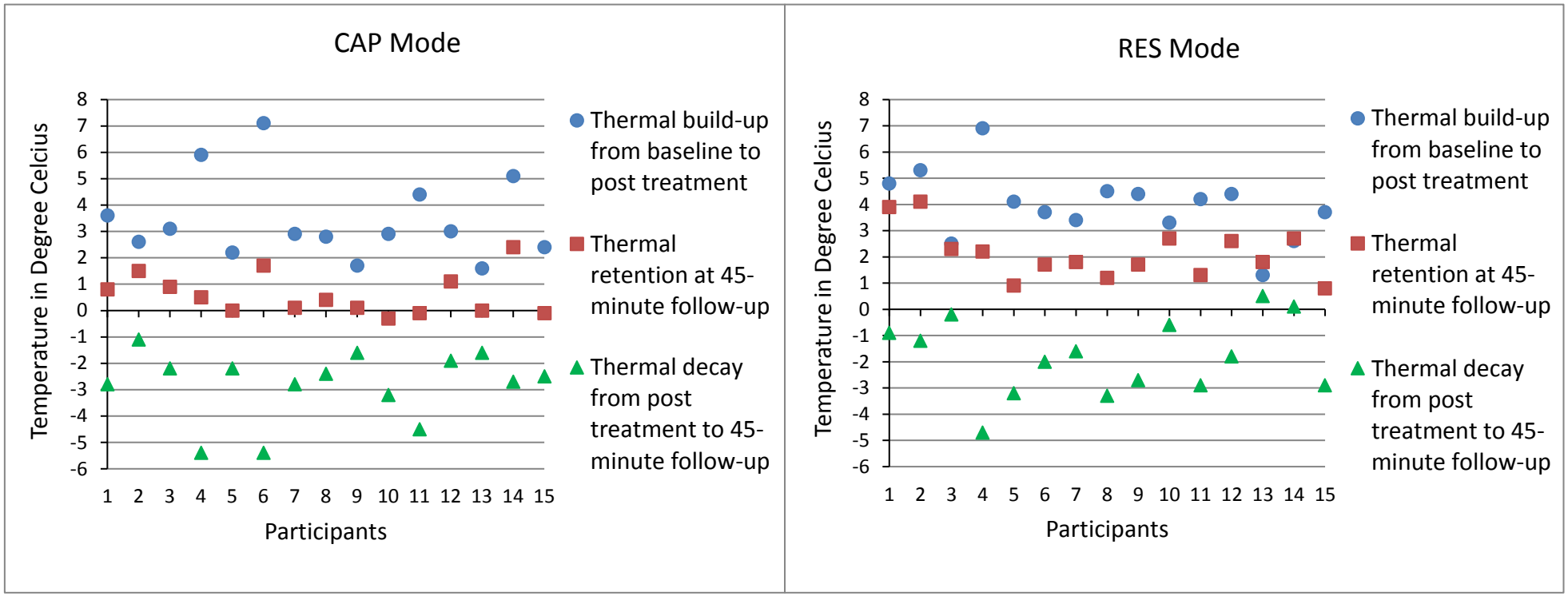


Figure 5.5a: CAP and RES mode mean skin thermal decay after localised CRMRF treatment (treated side). The data are from 15 participants, showing the decay process from post treatment to 45-minute follow-up.

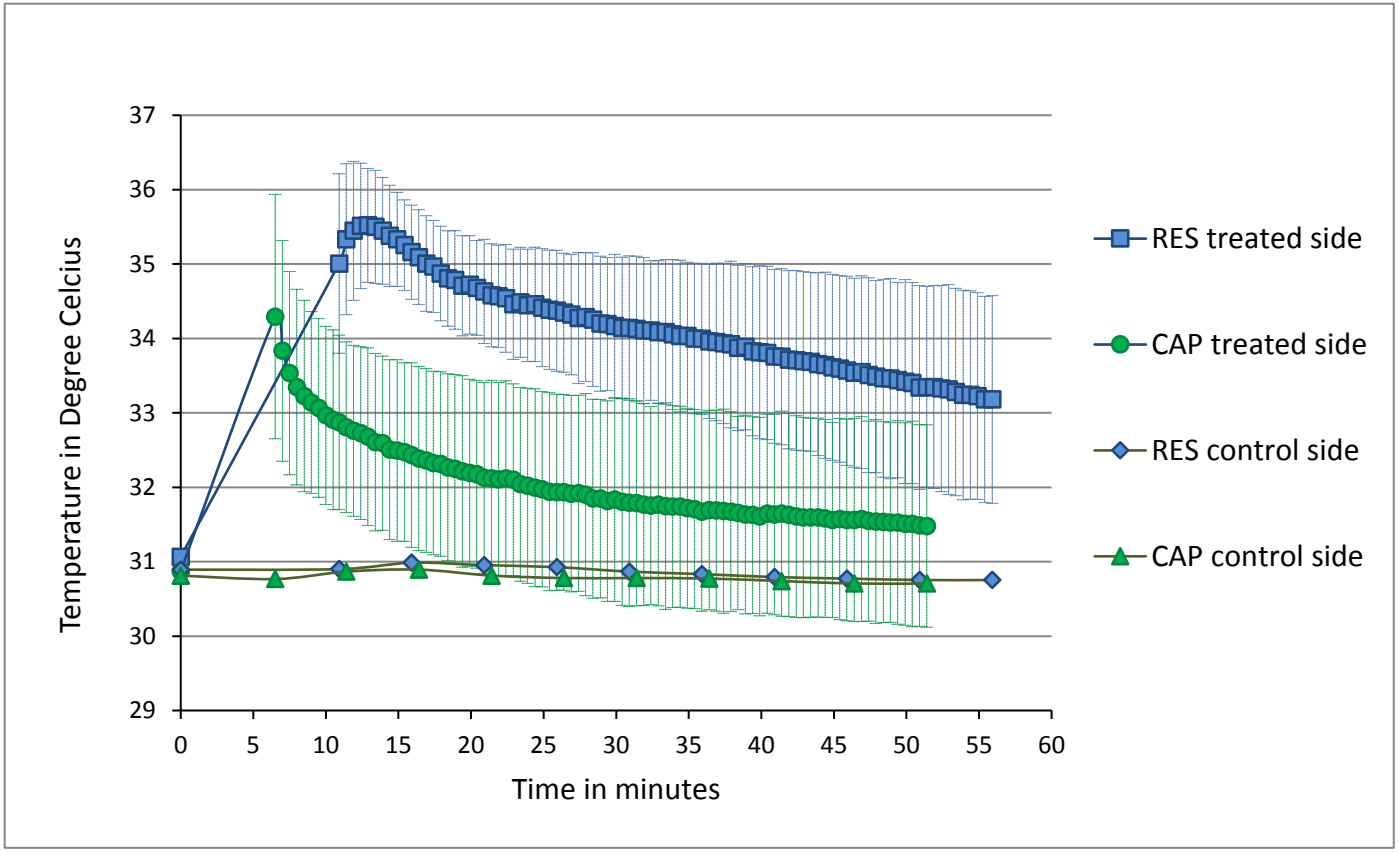


Figure 5.5b: CAP and RES mode individual skin thermal decay after localised CRMRF treatment (treated side). The data are from 15 participants, showing the decay process from post treatment to 45-minute follow-up.

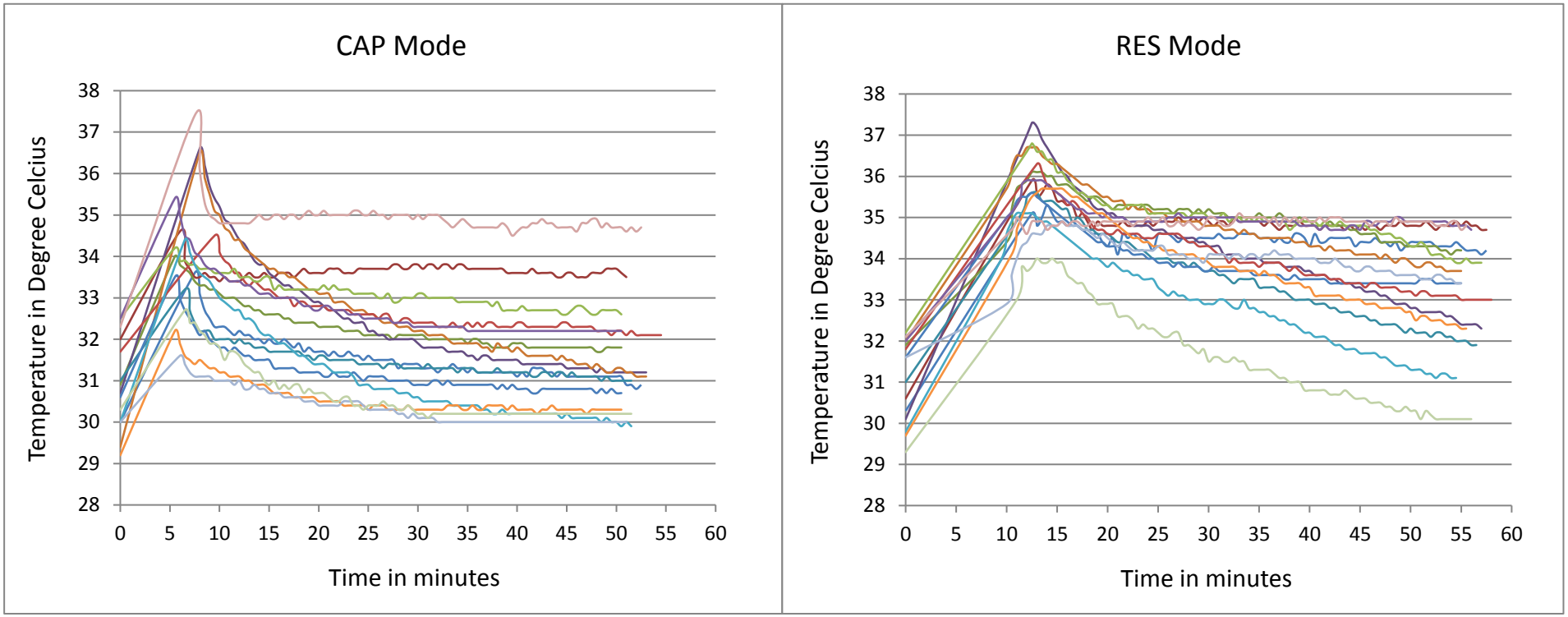


Figure 5.6a: CAP and RES mode time-specific individual skin thermal responses to localised CRMRF treatment (treated side). The data shown (thermal onset, definite thermal and thermal discomfort) are from 15 participants.

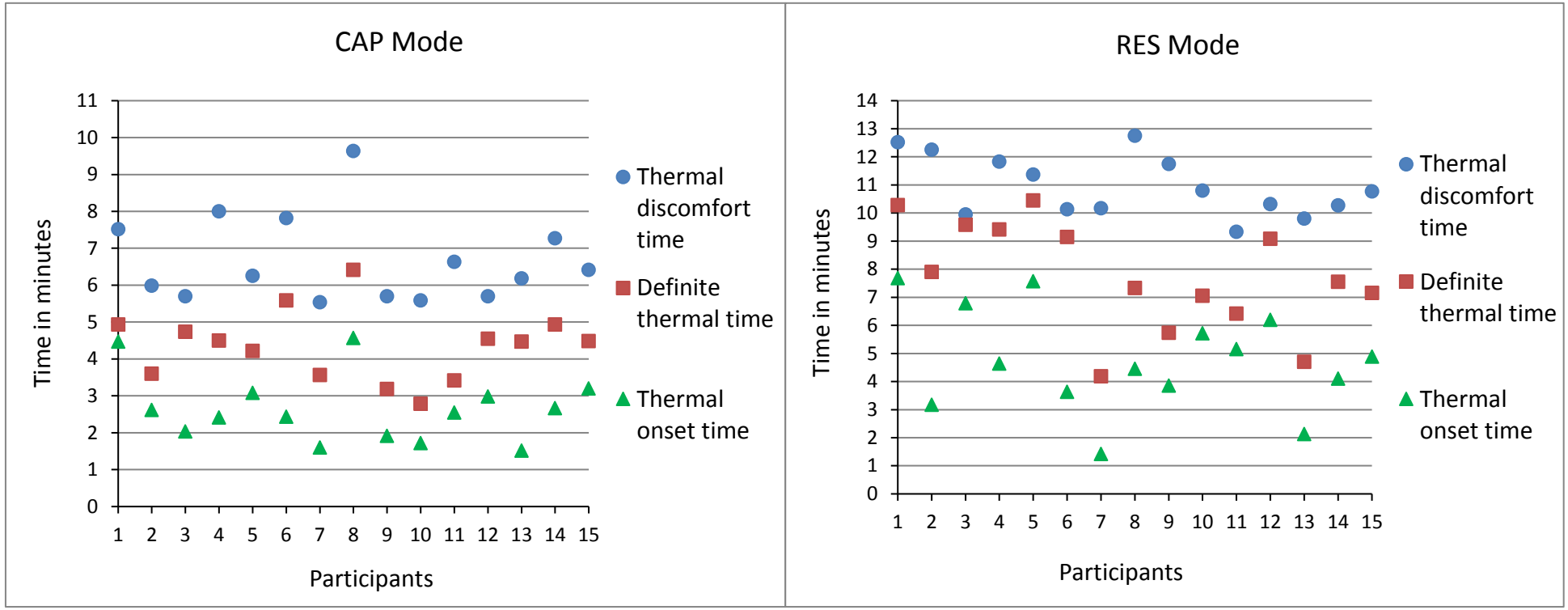


Figure 5.6b: CAP and RES mode energy-specific individual skin thermal responses to localised CRMRF treatment (treated side). The data shown (thermal onset, definite thermal and thermal discomfort) are from 15 participants.

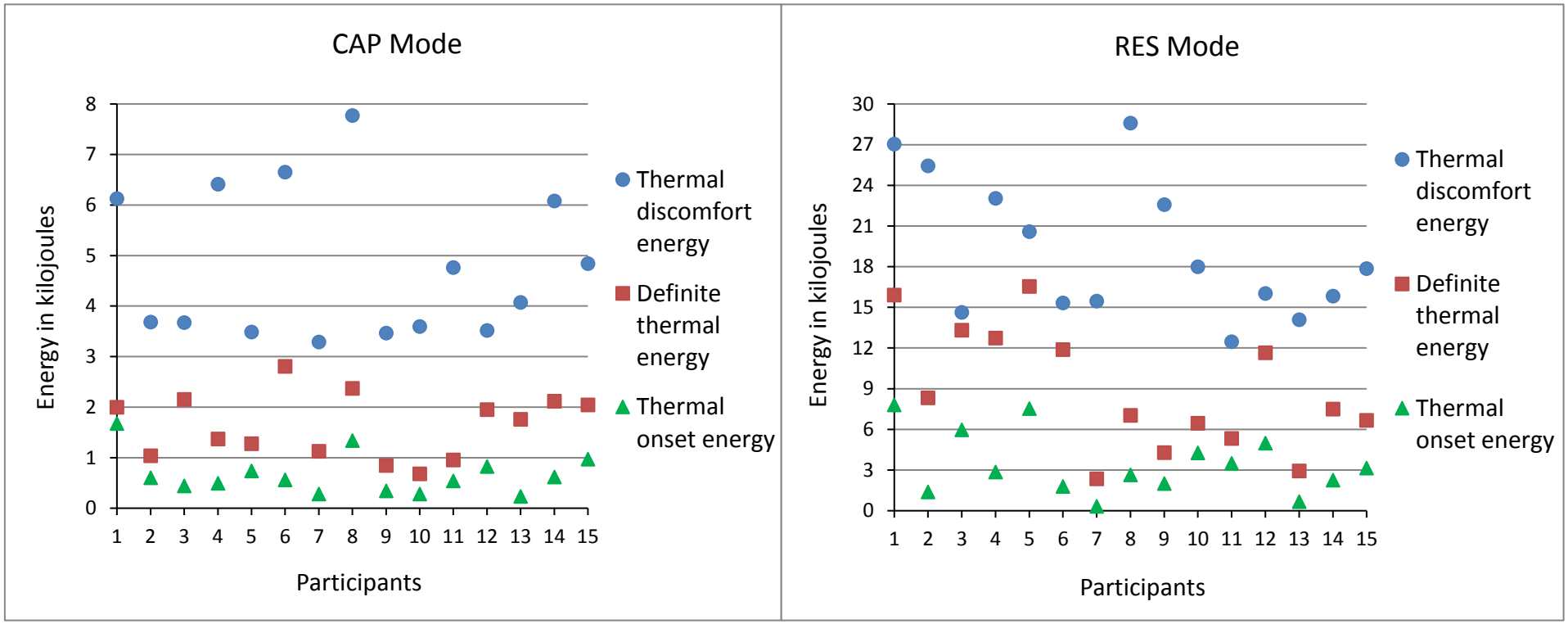
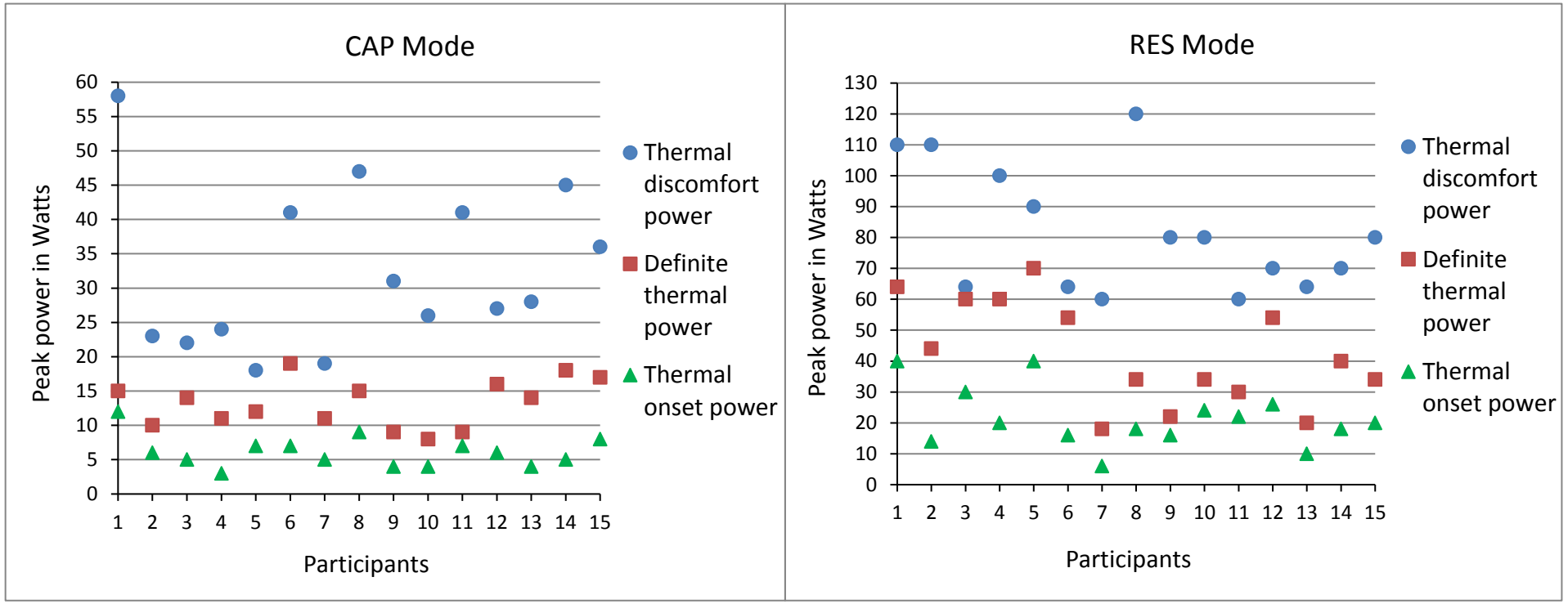


Figure 5.6c: CAP and RES mode power (peak)-specific individual skin thermal responses to localised CRMRF treatment (treated side). The data shown (thermal onset, definite thermal and thermal discomfort) are from 15 participants.



5.8 Discussion

The type of energy delivered by the EPA and its depth of penetration are the two main external factors that decide the extent of physiological effects induced by the heating modalities (EPAs).[101] Exposure to pulsed RF is likely to induce certain biological effects that are more likely to occur than when exposed to continuous RF at the same average incident pulse density (and vice versa). Similarly, whilst the IR energy (non-RF) is low penetrative and gets absorbed in the most superficial layers of skin causing superficial heating, RF frequency bands are more complexly absorbed at other depths,[22] potentially leading to deeper thermophysiological effects. Any potential deep heating effects of either CAP or RES were not measured in this study. However, other researchers have reported that RF-based EPAs may be used to achieve deep heating and are more effective in inducing physiological effects such as increasing tissue extensibility, compared to superficial heating.[195,469]

The CAP and RES modes of CRMRF therapy differ significantly in the patterns of skin heating they produce, as shown by the results of this study (when intermittently measured using a hand-held skin thermometer). In relation to the three thermal stages (onset, definite heating and heat discomfort), the CAP mode reached these stages considerably faster. However, the gained temperature decayed faster leading to a smaller overall retention in the CAP mode when compared to that of the RES mode. It needs to be considered that there was a lack of linearity between the intensity settings of the two modes, which renders any objective comparison problematic. The lack of linearity would also have had a telling influence on the peak power achieved at each time point. The greater the temperature increase due to heating, the greater was the drop during the follow-up phase for either mode, as suggested by the individual data (Figure 5.4b).

As stated, the mean (SD) peak skin temperature reached was 34.3 (±1.6) ^{o}C for the CAP mode and 35.0 (±1.2) ^{o}C for the RES mode (Figure 5.3a). The highest temperature recorded for a participant was 37.4 ^{o}C in the CAP mode and 37.0 ^{o}C in the RES mode (Figure 5.3b). These two values are at the level of the normal core temperature. Hence, the rise in skin temperature achieved are solely in relation to the baseline skin temperatures recorded at the treatment site and can only be termed ‘mild hyperthermia’ at best. *Per se*, it is only when the temperature is raised to supra-physiological levels, that it can be termed hyperthermia (that is, to around 40–45 ^{o}C, or even higher for thermal ablation). The cytotoxic effects of heat and cell death are prominent over a temperature range of 40–55 ^{o}C, with a ‘break point’ at around 43 ^{o}C as *in vitro* cell studies have shown.[470-473]

Quantification of a thermal dose given during a heat treatment can be represented as cumulative or equivalent thermal dose.[474] The cumulative or total equivalent thermal dose is expressed as Cumulative Equivalent Minutes (CEM) in relation to the arbitrarily chosen

temperature of 43 ºC (CEM 43). This was proposed by Sapareto and Dewey.[475] A 'time–temperature' history can be converted to a single number by using this method. This single number represents a 'thermal isoeffect dose', which is an equivalent number of minutes of heating at 43 °C. If the temperature remained constant, the following formula can be used for this calculation:

$$\text{CEM 43 }^{o}\text{C} = tR^{(43-T)}$$

'CEM 43 °C' is the cumulative number of equivalent minutes at 43 °C, 't' is the time (duration) of treatment, 'R' is a constant related to the temperature dependence of the rate of cell death (R (T< 43 °C) = 0.25, R (T>43 °C) = 0.5) and 'T' is the temperature during 't'.

For a complex time-temperature history, the CEM 43 °C is calculated for each small time interval (t) where the temperature (T) has remained relatively constant and summated over the entire period using the formula:

$$\text{CEM 43 }^{o}\text{C} = \sum tR^{(43-Tavg)}$$

In this formula 'T_{avg}' is the average temperature for each time interval (t). The resulting CEM 43 °C value represents the effect of the entire history of heat exposure.

In the dosimetry of cancer thermotherapy and of magnetic resonance (MR) systems,[474] estimates of 'thermal isoeffect dose' are routinely used. This estimation can also be done for CRMRF therapy as it has been used to induce hyperthermia for cancer[98-100,102] and to produce other cellular effects.[203]

In the current study, only the baseline and peak temperatures were recorded, which means the temperature variations in the tissues during the treatment delivery is unknown. If it is assumed that the peak temperature attained was maintained for the total duration of treatment for each participant, the mean (SD) CEM 43 °C thermal dose for the sample was 0.0004 (±0.0008) minutes for the CAP mode and 0.0005 (±0.0008) minutes for the RES mode. However, this estimation is only relevant to the skin area from which the temperature measurements were attained. For the deeper tissues, the thermal dose might have been completely different, so no such estimation can be done using the current data.

In a normal treatment session where a set treatment dose may be delivered from the beginning, the CRMRF powers required to achieve the three time points could be different to that obtained in this study. The peak powers reported in Table 5.2 and Figure 5.6c only denote the peak powers that may be achieved if the intensity is incrementally raised every 30 seconds starting at the minimum dose. The mean (SD) of mean powers (MP) (the 'mean overall power' provided for each participant for the duration of the treatment) delivered to reach the thermal onset, definite thermal and thermal discomfort stages were 3.89 (±0.99),

6.05 (±1.36) and 11.70 (±1.67) Watts respectively for the CAP mode and 10.61 (±3.78), 17.87 (±5.36) and 28.74 (±4.74) Watts respectively for the RES mode.

Temperature recordings were not made at the thermal onset and definite thermal stages, as this would have affected the continuity of treatment. Also, this could have delayed the attainment of the following thermal stage due to a 'thermal washout'. Despite the non-linearity of their intensity settings, the peak skin temperatures attained were not significantly different between the two modes. However, while the CAP mode (mean) temperature declined sharply in the immediate post treatment phase, the RES mode (mean) temperature increased in the first few minutes after the treatment stopped. This post treatment behaviour is unlikely to have been influenced by the intensity settings.

Heat retention in RES mode at the end of the 45-minute follow-up was more than 60% (Mean (SD) of 60.3 (±34.5)%) as against 15% (Mean (SD) of 15.5 (±20.1)%) in the CAP mode (Figure 5.4a). Neither the core temperature nor the untreated control leg showed any significant change at any time point for either condition. The core temperature was not expected to change since a local application of RF energy may not influence the core temperature.[22] The result from the control leg was contrary to the 'crosstalk' effect (undesirable effect generated in the neighbouring untreated area) that was reported from PSWT research.[80] This indicates that potentially, there may be only lower levels of 'scattering' of the waves from CRMRF therapy compared to SWT.

The CAP mode CRMRF may be relatively superficial in its penetration of the tissues. The faster heating and faster thermal decay shown to be associated with it the may be indicative of the same. Comparable to the 'capacitive method' of application in SWT, there may be a higher proportion of 'electric' (E) than 'magnetic' (H) field causing a capacitive (faradic) effect in the tissues.[18,462] There is a higher concentration of field in the superficial tissues, hence proportionally more faradic energy is absorbed in the superficial tissues (such as the skin and fat layers) than in the deeper tissues (underlying tissues such as muscles).[476]

The RES mode CRMRF may be compared to the 'inductive method' in SWT in a similar manner as they both generate an effect that is predominantly due to an H field.[18,462] A higher penetration of energy in the RES mode is suggested by the higher retention of heat and the fact that there was no sharp fall in the post-treatment temperature. The energy absorption for inductive treatment is greater in deeper tissues such as blood and muscles. This is due to their lower resistance and higher electrolyte content. In tissues such as skin and subcutaneous fat that have higher resistance, the absorption of inductive energy is less and therefore heat up less compared to the deeper tissues.[18]

The conductivity of the tissues and the strength of the field have a proportionate influence on the amount of heat generated.[462] The size of treatment electrodes will also influence the

penetration of RF energy; with the larger electrodes having more penetrative ability than the smaller electrodes.[18] SWT and CRMRF are fundamentally different from each other when the frequency and other characteristics of their RF waves are considered. Therefore, the physical principles underpinning the shortwave-tissue interactions may not apply to CRMRF. Compared to SWT, there is little published research on the physical principles of CRMRF-tissue interaction.

Data reported in Table 5.3 shows that the temperature of the electrodes at any point (as in the main experiment) was not notably higher than the peak skin temperature reached. The peak electrode temperature in RES mode stayed consistently below that of the skin. The electrode temperature in CAP mode increased marginally when the intensity of exposure was sustained for longer periods. These suggest that the rise in skin temperature was due to RF-tissue interaction, and not due to contact heating from a hot electrode.

The participants felt superficial heating in the CAP mode, with the heating reported mainly on the skin of the treated area. They did not report much heat sensation through the knee joint or into the calf. However, they generally reported deeper and more homogenous heating with the RES mode, with the knee joint and calf both giving sensation of heat. Nevertheless, caution should be exercised when interpreting these claims about perception of heat at depth. Cutaneous receptors are primarily responsible for localised thermal perception and it is somewhat controversial as to whether thermal perception at depth is in fact nociception.[341] The evidence on the existence of subjective perception of temperature from deeper tissues such as muscle is scant.

Thermal perception at depth might exist, but when tissue temperature is approximately between 25–41 ^{o}C that mechanism may be at a subconscious level. Beyond this level of temperature, nociception is arguably more potent than thermal perception. It is also debated that, in humans nociceptors and other pressure and mechanosensitive receptors in the muscle might also function as peripheral sensors for subjective temperature sensation.[341,342] The sensation of heat in the tissues depends on thermal change and the rate of thermal change (the pattern of thermal energy delivery).[22,254,341] Deep heating may have occurred from the CRMRF therapy; however, given the above reasons it is proposed that a variation in the rate and distribution of temperature change (resulting from the CAP and RES modes) in the more superficial tissues such as the skin and superficial fascia, where there is a presence of thermoreceptors may have led to the participants reporting the different heating sensations from these two treatments.

Variability in the anthropometric factors of participants may explain any potential variability in the thermal response data between individual participants. The correlation between the anthropometric factors and the thermal responses were statistically analysed. The body fat percentage showed a moderate negative correlation (significant at $p<0.05$ level) with the

CAP thermal onset and discomfort points. The same was noted for the RES mode thermal discomfort. A moderate negative correlation (significant at $p<0.05$ level) also existed between the room temperature and the RES mode thermal onset and definite thermal points. No other meaningful correlations were noted to draw any conclusions.

Several RF (predominantly the shortwave frequencies) studies investigating their skin and/or deep thermal responses on humans have been identified,[77,80,81,83,85,95,96,105,194] in which a significant rise and maintenance of both skin and intra-muscular temperatures were reported by many of the earlier published studies.[77,81,85,96] As stated previously, all those studies have been either shortwave frequencies or above, making the current study the first of its kind. Unlike this one only a limited number of those studies have mapped skin temperature for as long as 45 minutes after treatment.

Earlier, Bricknell and Watson[105] employed incremental dosing of PSWT in their study and reported their dose parameters that produced a 'possible thermal perception' (Mean 'mean power (MP)' of 6.58 (±3.50) W) and a 'definite thermal perception' (Mean MP 10.88 (±3.32) W) on the skin. From baseline to the definite thermal stage, a mean temperature elevation of 2.10 ^{o}C was reported. A significant rise in the skin temperature with high (MP 24 W) and low (MP 3 W) doses of PSWT was also reported in another study by Al-Mandeel and Watson.[80]

Temperature changes inside the gastrocnemius muscle in response to a 20-minute treatment with PSWT (MP 48 W) was investigated (invasive study) by Draper et al.[83] A mean (SD) temperature rise of 3.49 (±1.13) ^{o}C was reported after the treatment and a decay of 1.78 (±0.69) ^{o}C was reported in the first 10 minutes post-treatment. Takahashi et al.[194] reported a 5 ^{o}C rise in temperature inside the knee joint with a 20-minute pulsed RF (8 MHz, 200 W) treatment (invasive, non-shortwave study) on patients affected by osteoarthritis of the knee. The temperature decay was not monitored by the authors.

5.9 Conclusions

This study confirmed that skin temperature can both be increased and sustained significantly by both CAP and the RES modes of CRMRF therapy, although the RES mode thermal retention is significantly greater than that of the CAP mode. The doses were delivered incrementally, and the average time, energy and power required in achieving thermal onset, definite thermal and thermal discomfort sensations were identified for both modes. There was a significant difference between the thermal response patterns produced by the CAP and RES modes; however, the lack of linearity in their intensity settings renders a direct comparison problematic.

6 Chapter 6 – Skin and deep tissue physiological effects of CRMRF treatment: single-blind randomised crossover study with a comparison to PSWT

6.1 Introduction

The first chapter of this section (Chapter 4) considered all the measurement principles and physiological outcome measures, described the CRMRF device and conducted various pilot experiments leading to the main laboratory studies. The second chapter (Chapter 5) explored the CAP and RES components of CRMRF therapy in more detail and studied their effects on the skin thermal responses (build-up, decay and retention) when applied as separate treatment components.

Skin physiological outcome measures such as SKT, SBF and NCV, and deep physiological outcome measures such as Doppler ultrasound and ultrasound Elastography have been explained in detail in chapter 4. For temperature measurement, good agreement was found between the hand-held thermometer and the Biopac SKT100C thermistor module. In deep blood flow and tissue extensibility measurements, good intrarater test retest reliability was established for Doppler ultrasound and ultrasound Elastography. Testing of various commercially available self-adhesive surface (ECG) electrodes were also undertaken to determine the best choice of electrodes for NCV measurements using the Biopac system.

The present chapter will explain in detail the main segment of the laboratory study, which compared multiple doses of CRMRF therapy and high dose PSWT on an array of physiological parameters including both skin and deep measurements mentioned above. More details on the rationale for the selection of body area to treat and the rationale for the selection of physiological outcomes have been discussed in chapter 4. Prior to the commencement of the main experiment, a pilot study was conducted on 15 volunteers to determine the interventional design and experimental protocol. This will be explained in detail in the relevant section below.

6.2 Aims

The main aims of this study were:

1) To compare the effects of multiple doses of CRMRF therapy on SKT, skin and deep blood flow, NCV and extensibility of tissues on a group of asymptomatic adults in a randomised crossover study.
2) To compare the above effects with those obtained from a high dose PSWT treatment in the same group of people.

3) Make recommendations for future research and clinical practice where possible.

6.3 Materials and methods

6.3.1 Apparatus

6.3.1.1 CRMRF device

The 'Indiba Activ' CRMRF machine has been described in chapter 4.

6.3.1.2 PSWT device

The 'Bosch Ultramed' machine has been described in chapter 4.

6.3.1.3 Skin data acquisition system

The Biopac MP150 physiological measurement system that was used to record the skin temperature (SKT), skin blood flow (SBF) and nerve conduction velocity (NCV) from the studied knee joint area has been described in chapter 4.

6.3.1.4 Doppler ultrasound and Elastography

Blood flow to the deeper tissues (two centimetres or more from the skin) and the indices of tissue extensibility were monitored by Doppler ultrasound and ultrasound Elastography using 'Esaote MyLab70 XVG' ultrasound scanner and a linear array probe 'LA523' that has been described in chapter 4.

6.3.1.5 Other devices

An infra-red (IR) tympanic thermometer (Braun ThermoScan IRT 4520) was used for core temperature measurement. Blood pressure (BP) and pulse rate (PR) were monitored using a digital upper arm BP monitor (Omron M2). A body composition monitor (Omron BF508) was used to obtain the anthropometric data. The room temperature and humidity were monitored using an electronic thermohygrometer (RS 212-124).

6.3.2 Sample and groups

A randomly selected cohort of 18 asymptomatic (self-reported) adults from among the 27,000 staff and Students of the University of Hertfordshire participated in the study. The recruitment was done through emails sent out university-wide along with the participant information sheet (Appendix 6.1). The respondents were screened for inclusion consecutively, and the first 18 eligible respondents were recruited (eligibility criteria explained below). Later, one participant withdrew from the study because of unrelated illness (respiratory infection) restricting the total number to 17. An *a priori* sample size calculation was unable to be performed as no baseline data was available. Hence an interim analysis of the data was decided to be undertaken after the first 15 participants completed the study, to determine the power and required sample size.

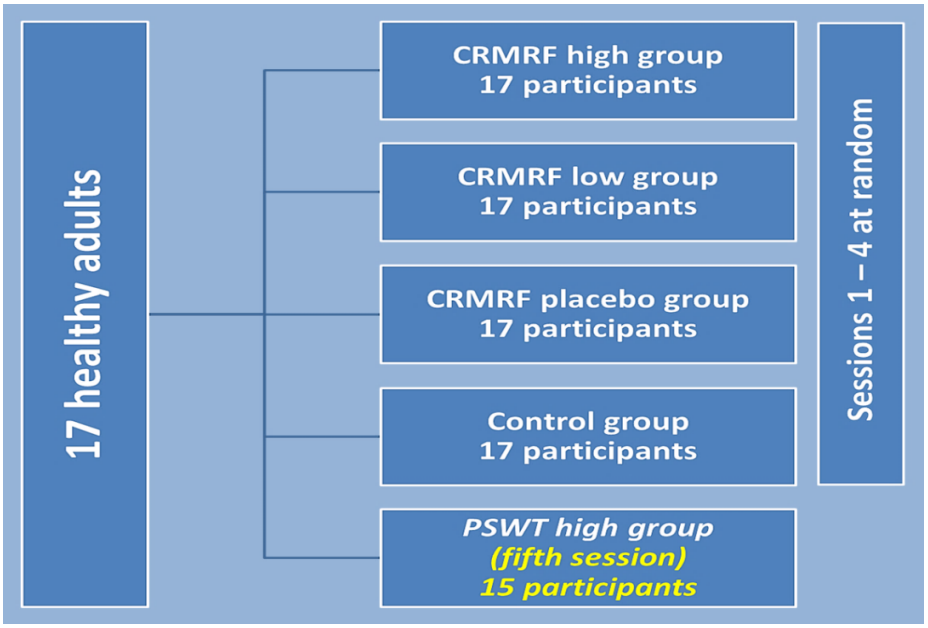
The study was approved by the Health and Human Sciences Ethics Committee with Delegated Authority (HHSECDA) of the University of Hertfordshire (Protocol number: cHSK/PG/UH/00143) (Appendix 6.2). The participants signed an informed consent on their first visit, prior to the commencement of the study (Appendix 6.3). All 17 participants attended four sessions, each representing one of the four experimental conditions listed below (Figure 6.1). The order of attendance to these conditions (otherwise experimental groups) was randomised by concealment using a computer-generated randomisation chart (IBM SPSS Statistics, Version 20) (Appendix 6.4), and blinded from the participants.

6.3.2.1 Experimental conditions

1) CRMRF high dose (with evident thermal perception)
2) CRMRF low dose (sub/minimal thermal perception)
3) CRMRF placebo dose (device turned off after thermal onset)
4) Control condition with no RF intervention

In addition to the above four conditions, fifteen participants who were available and willing to appear for a fifth session attended the 'PSWT high dose condition'. Attendance to the PSWT session was neither randomised nor blinded; however, the participants were only informed that it was 'a type of RF-based treatment'. Like the previous study (Chapter 5), based on pilot experiments and existing literature a minimum gap of 48 hours was allowed between the sessions so that no residual effects from the preceding session were present at the following session.[80,458] Similar times (±1 hour) of the day were chosen for all the sessions for each participant to avoid unwanted impacts from any core temperature variations.[80,341]

Figure 6.1: Schematic representation of the five study conditions (groups). Groups 1–4 were represented by all 17 participants. Group 5 was represented by 15 participants only.



6.3.3 Experimental procedure

Like the previous experiment (Chapter 5), on the days of the study the participants were asked to attend the sessions by avoiding food, beverages and strenuous exercises within one hour before the start. This was to ensure that their physiological condition remained stable during the sessions.[80,455,456] The experimental procedure was undertaken as per the designed and pretested experimental protocol. The participants were screened using an eligibility questionnaire including questions relating to any recent injury or illness and accepted contraindications to RF therapy (pregnancy, malignancy, metal or electronic implants in the body) (Appendix 6.5). Subsequently, their 'skin thermal sensitivity' and the ability to distinguish between warm and cold was tested using test tubes filled with water at approximately three different temperatures (±0.5 ^{o}C): 45 ^{o}C (warm), 35 ^{o}C (neutral) and 25 ^{o}C (cold). After this screening, demographic and anthropometric data were collected.

To start the experiment the participants positioned themselves in supine on a treatment plinth and were fully supported using pillows. Skin over the medial aspect of both thighs was prepared and a square area covering the lower one-fourth of the medial aspect of the right and left thighs were marked with tape to deliver the treatment and obtain the physiological measurements. For all participants, the right leg was chosen as the active (treated) side, while the untreated left leg served as control. Skin temperature was recorded from the middle of the square area on the treated leg as well as the corresponding area of the untreated leg. This was repeated every two minutes until stabilised. The stabilised temperature was considered the baseline temperature. The core (tympanic) temperature was also monitored at the same time. All data, except those from the Biopac and Doppler were entered manually into a participant data collection form (Appendix 6.6).

6.3.4 Data acquisition

6.3.4.1 Skin physiological measurements

All skin physiological measurements on both sides were performed pre-treatment, immediately post treatment and 20-minute post treatment for all conditions. The PPG and SKT probes and the NCV electrodes from the Biopac data acquisition system were attached to the predetermined marked areas on both legs. The probes were positioned within the treatment zone and attached using Micropore™ (3M™) tape. For NCV, self-adhesive monitoring electrodes (3M™ Red Dot™) were used and placed with 22 cm between the stimulating and measuring electrodes, close to the outer border of the treatment zone (established during pilot). During each assessment, the outcome measurements were performed in the following order.

1st NCV on the treated side

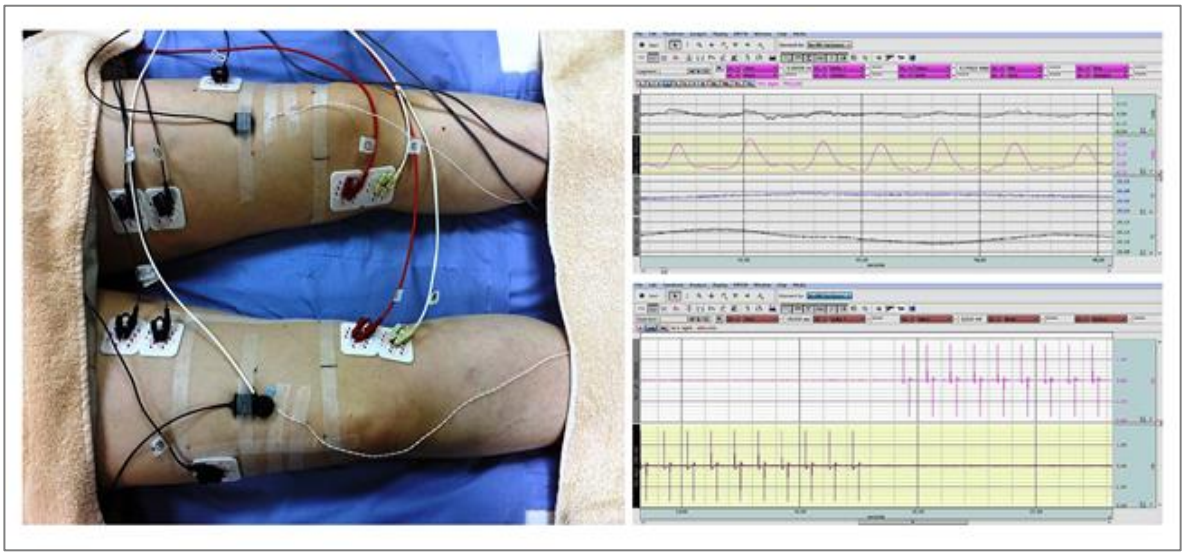
2nd NCV on the untreated side

3rd SKT and SBF performed together for both sides

The NCVs were performed separately since it was identified in the pilot that they were interfering with each other. Performing unilaterally also minimised the skin discomfort for the participants. All the probes and connecting leads on the treated leg, except the NCV electrodes were removed from the skin prior to the RF treatment and reattached for post treatment measurements. This was done to avoid potential signal interference, probe damage and tissue irritation, as explained in chapter 4 (pilot experiments). The NCV electrodes were left in place since they were situated outside the treated area, and to minimise the discomfort caused to the skin while removing them. No signal interference or unwanted heating was noted from these electrodes once the leads were detached. All the attachments on the control leg remained in place throughout the experiment since they did not cause any interference or skin irritation (established during pilot). Reliability of probe and electrode placements was established by extensive pilot works. The sampling rate for Biopac was chosen to be 200 samples/second based on previous evidence.[192]

The Biopac system was set up to run one hour before the start of the experiment to ensure proper baselining of the data streams. Both SKT and PPG data were collected for 10 minutes pre-treatment, and once restarted post treatment, they were kept running through to the 20-minute follow-up phase. The NCV was recorded for a fixed 30 seconds at each assessment. The core (tympanic) temperature, BP and PR were also concurrently monitored at the three time points. The probe and electrode attachments and sample Biopac data streams are shown in Figure 6.2.

Figure 6.2: Images showing the Biopac electrode placement and sample data streams from the SKT, PPG (top) and NCV (bottom) modules



6.3.4.2 Deep physiological measurements

The deep blood flow and Sonoelastography measurements were performed pre-and post-intervention only, and only from the treated side unlike the skin measurements. For each participant, blood flow was identified by manoeuvring the ultrasound probe over the lower anteromedial aspect of the quadriceps femoris muscle. Once the most prominent pulsatile (arterial) flow was identified, skin markings were used to establish the accuracy of probe placement and ensure repeatability. Prior to this study, the intra-rater reliability for both Doppler and Sonoelastography measurements was established in a separate pilot study that involved 12 healthy adult participants (explained in chapter 4, pilot experiments).

For Sonoelastography measurements, a fixed position was adopted for all participants. The probe was placed parallel to the longitudinal axis of thigh, perpendicular to the skin in the middle lower part of the marked area. Minimal probe pressure and liberal amount of conductive gel were used to avoid any undue compression of the tissues. For all participants, the machine settings remained the same for both pre-treatment and post treatment measurements. Recordings were performed from the treated side in the following order.

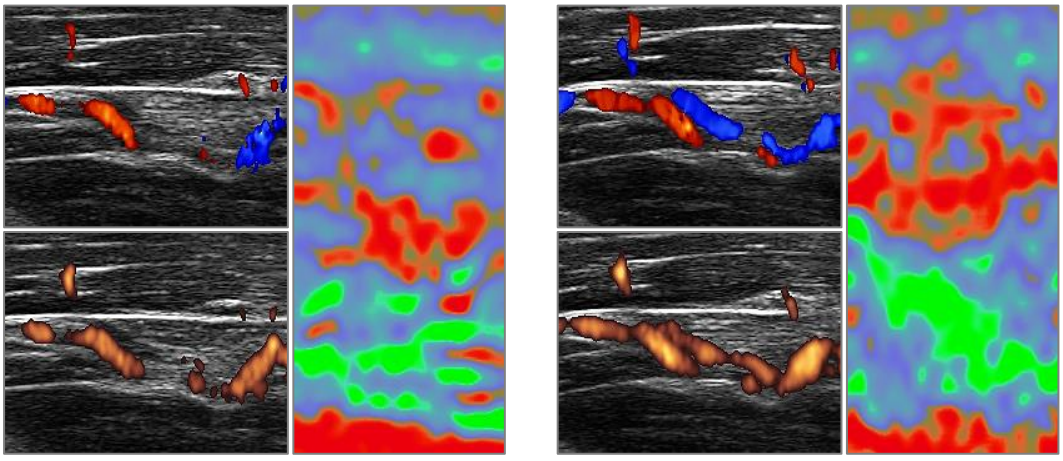
1st Colour Doppler for velocity of flow

2nd Power Doppler for volume and intensity of flow

3rd Elastography for the softness and hardness of tissues

Up to five seconds of blood flow data clips were recorded with colour Doppler, power Doppler and Sonoelastography during each measurement, which was then broken down into image frames for analysis. Sample ultrasound images obtained from one participant before and after treatment are shown in Figure 6.3.

Figure 6.3: Sample images showing Doppler Ultrasound and Elastography recordings before (left side) and after (right side) CRMRF treatment. The images shown are: Colour Doppler (top left), Power Doppler (bottom left), and Elastography (right side) showing the hard (red), intermediate (blue) and soft (green) tissue types.



6.3.5 The CRMRF intervention

6.3.5.1 Pilot study to determine the intervention

The design of the CRMRF intervention was determined using a pilot randomised crossover study on a similar cohort of asymptomatic volunteers, prior to the commencement of the main study being described in this chapter. The methods adopted for this pilot study were identical to the main study except that the pilot study employed only three groups with a maximum of 15 participants in each group; and that it only employed SKT and SBF as outcome measures, with measurements obtained only from the treated leg without follow-up.

6.3.5.2 Pilot study rationale, aims and methodology

There are no evidence-based recommendations currently available with regards to the optimum intervention design for CRMRF therapy beyond the recommendations from the manufacturer derived from user experience and product development. Besides the lack of understanding on the time and sequencing of the CAP and RES modes, there is a lack of awareness on the optimum treatment delivery methods too. For example, with regards to the application, the manufacturer actively encourages the use of manual therapy techniques (such as soft tissue mobilisations or massage) to be simultaneously delivered with CRMRF. This is achieved by holding the treatment electrode in one hand and the manual techniques delivered using the other hand. However, such suggestions are not based on published evidence and are backed only by 'in-house research' by the manufacturer and anecdotal evidence from the users of this device.

Nonetheless, it can be argued that employing manual therapy techniques such as massage or other soft tissue treatment techniques combined with a thermal modality employing RF may generate a cumulative physiological response in the tissues by increasing fluid drainage, improving thermal distribution and improving tissue compliance although the quality of current evidence is lacking.[84,91,326,459] In general, the physiological effects of various manual therapy techniques such as massage, joint mobilisation and manipulation are well documented through reviews of literature[477-480] and in relevant text books.[481,482] There is considerable evidence in the literature suggesting that massage and soft tissue mobilisation can influence tissue temperature superficially[483-485] and possibly at depth,[455] and can improve peripheral blood flow.[486-488] If the addition of similar manual therapy techniques (massage) to the CRMRF application has a significant additional effect on the tissue physiological responses, then its inclusion would need to be incorporated into the experimental protocol. If, however the addition of the manual therapy component, as advocated by the manufacturer, made no significant difference to the physiological response, then it could be reasonably omitted from further experimentation, thereby reducing it as a potential confounding factor.

Hence, the key aim of this pilot study was to determine whether CRMRF delivered in conjunction with manual therapy in the form of soft tissue mobilisation (massage) has a greater physiological effect compared to a same thermal dose of CRMRF delivered without the manual therapy component. To address this aim 15 volunteers attended two study groups (groups 1 & 2 stated below) in a random order using a computer-generated randomisation chart (IBM SPSS Statistics, Version 20) (Appendix 6.7) in a crossover study. Nine of the participants also attended a third session (non-random control session) receiving similar treatment, but with the CRMRF device output turned off.

The three study groups and the number of participants attending those groups are as below.

Group 1 – CRMRF high (15 participants)

Group 2 – CRMRF high + manual therapy (15 participants)

Group 3 – CRMRF zero output + manual therapy (9 participants)

The CRMRF treatment was delivered for 15 minutes (5 minutes CAP followed by 10 minutes RES) within the marked area of the right lower limb, using 20 ml of conductive cream for each mode. The active electrode produced firm circles on the skin, at a rate of approximately one per second. The return plate electrode was smeared with 20 ml of conductive cream and placed under the calf muscle belly, one-fourth way down the distance from the fibular head to the lateral malleolus of the treated leg.

Predetermined treatment doses were not delivered for either of the two CRMRF groups, but rather the dosage was adjusted based on the concurrent feedback given by the participants, as would be the case in a real clinical situation. The intensity of application was gradually increased, by one level at a time (standardised as once every five seconds until the intensity reached 25% output and once every 30 seconds thereafter, based on pilot) using the remote controller till the participants reported moderate yet comfortable heating. This moderate level of heating was then maintained throughout the session by adjusting the intensity if required. In the treatment group where manual therapy was also delivered, circular kneading massage was applied alongside the electrode movements using the web of fingers of the free hand. There is no evidence available as to which manual therapy technique works best alongside CRMRF. The current technique was adopted based on pilot work, where it was found to best suit the proposed methodological protocol.

SKT and SBF measurements were obtained using the Biopac system before and immediately after treatment employing the same methodology described above. All data was processed and analysed using Microsoft Office Excel Version 2010 (Microsoft Corporation, USA) and IBM SPSS Statistics Version 20 (IBM Corporation, USA). Two separate data analyses, first with the two active CRMRF groups (two-group analysis) and secondly with all three groups including the manual therapy-only group (three-group analysis) were carried

out. While the first analysis had 15 participants per group, the second analysis was based on nine participants. To ascertain whether there were any statistically significant differences between the treatment conditions, the group data were compared using either a two-way (intervention and time) repeated measures analysis of variance (ANOVA) model at three time points (baseline, post treatment and 20-minute follow-up) or using Friedman's two-way ANOVA by ranks, depending on the distribution of data (Shapiro-Wilk). The statistical significance was set at $p \leq 0.05$ (0.8 P, 95% CI).

6.3.5.3 Pilot study results

All 15 participants completed the two RF sessions of CRMRF therapy and/or manual therapy, and the assessments as anticipated. Nine participants attended a third session and underwent its assessments. All treatment types were well tolerated and there were no reports of any adverse events that might be a consequence of the intervention, including any issues due to potential overheating.

The demographic and the mean (SD) anthropometric data from the participants are reported in Table 6.1. There were no differences between any of the three conditions in either characteristic since this was a crossover (repeated measures) study. The mean (SD) RF dose received by the participants is given in Table 6.2, along with the mean (SD) room temperature and humidity at the time of the experiment. Figure 6.4 shows the mean (SD) SKT results recorded at the two time points from all three groups. Figure 6.5 shows the mean (SD) SBF results recorded at the two time points from all three groups.

Table 6.1: Demographic and the mean (SD) anthropometric data from the 15 participants who received CRMRF treatment

Sample	Demographic data			Mean (±SD) anthropometric data				
	Mean (±SD) age (years)	Gender: Males	Gender: Females	Height (m)	Weight (kg)	Body fat (%)	Visceral fat	BMI
15	47.33 (12.55)	4	11	1.69 (0.06)	70.11 (11.70)	33.44 (7.52)	7.00 (3.64)	24.57 (3.84)

kg – kilogram; m – metre; BMI – body mass index

Table 6.2: The mean (SD) treatment doses received by the participants of three experimental groups, and the mean (SD) room temperature and humidity

	CRMRF High	CRMRF High & MT	CRMRF Zero & MT
RF dosage in Watts (W)	32.10 (3.79)	32.17 (3.69)	0
Room temperature (°C)	24.70 (0.65)	24.50 (1.05)	24.78 (0.67)
Humidity (%)	26.77 (3.17)	29.47 (3.48)	27.17 (5.10)

CRMRF – Capacitive Resistive Monopolar Radiofrequency; RF – radiofrequency; MT – manual therapy

In the two-way ANOVA no significant main effects, interactions or changes between groups were noted for any of the intervention groups for any time point in either SBF analysis. In the SKT analysis, no significant main effects, interactions or changes between groups were noted for any of the intervention groups for any time point in the two-group analysis. In the three-group SKT analysis, the third group (manual therapy only group) differed significantly from both the other groups ($p < 0.001$; Bonferroni). Significant within group changes were noted in both the RF groups for both SKT and SBF ($p < 0.001$), but not in the third group.

Figure 6.4: Mean (SD) SKT responses from three groups

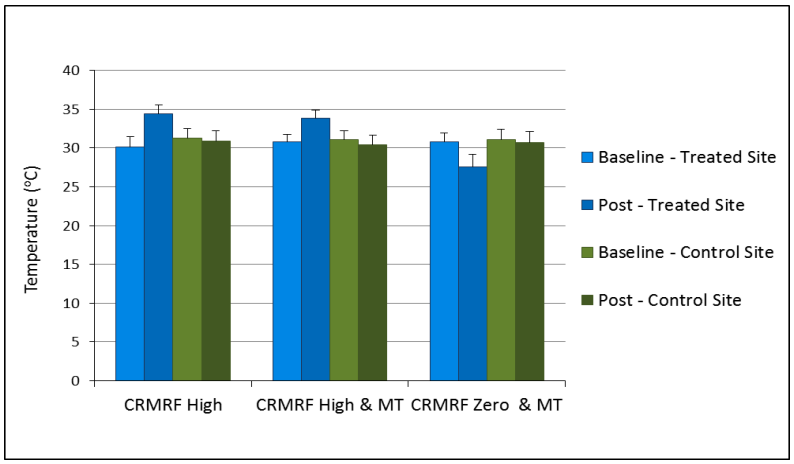
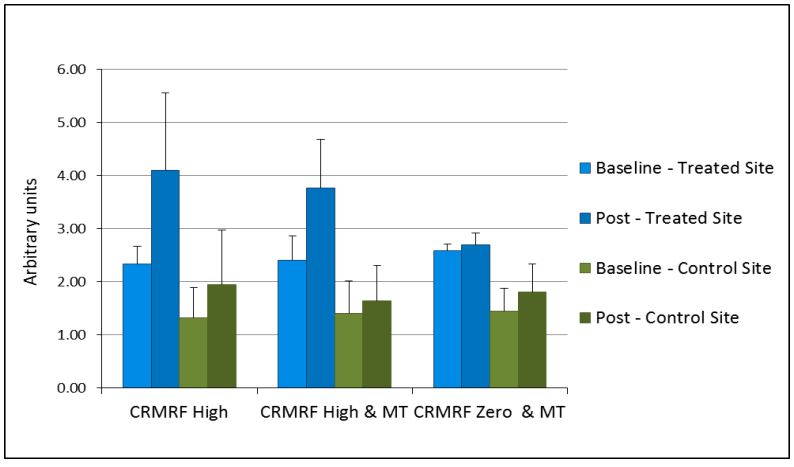


Figure 6.5: Mean (SD) SBF responses from three groups



6.3.5.4 Pilot study conclusions

The aim of this pilot study was to determine if delivering CRMRF in combination with manual therapy had a greater physiological effect than CRMRF delivered on its own. The results obtained here suggest that there is no greater effect generated by the addition of manual therapy for the employed experimental protocol. Besides, the group means suggests that CRMRF delivered on its own may induce a more pronounced physiological response. The manual therapy component was hence excluded from the intervention delivered in the main study.

6.3.5.5 CRMRF treatment in the main study

The treatment was delivered for 15 minutes in all conditions (5 min CAP followed by 10 min RES). For the CRMRF high dose condition, the intensity of application was gradually increased till the participants reported moderate, yet comfortable heating as explained in the above section. This moderate level of heating was then maintained throughout the session by adjusting the intensity if required. For the CRMRF low dose condition, the intensity was gradually increased till the participants reported a feeling of heat, using the same method as above. It was then reduced marginally to avoid the heating sensation, and this sub-thermal level was maintained throughout the session. For CRMRF placebo, the intensity was gradually increased till the participants felt heat as in for the low dose, but the device output was then turned off for the rest of the session. The control condition did not involve any intervention, hence the participants only rested on the treatment plinth for 15 minutes.

6.3.6 PSWT treatment

The nearest available PSWT dose to the mean CRMRF high dose (42.37 W) used in the study was 47 W (PD–400 µs, PRR–200 Hz, PP–600 W). Hence, a MP dose of 47 W was delivered to all 15 participants who attended the PSWT session, for the duration of 15 minutes. The treatments were applied using a drum (monode) applicator electrode placed 1.5 cm from the skin over the marked area.

6.3.7 Data analysis

6.3.7.1 Processing of Biopac data and the ultrasound images

This has been explained in detail in chapter 4.

6.3.7.2 Statistical analysis of data

All data including the Biopac data and the ultrasound image data (after MATLAB analysis) were processed using Microsoft Office Excel Version 2010 (Microsoft Corporation) and statistically analysed using IBM SPSS Statistics Version 20 (IBM Corporation). It was decided to perform two separate data analyses, first with the three CRMRF and the control

groups (four-group analysis) and secondly with all five groups including the PSWT high group (five-group analysis). While the first analysis had 17 participants per group, the second analysis was based on 15 participants. To ascertain whether there were any statistically significant differences between the treatment conditions, the Biopac group data were compared using either a two-way (intervention and time) repeated measures analysis of variance (ANOVA) model at three time points (baseline, post treatment and 20-minute follow-up) or using Friedman's two-way ANOVA by ranks, depending on the distribution of data (Shapiro-Wilk). The ultrasound data was subjected to the same analysis, but at two time points (baseline and post treatment). The statistical significance was set at $p \leq 0.05$ (0.8 P, 95% CI).

6.4 Results

All 17 participants completed three sessions of CRMRF therapy and the control condition, and the accompanying assessments as anticipated. Among them, 15 participants attended the fifth session (PSWT) and underwent the assessments. Both types of RF were well tolerated and there were no reports of any adverse events that might be a consequence of the intervention, including any issues due to potential overheating.

The demographic and the mean (SD) anthropometric data from the participants are reported in Table 6.3. There were no differences between any of the five conditions in either characteristic since this was a crossover (repeated measures) study (the conditions will be referred to as 'groups' from here on for convenience, although they were not independent groups).

The mean (SD) RF dose received by the participants is given in Table 6.4, along with the mean (SD) room temperature and humidity at the time of the experiment. As identified, the CRMRF placebo group received a negligible average dose of treatment, while the PSWT high group received a fixed dose of 47 W. To illustrate the level of variation that was observed in the doses of CRMRF high and low groups, the individual data from the three actively treated groups are plotted in Figure 6.6.

Figure 6.6: Data from CRMRF high, CRMRF low and PSWT high groups, showing the individual treatment doses delivered. Participants 9 & 10 did not attend the PSWT session.

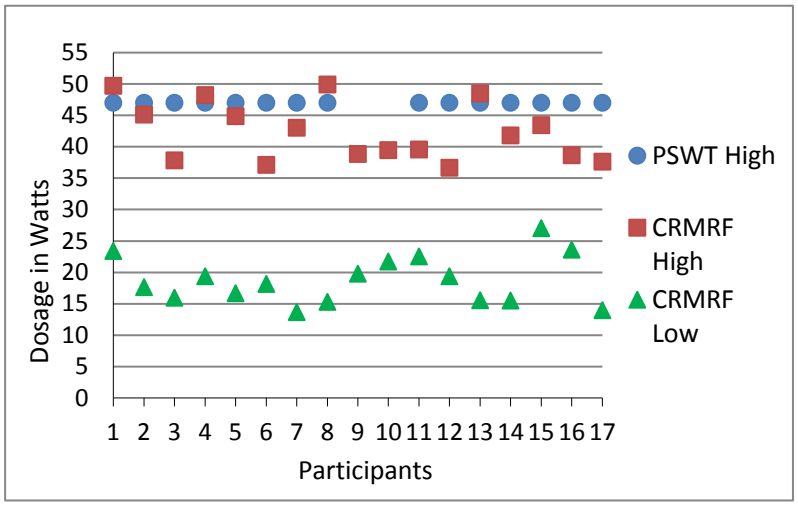


Table 6.3: Demographic and the mean (SD) anthropometric data from the 17 participants who received localised CRMRF treatment

Sample	Demographic data			Mean (±SD) anthropometric data				
	Mean (±SD) age (years)	Gender: Males	Gender: Females	Height (m)	Weight (kg)	Body fat (%)	Visceral fat	BMI
17	45.71 (12.70)	7	10	1.70 (0.08)	71.48 (10.02)	30.32 (7.61)	7.24 (2.54)	24.68 (2.71)

Table 6.4: The mean (SD) treatment doses received by the participants in the five experimental groups, and the mean (SD) room temperature and humidity during the experimental sessions

	CRMRF High	CRMRF Low	CRMRF Placebo	Control	PSWT
RF dosage in Watts (W)	42.37 (4.64)	18.77 (3.82)	2.79 (1.23)	0	47
Room temperature (°C)	25.12 (1.14)	25.53 (1.11)	25.35 (1.06)	25.18 (1.04)	24.30 (0.56)
Humidity (%)	41.21 (6.38)	41.06 (7.40)	39.68 (6.24)	41.79 (6.50)	32.70 (4.37)

The results of each physiological parameter obtained from the treated leg are reported below.

6.4.1 Skin temperature results

Figures 6.7 (a–b) shows the mean (SD) SKTs recorded at three time points and the percentage changes of mean. Figures 6.7 (c–g) shows the individual SKT responses at the three time points and the individual percentage changes in SKT (from baseline to post treatment and from baseline to the 20-minute follow-up) within the three actively treated groups (CRMRF high, CRMRF low and PSWT high).

For SKT of the treated side, a 4*3 (intervention, time) repeated measures ANOVA revealed a significant main effect for the intervention (the applied dose between CRMRF high, CRMRF low, CRMRF placebo and control groups) [F (3, 48) = 29.545, $p < 0.001$, observed power = 1.00]; for the time (pre, post and follow-up) [F (2, 32) = 8.458, $p = 0.001$, observed power = 0.95]; and a significant interaction between the intervention and time [F (2.997, 47.952) = 62.261, $p < 0.001$, observed power = 1.00]. Therefore, the applied dose made a significant difference to the observed SKT changes and there was a significant overall difference between the pre, post and follow-up data. There was no significant difference between the baseline SKTs of the four groups.

In the five-group analysis (15 participants; repeated measures ANOVA), similar results were obtained for all the above comparisons in terms of significance values (all $p < 0.001$). However, the baseline SKT of the PSWT high group was significantly lower compared to the other four groups [F (4, 56) = 10.341, $p < 0.001$].

Within the CRMRF high group there was a significant rise in SKT from baseline to post treatment [F (1, 16) = 129.695, $p < 0.001$, $r = 0.943$, observed power = 1.00] and a significant retention of this gained temperature at the 20-minute follow-up when compared to the baseline [F (1, 16) = 96.567, $p < 0.001$, $r = 0.926$, observed power = 1.00]. A similar significant response, although less strong was noted from baseline to post [F (1, 16) = 5.404, $p = 0.034$, $r = 0.502$, observed power = 0.589] and from baseline to the 20-minute follow-up [F (1, 16) = 5.901, $p = 0.027$, $r = 0.519$, observed power = 0.626] also in the CRMRF low group. No meaningful changes were noted in the temperature recordings of either placebo or control groups. In the PSWT high group although a significant rise in SKT was noted from baseline to post treatment [F (1, 14) = 146.312, $p < 0.001$, $r = 0.955$, observed power = 1.000], there was no significant retention of this gained temperature at the follow-up.

The key results of planned comparisons (contrasts) between all five groups are reported in Table 6.5. Effect sizes (r) and the results of a post-hoc power analysis using G*Power (Version 3.1) are also reported (where the interaction was significant). As it can be noted, both the high and low dose CRMRF groups differed significantly from both the placebo and

control groups, but the high dose group response was significantly stronger than that of the low dose group. There was no meaningful difference between the placebo and control groups apart from the fact that placebo group temperature decreased, potentially due to the application of the cold conductive cream. The overall SKT responses within the PSWT high group was less strong compared to the CRMRF high and low groups, but stronger (except for follow-up) than that in the placebo and control groups.

Table 6.5: Key results from the planned comparisons (contrasts) on the SKT responses across five experimental groups. Comparisons involving PSWT high group are based on 15 participants, and all others are based on 17 participants.

Comparison		F-ratio	Significance value (*p*)	Effect size (*r*)	Power (P)
CRMRF high vs.	CRMRF low	9.270	0.008	0.606	0.881
	CRMRF placebo	83.807	< 0.001	0.916	1.000
	Control	31.979	< 0.001	0.816	0.991
	PSWT high	61.449	< 0.001	0.902	0.994
CRMRF low vs.	CRMRF placebo	27.270	< 0.001	0.794	0.987
	Control	11.255	0.004	0.643	0.917
	PSWT high	29.583	< 0.001	0.824	0.982
PSWT high vs.	CRMRF placebo	0.019	0.892 (NS)	0.037	
	Control	12.611	0.003	0.688	0.918

Figure 6.7a: The mean (SD) SKT responses showing the baseline, post treatment and 20-minute follow-up data from all five groups.

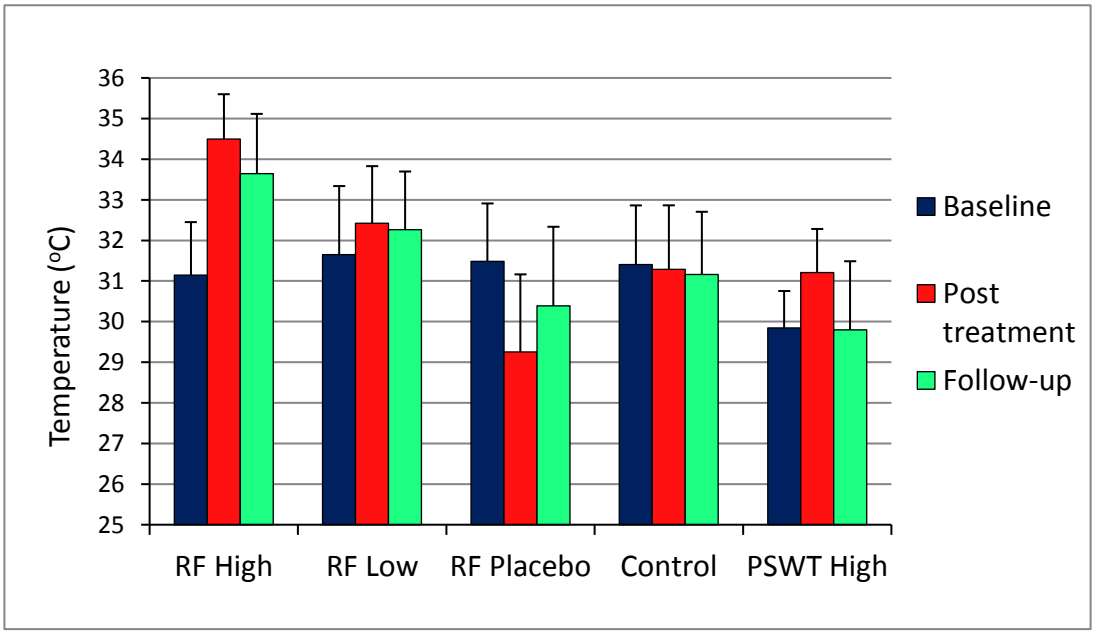


Figure 6.7b: Percentage change of the mean SKT from the baseline to post treatment and from the baseline to the 20-minute follow-up for all five groups.

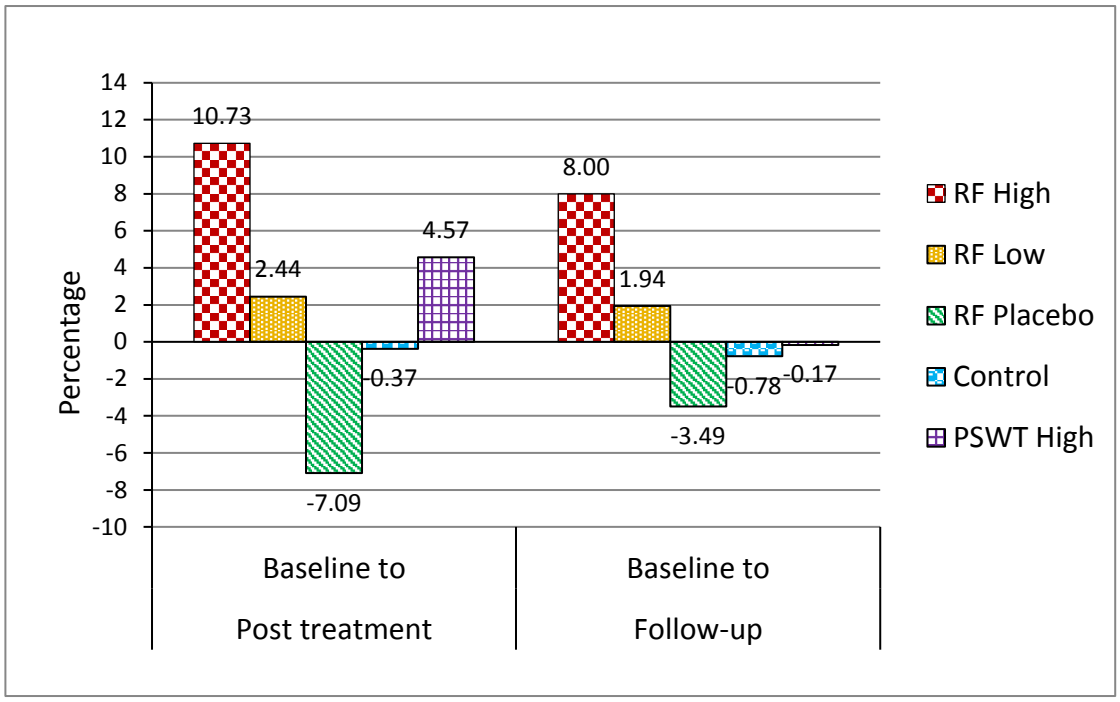


Figure 6.7c: SKT data from the three active groups showing individual responses at the baseline

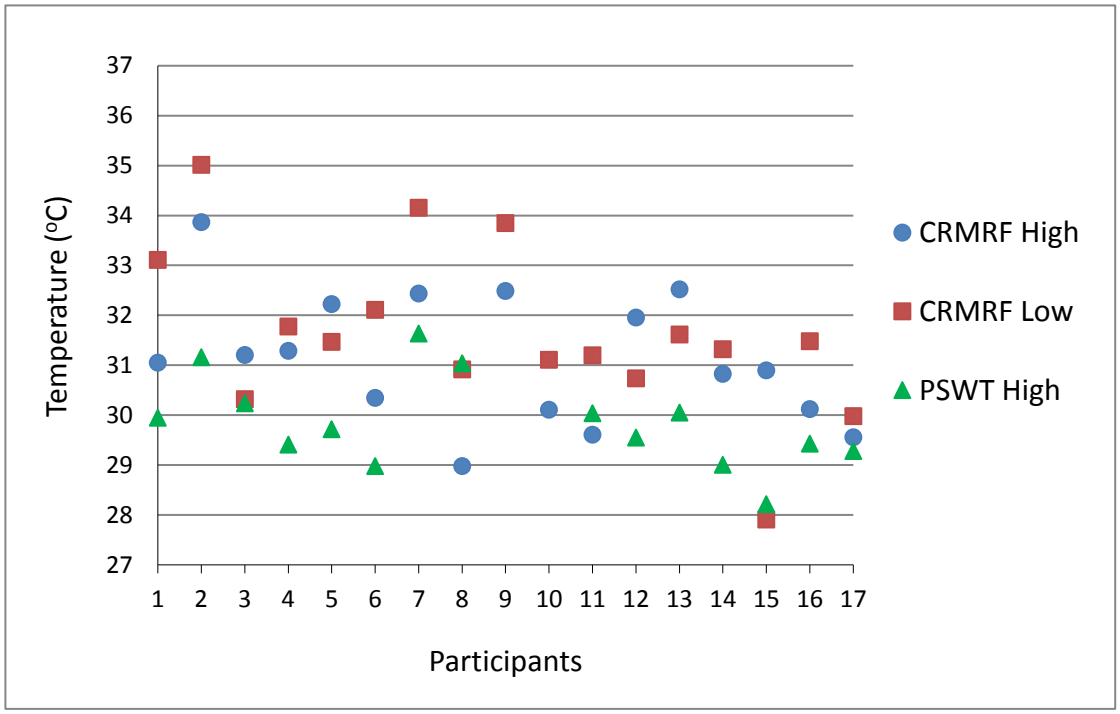


Figure 6.7d: SKT data from the three active groups showing individual responses at post treatment

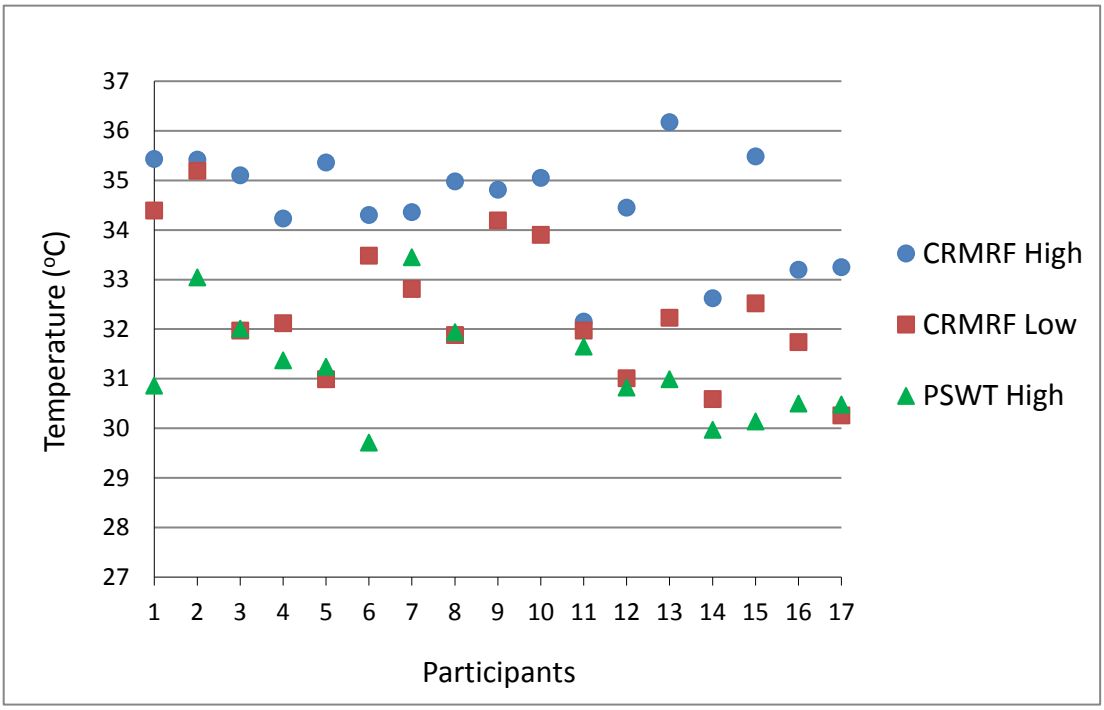


Figure 6.7e: SKT data from the three active groups showing individual responses at the 20-minute follow-up

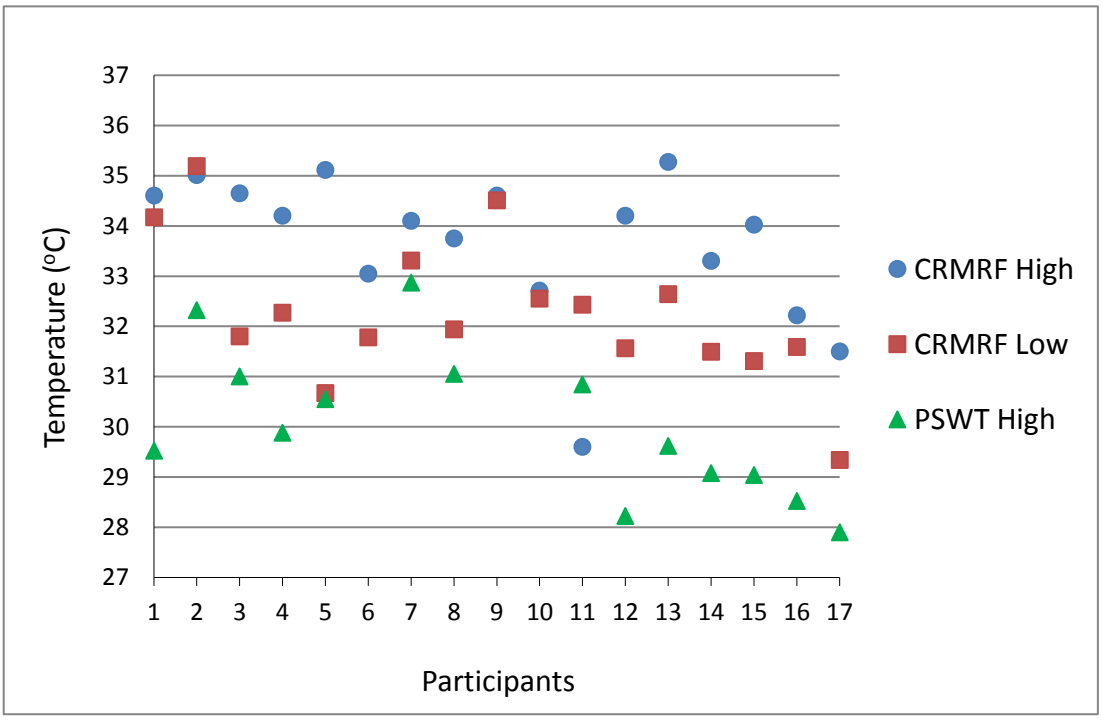


Figure 6.7f: SKT data from the three active groups showing individual percentage changes from the baseline to post treatment

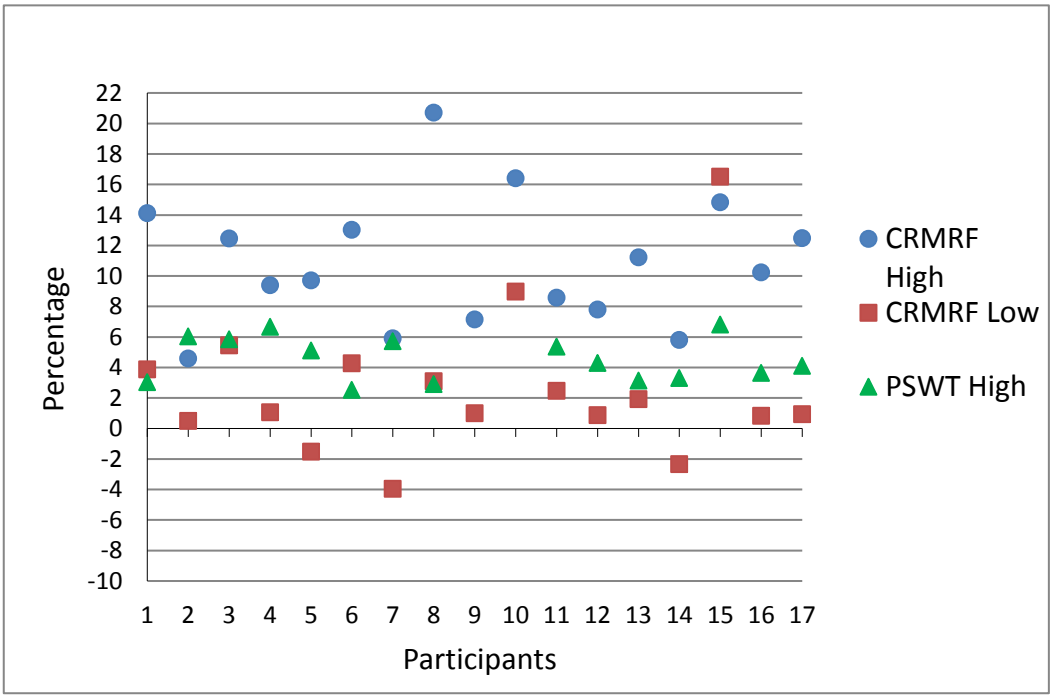
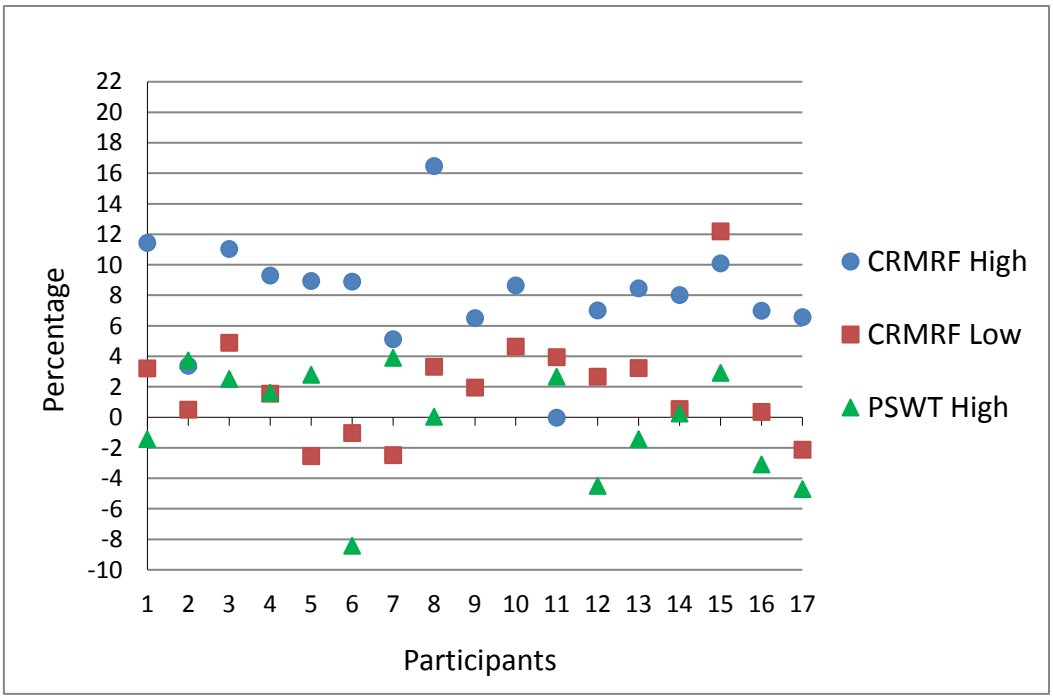


Figure 6.7g: SKT data from the three active groups showing individual percentage changes from the baseline to the 20-minute follow-up



6.4.2 Skin blood flow results

Figures 6.8 (a–b) shows the mean (SD) SBFs recorded at three time points and the percentage changes of the mean. Figures 6.8 (c–g) shows individual SBF responses at the three time points and the individual percentage changes (from baseline to post treatment and from baseline to the 20-minute follow-up) within the three actively treated groups.

Analysis of the SBF data was performed using Friedman's two-way ANOVA by ranks, since several data sets broke the assumptions of normality (Shapiro-Wilk). In the four-group analysis (excluding the PSWT high group), a significant main effect for the interventions was found at the post treatment stage [χ^2 (3) = 27.494, $p < 0.001$] and at the 20-minute follow-up [χ^2 (3) = 31.047, $p < 0.001$]. Therefore, the applied dose made a significant difference to the observed SBF changes. There was no significant difference between the baseline SBFs of the four groups.

In the five-group analysis (15 participants per group; Friedman's two-way ANOVA), similar results were obtained for both the above comparisons in terms of significance values (all $p <$ 0.001). There was no significant difference in SBF between the five groups at baseline.

As the participants rested on the plinth over the course of the experiment, it was noted that the SBF went up marginally and somewhat plateaued after the first 20–30 minutes (based on the control group data) even after the initial stabilisation period (20 minutes). Within the CRMRF high group there was a substantial and highly significant rise in SBF from baseline to post treatment (Friedman, $p < 0.001$, $r = -0.780$, 1.000 P), with almost all that gain being retained at the 20-minute follow-up (Friedman, $p = 0.001$, $r = -0.632$, 0.970 P). A significant change, although less strong (like the SKT response), from baseline to post (Friedman, $p =$ 0.006, $r = -0.529$, 0.904 P) and a significant retention at the 20-minute follow-up (Friedman, $p = 0.001$, $r = -0.618$, 0.964 P) was noted also in the CRMRF low group. No such meaningful changes were noted in the SBF recordings of either CRMRF placebo or PSWT high groups.

The key results of pairwise comparisons (Friedman) between all five groups are reported in Table 6.6. Effect sizes (r) and the results of a post-hoc power analysis using G*Power (Version 3.1) are also reported (where the interaction was significant). Only the CRMRF high group differed significantly from the responses of other groups. Although the CRMRF low group showed a significant within group change (as detailed above), it appears that this change was not significantly higher than the random changes noted in the control group and is hence unlikely to be clinically meaningful.

Table 6.6: Key results from the planned comparisons (contrasts) on the SBF responses across five experimental groups. Comparisons involving PSWT high group are based on 15 participants, and all others are based on 17 participants.

Comparison		Test statistic	Adjusted significance value (*p*)	Effect size (*r*)	Power (P)	Test statistic	Adjusted significance value (*p*)	Effect size (*r*)	Power (P)
		At post treatment				At follow-up			
CRMRF high vs.	CRMRF low	1.412	0.009	0.546	0.920	1.324	0.017	0.513	0.888
	CRMRF placebo	2.235	< 0.001	0.866	1.000	2.294	< 0.001	0.889	1.000
	Control	1.647	0.001	0.638	0.972	1.912	< 0.001	0.740	0.993
	PSWT high	3.267	< 0.001	1.033	1.000	3.000	< 0.001	0.949	1.000
CRMRF low vs.	CRMRF placebo	0.824	0.377 (NS)	0.319		0.971	0.170 (NS)	0.376	
	Control	0.235	1.000 (NS)	0.091		0.588	1.000 (NS)	0.228	
	PSWT high	1.667	0.039	0.527	0.866	1.333	0.209 (NS)	0.422	
PSWT high vs.	CRMRF placebo	0.867	1.000 (NS)	0.274		0.467	1.000 (NS)	0.148	
	Control	1.533	0.079 (NS)	0.485		0.867	1.000 (NS)	0.274	

Figure 6.8a: The mean (SD) SBF responses showing the baseline, post treatment and 20-minute follow-up data from all five groups

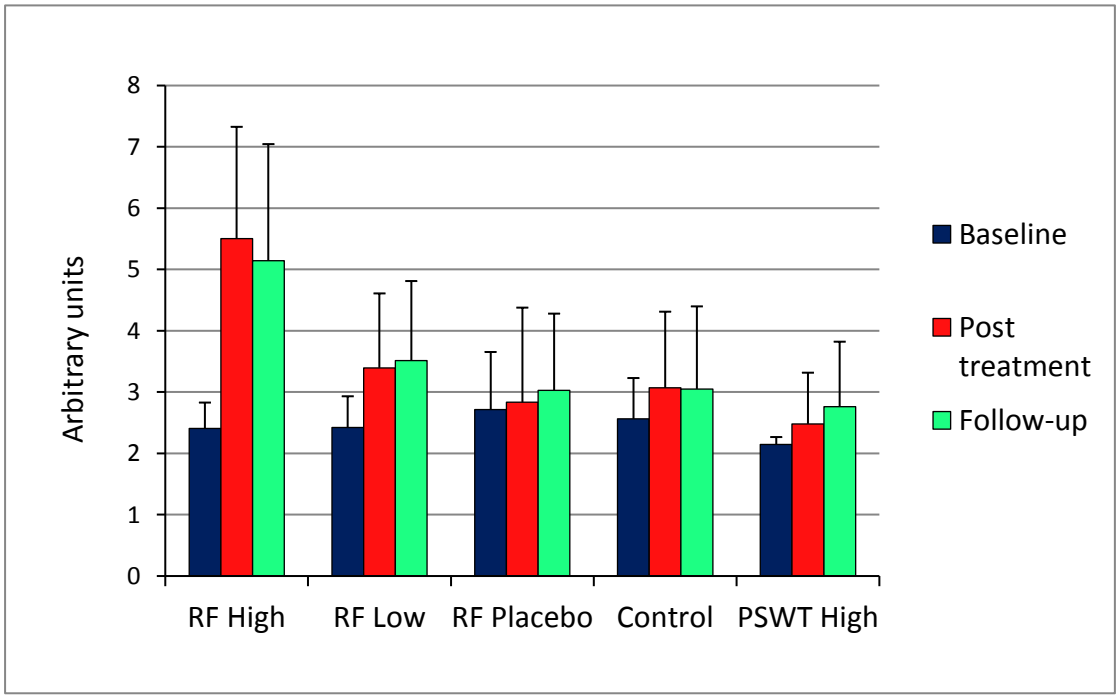


Figure 6.8b: Percentage change of the mean SBF from the baseline to post treatment and from the baseline to the 20-minute follow-up for all five groups

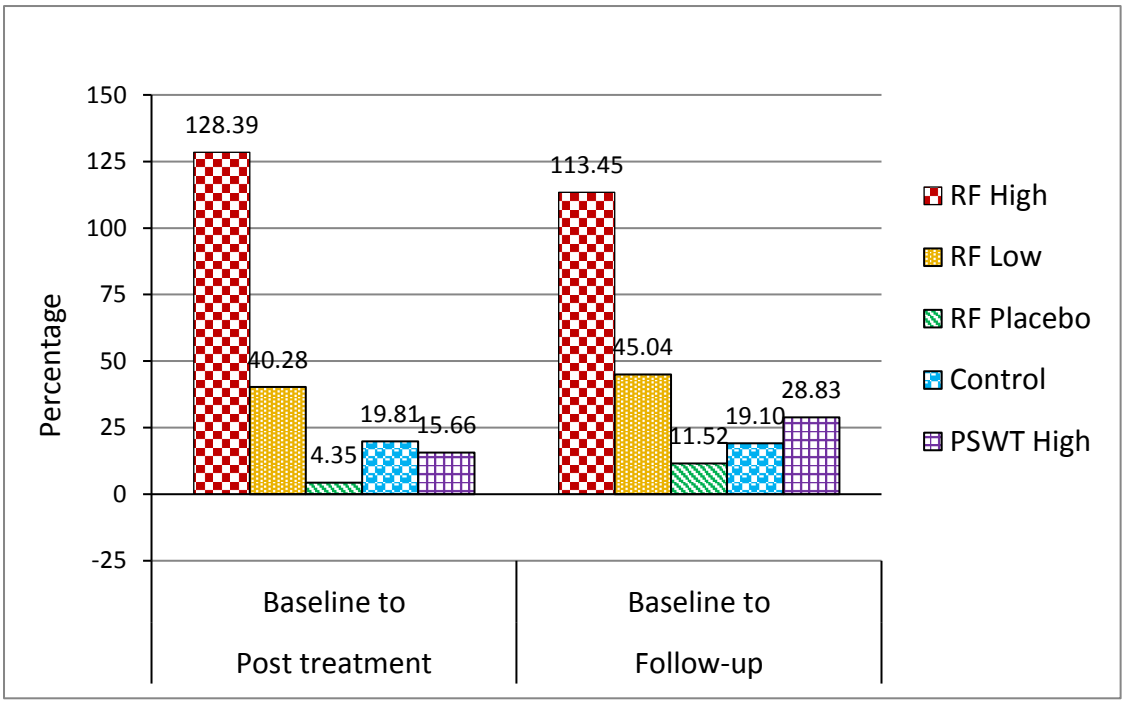


Figure 6.8c: SBF data from the three active groups showing individual responses at the baseline

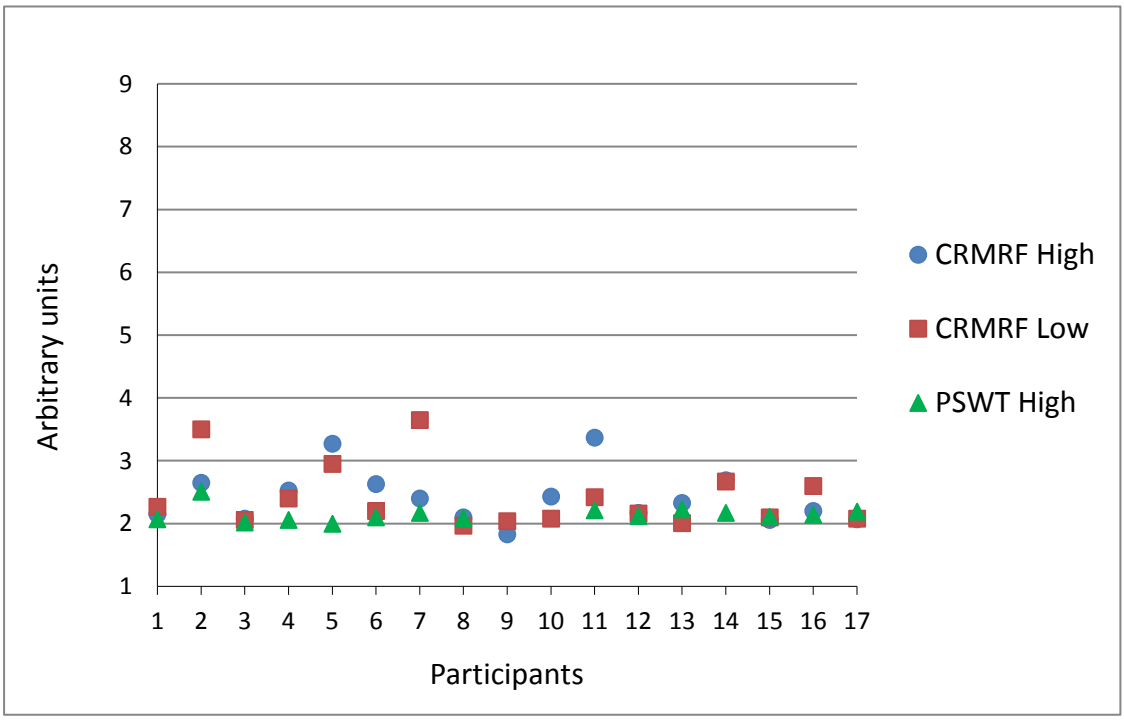


Figure 6.8d: SBF data from the three active groups showing individual responses at post treatment

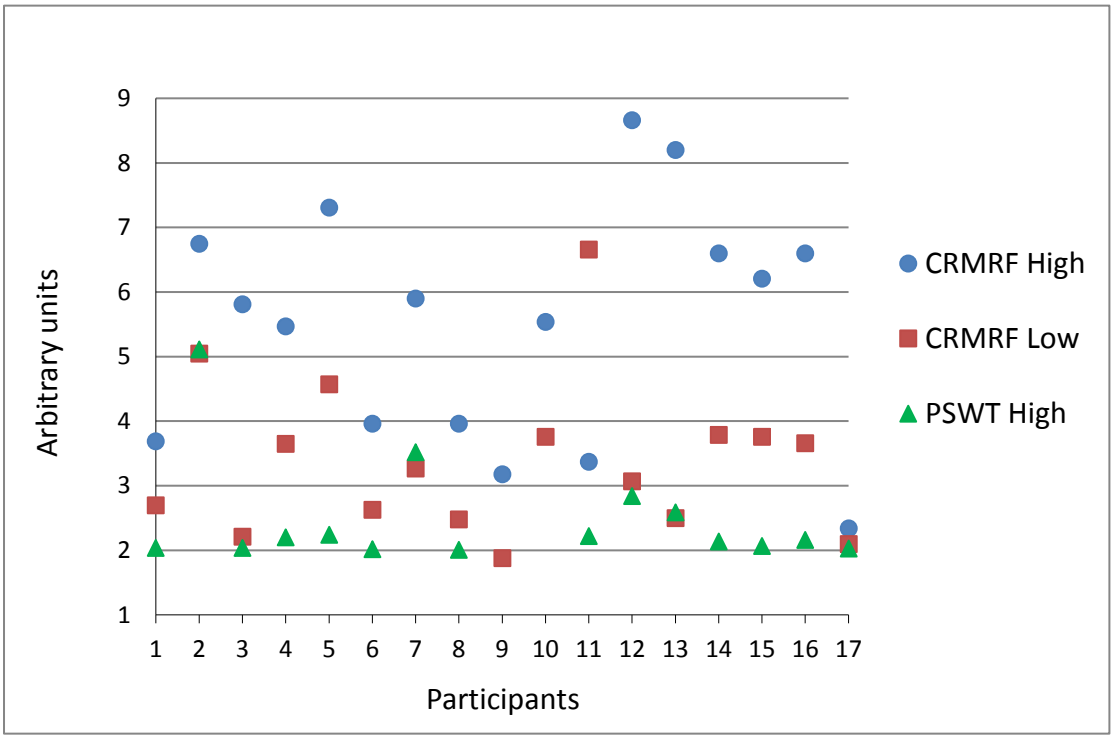


Figure 6.8e: SBF data from the three active groups showing individual responses at the 20-minute follow-up

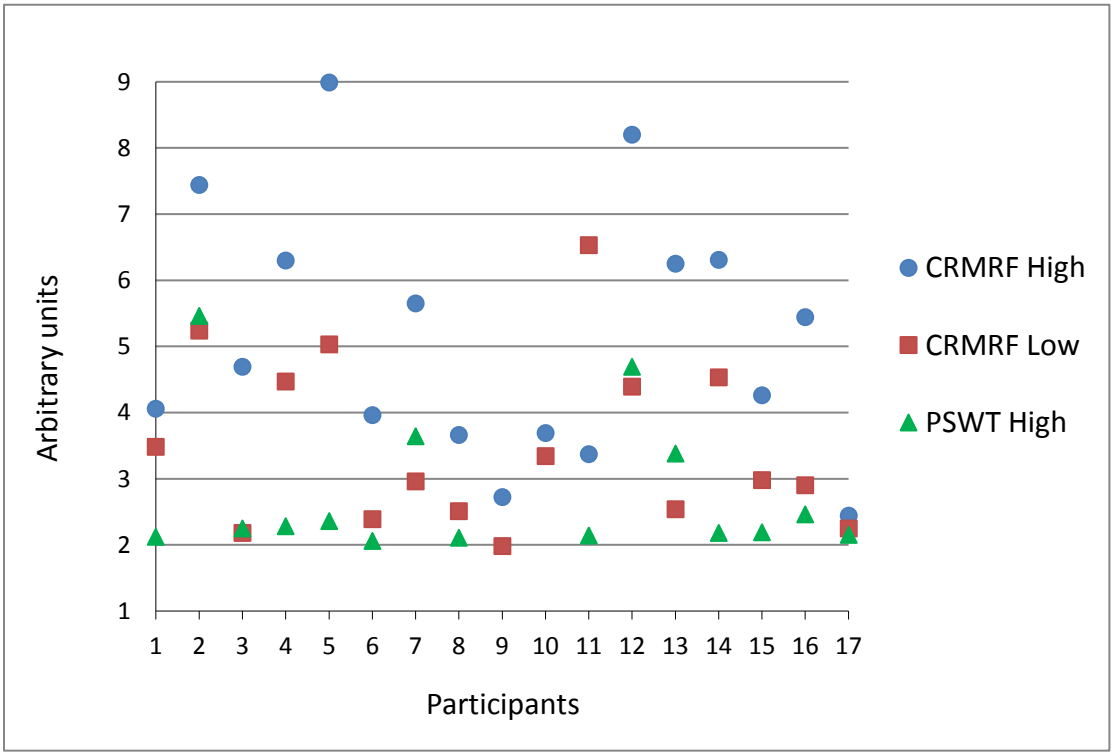


Figure 6.8f: SBF data showing individual percentage changes from the baseline to post treatment

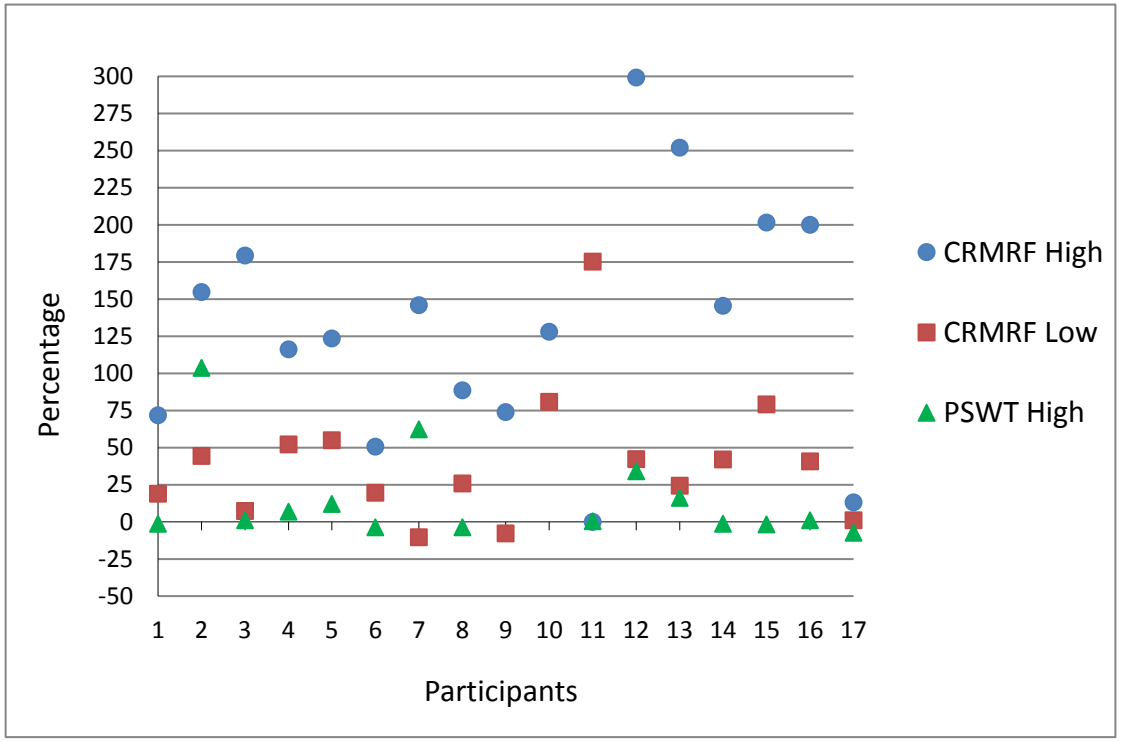
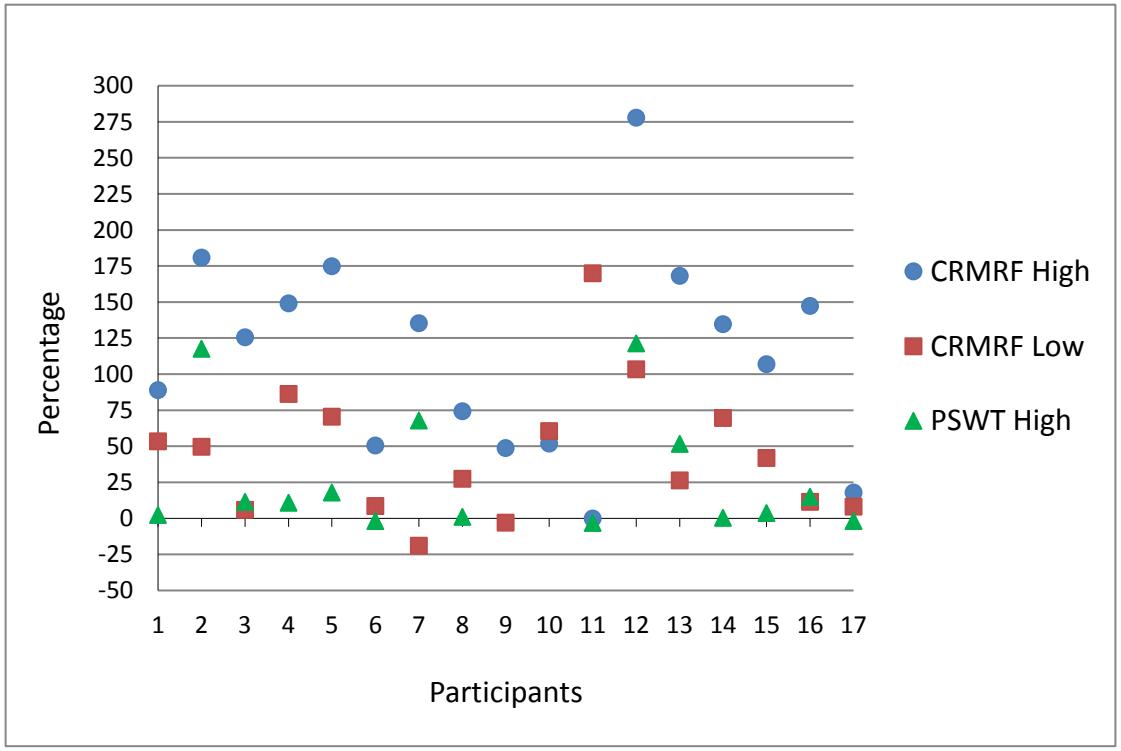


Figure 6.8g: SBF data showing individual percentage changes from the baseline to the 20-minute follow-up

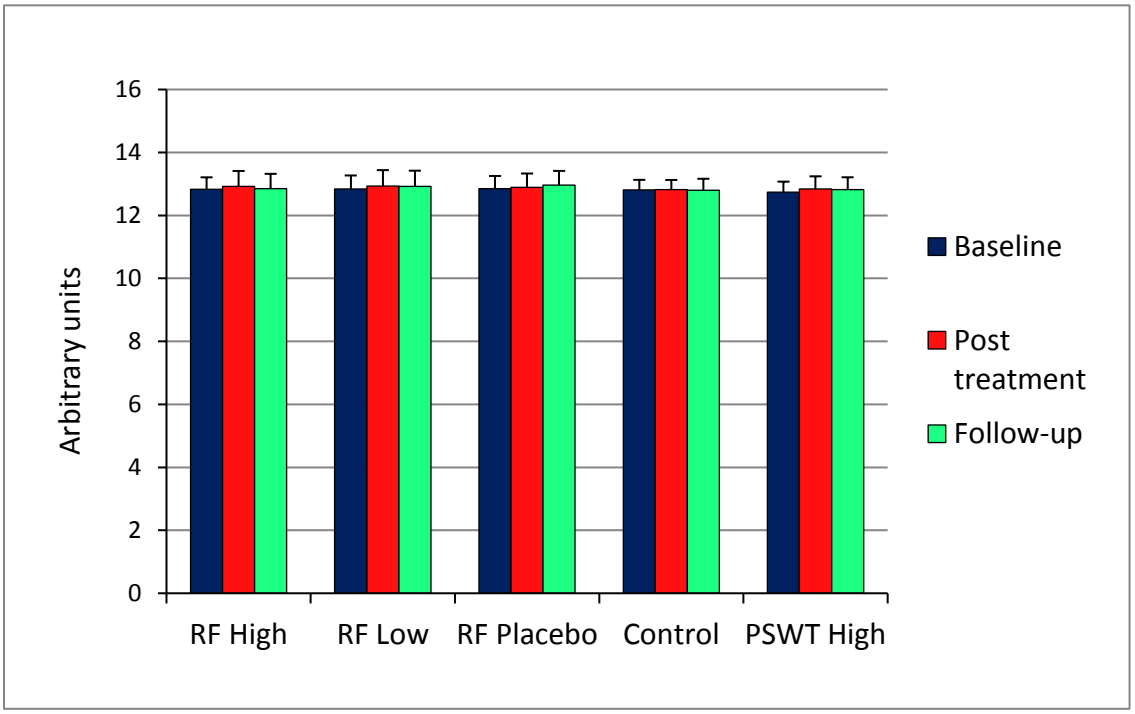


6.4.3 Nerve Conduction Velocity results

For NCV of the treated side, the four-group analysis was performed using a Friedman's two-way ANOVA by ranks, since several data sets broke the assumptions of normality (Shapiro-Wilk), while the five-group analysis was performed using 4*3 (intervention, time) repeated measures ANOVA. No significant main effects, interactions or changes within groups were noted for any of the intervention groups for any time point in either analysis. Figure 6.9 shows the mean (SD) NCVs recorded at the three time points for all five groups.

A post-hoc power analysis using G*Power (Version 3.1) was undertaken for the SKT and SBF main effects using the data (four groups only) obtained from 14 participants (not 15 participants as originally planned, since one participant had withdrawn after attending two sessions). The analysis showed that sufficient power had been achieved (SBF 0.99; SKT 1.00). Hence the recruitment was stopped. Three more participants who had already started went on to complete the study, taking the total sample to 17 participants. The final analysis revealed that the overall power obtained for both the four-group (17 participants) and the five-group (15 participants) analyses were '1.00' for SBF as well as SKT.

Figure 6.9: The mean (SD) NCV responses showing the baseline, post treatment and 20-minute follow-up data from all five groups



6.4.4 Blood flow volume

Figures 6.10 (a–b) shows and compares the mean (SD) blood flow volumes recorded at the two time points and the percentage changes of the mean, for all five groups. Figures 6.10 (c–e) shows and compares the individual blood flow volume responses at the two time points and the individual percentage changes (from baseline to post treatment) of the three active intervention groups (CRMRF high, CRMRF low and PSWT high). All data are represented in arbitrary units.

Analysis of the blood flow volume data was performed using Friedman's two-way ANOVA by ranks, since several data sets broke the assumptions of normality (Shapiro-Wilk). In the four-group analysis (excluding the PSWT group), a significant main effect for the interventions was found at the post treatment stage [χ^2 (3) = 13.659, p = 0.003]. Therefore, the applied dose made a significant difference to the observed changes in blood flow volume. At the baseline, the groups did not differ significantly, except for the control and placebo groups, which showed a significant difference between them (Friedman, p = 0.009).

In the five-group analysis (15 participants; Friedman's two-way ANOVA) that also included the PSWT group, similar result was obtained for the between-group comparison at the post treatment stage [χ^2 (4) = 20.000, p < 0.001]. There was no significant difference between any of the five groups at the baseline.

Within the CRMRF high group there was a substantial and highly significant rise in the flow volume from baseline to post treatment (Wilcoxon, p = 0.001, r = 0.60, 0.95 P). A significant increase, although less strong was also noted in the CRMRF low group (Wilcoxon, p = 0.006, r = 0.47, 0.84 P). No such meaningful changes were noted in the blood flow volume recordings of the other three groups.

The key results of pairwise comparisons (Friedman) between all five groups are reported in Table 6.7. Effect sizes and the results of a post-hoc power analysis using G*Power (Version 3.1) are also reported (where the interaction was significant). The CRMRF high group differed significantly from the responses of all the other groups except the CRMRF low group. The CRMRF low group only differed significantly from The PSWT group.

Table 6.7: Key results from the pairwise comparisons on blood flow volume responses across five experimental groups. Comparisons involving PSWT group are based on 15 participants, while all others are based on 17 participants.

Comparison		Test statistic	Adjusted significance value (*p*)	Effect size (*r*)	Power (P)
CRMRF high vs.	CRMRF low	0.353	1.000 (NS)	0.137	
	CRMRF placebo	1.176	0.047	0.456	0.815
	Control	1.412	0.009	0.547	0.920
	PSWT	2.067	0.003	0.654	0.961
CRMRF low vs.	CRMRF placebo	0.824	0.377 (NS)	0.319	
	Control	1.059	0.101 (NS)	0.410	
	PSWT	1.867	0.012	0.590	0.924
PSWT vs.	CRMRF placebo	0.600	1.000 (NS)	0.190	
	Control	0.467	1.000 (NS)	0.148	

Figure 6.10a: The mean (SD) deep blood flow volume responses showing the baseline and post treatment data from all five groups

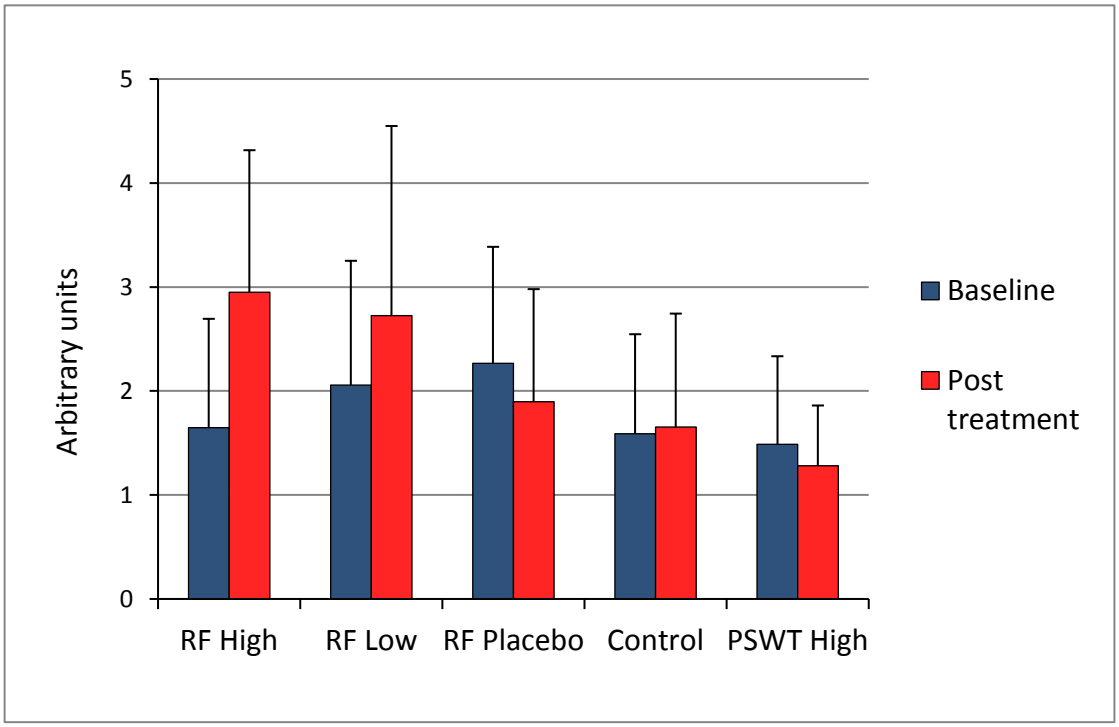


Figure 6.10b: Percentage change of the mean deep blood flow volume from the baseline to post treatment for all five groups

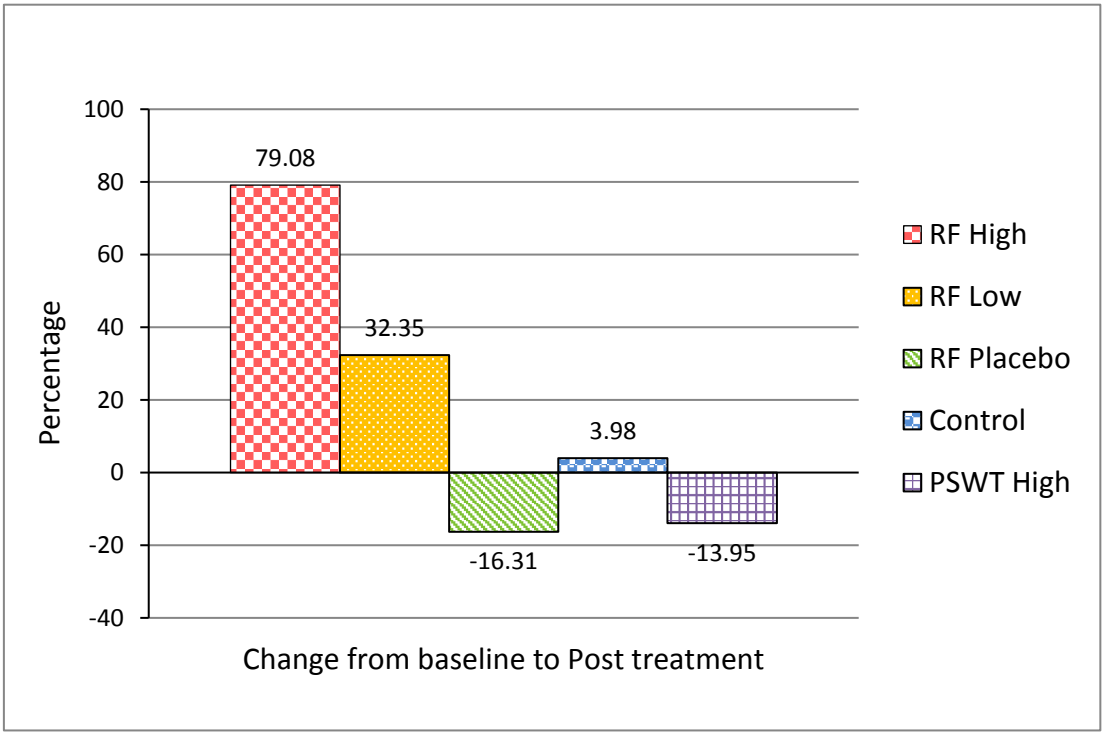


Figure 6.10c: Deep blood flow volume data from the three active groups showing individual responses at the baseline

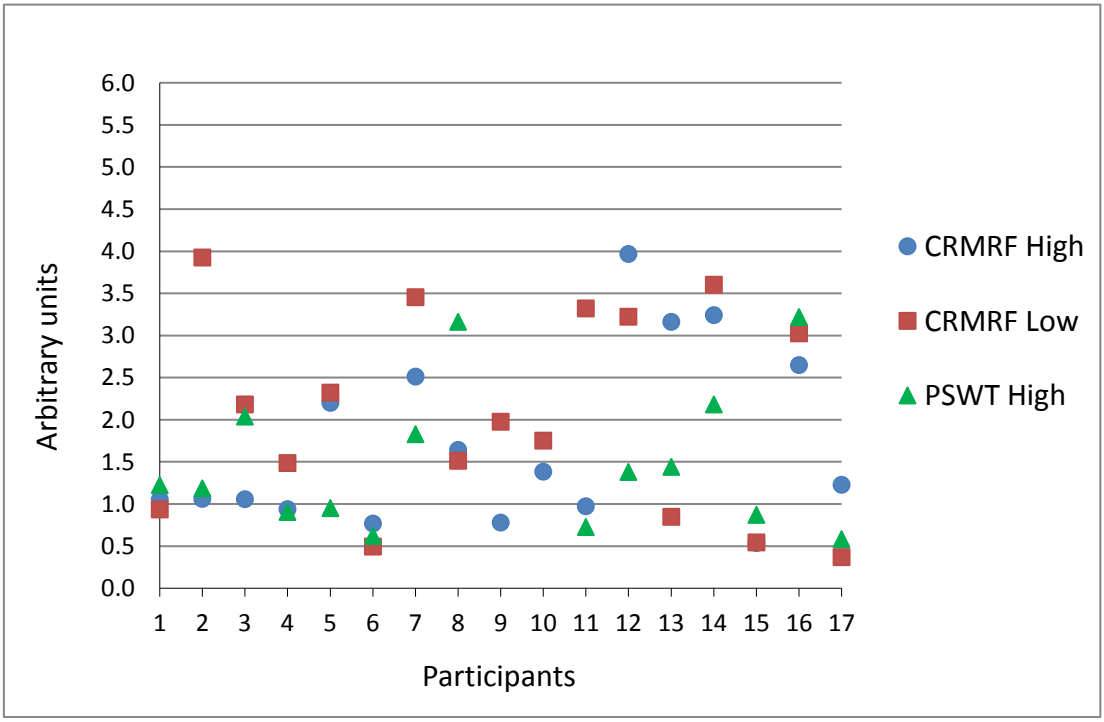


Figure 6.10d: Deep blood flow volume data from the three active groups showing individual responses at post treatment

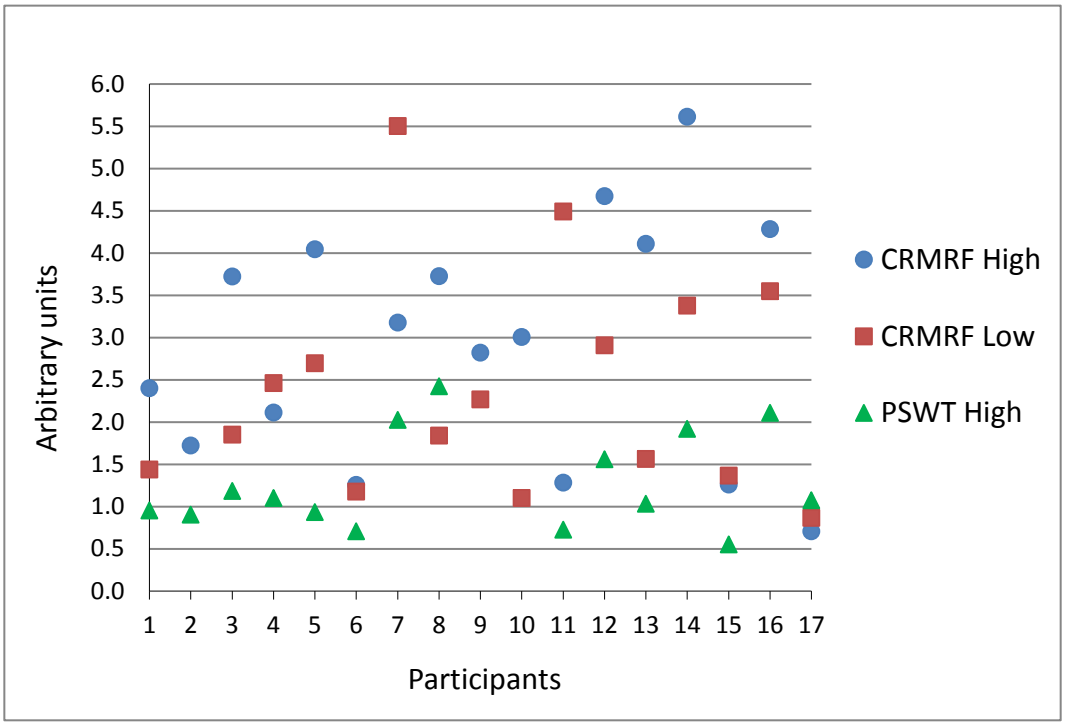
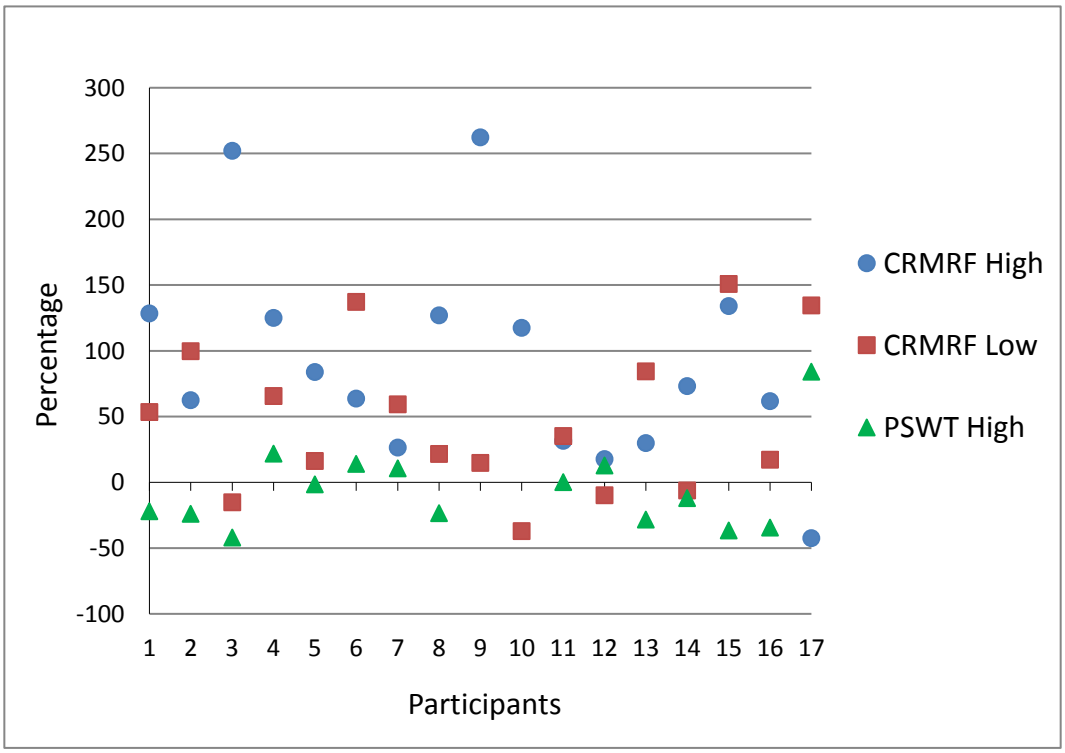


Figure 6.10e: Deep blood flow volume data from the three active groups showing individual percentage changes from the baseline to post treatment



6.4.5 Blood flow intensity

Figures 6.11 (a–b) shows and compares the mean (SD) blood flow intensities recorded at the two time points and the percentage changes of mean, for all five groups. Figures 6.11 (c–e) shows and compares the individual blood flow intensity responses at the two time points and the individual percentage changes (from baseline to post treatment) of the three active groups (CRMRF high, CRMRF low and PSWT high). All data are represented in arbitrary units.

Analysis of the blood flow intensity data was performed using Friedman's two-way ANOVA by ranks, since several data sets broke the assumptions of normality (Shapiro-Wilk). In the four-group analysis (excluding the PSWT group), a significant main effect for the interventions was found at the post treatment stage [χ^2 (3) = 14.788, p = 0.002]. Therefore, the applied dose made a significant difference to the observed changes in blood flow intensity. There was no significant difference between the baseline scores of the four groups.

In the five-group analysis (15 participants; Friedman's two-way ANOVA) that also included the PSWT group, similar result was obtained for the between-group comparison at the post treatment stage [χ^2 (4) = 18.240, p = 0.001]. There was no significant difference between any of the five groups at the baseline.

Within the CRMRF high group there was a substantial and highly significant rise in flow intensity from baseline to post treatment (Wilcoxon, p = 0.001, r = 0.55, 0.92 P). No such meaningful changes were noted in the blood flow intensity recordings of the other four groups.

The key results of pairwise comparisons (Friedman) between all five groups are reported in Table 6.8. Effect sizes and the results of a post-hoc power analysis using G*Power (Version 3.1) are also reported (where the interaction was significant). The CRMRF high group differed significantly from the responses of the control and PSWT groups. Although the CRMRF low group also showed a significant difference with the control group, this is not a meaningful change as there was no significant within group change in the CRMRF low group.

Table 6.8: Key results from the pairwise comparisons on the blood flow intensities across five experimental groups. Comparisons involving PSWT group are based on 15 participants, while all others are based on 17 participants.

Comparison		Test statistic	Adjusted significance value (*p*)	Effect size (*r*)	Power (P)
CRMRF high vs.	CRMRF low	0.471	1.000 (NS)	0.182	
	CRMRF placebo	0.824	0.377 (NS)	0.319	
	Control	1.647	0.001	0.638	0.972
	PSWT	2.000	0.005	0.632	0.951
CRMRF low vs.	CRMRF placebo	0.353	1.000 (NS)	0.137	
	Control	1.176	0.047	0.456	0.815
	PSWT	1.467	0.111 (NS)	0.464	
PSWT vs.	CRMRF placebo	0.800	1.000 (NS)	0.253	
	Control	0.067	1.000 (NS)	0.020	

Figure 6.11a: The mean (SD) deep blood flow intensity responses showing the baseline and post treatment data from all five groups

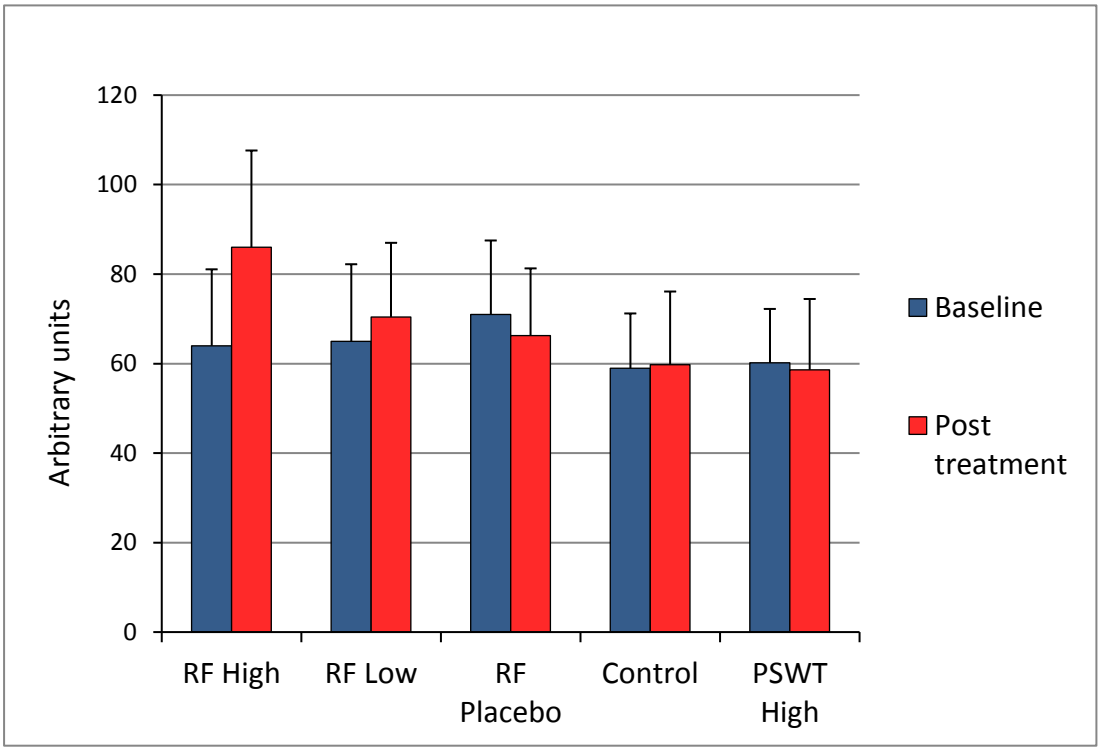


Figure 6.11b: Percentage change of the mean deep blood flow intensity from baseline to post treatment for all five groups

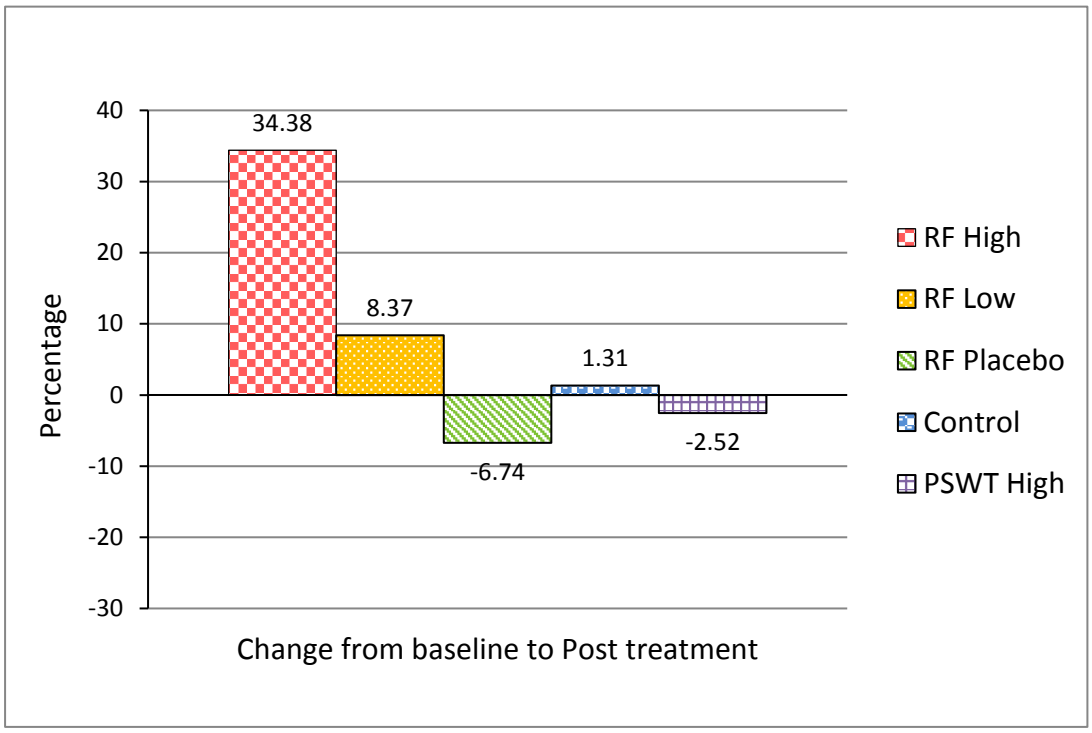


Figure 6.11c: Deep blood flow intensity data from the three active groups showing individual responses at the baseline

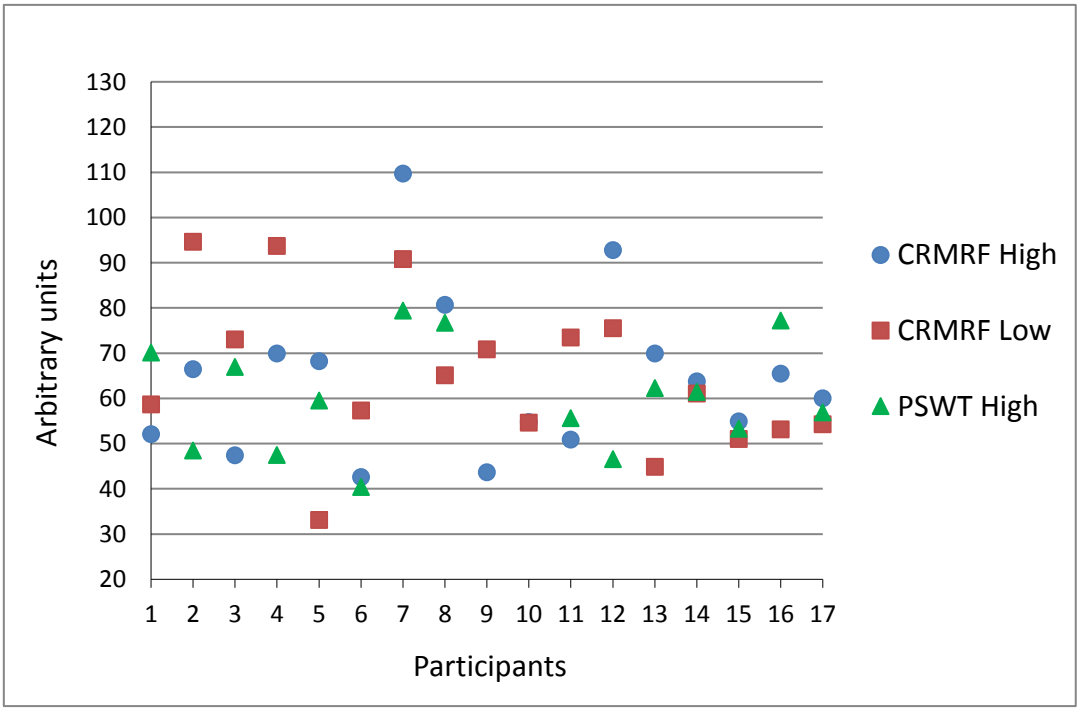


Figure 6.11d: Deep blood flow intensity data from the three active groups showing individual responses at post treatment

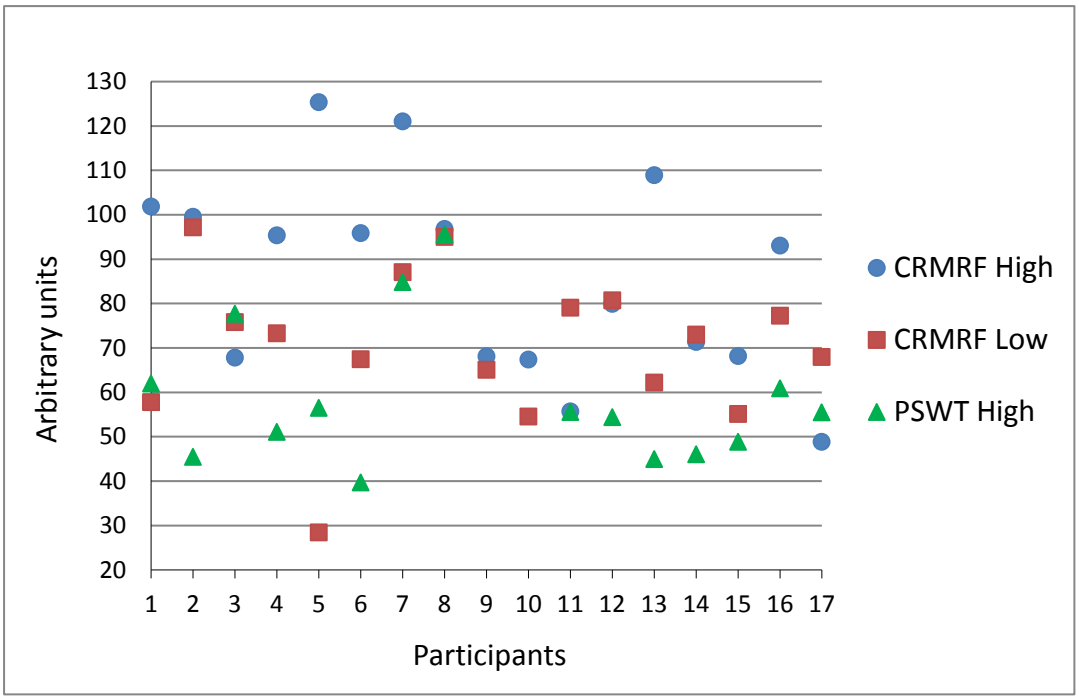
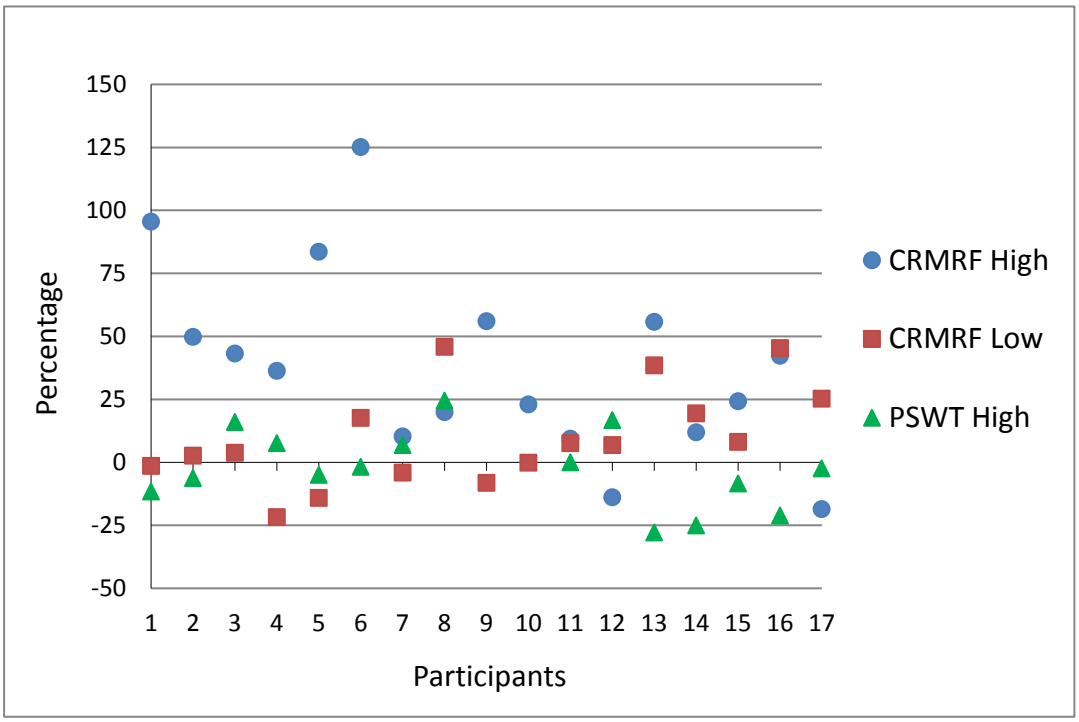


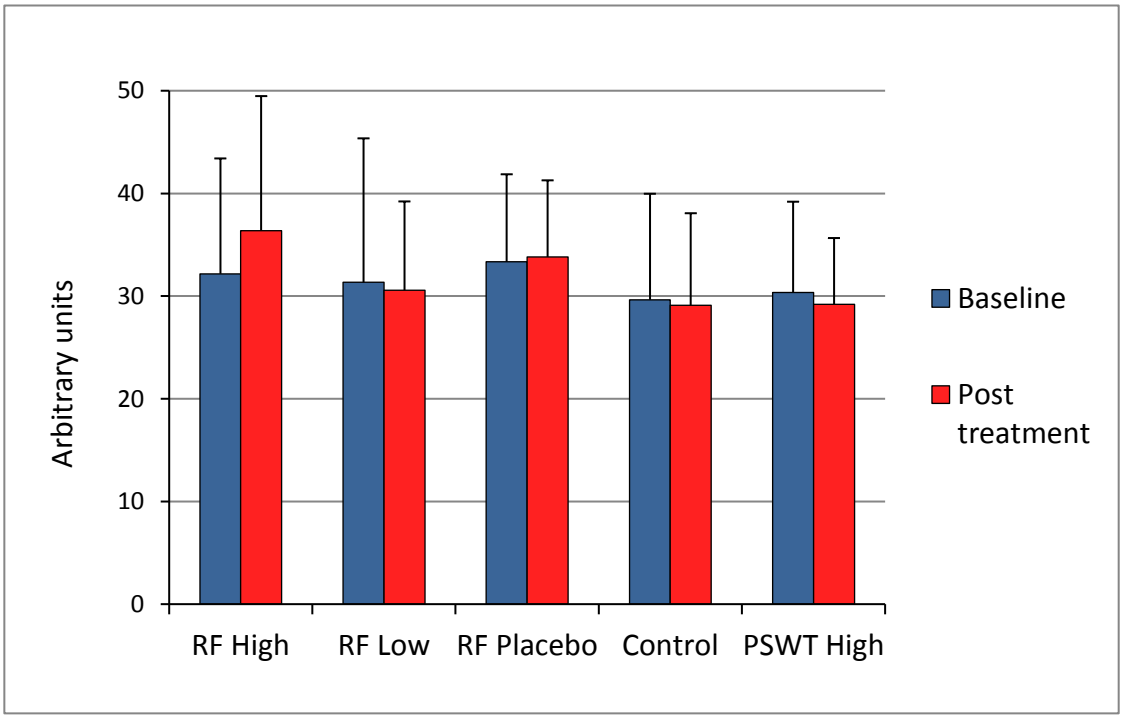
Figure 6.11e: Deep blood flow intensity data from the three active groups showing individual percentage changes from the baseline to post treatment



6.4.6 Blood flow velocity

For the blood flow velocity of the treated side, the four-group analysis was performed using Friedman's two-way ANOVA by ranks since several data sets broke the assumptions of normality (Shapiro-Wilk), while the five-group analysis was performed using a 4*2 (intervention, time) repeated measures ANOVA model. No significant main effects, interactions or changes within groups were noted for any of the intervention groups for any time point in either analysis. Figure 6.12 shows and compares the mean (SD) blood flow velocities (measured in arbitrary units) recorded at the two time points for all five groups.

Figure 6.12: The mean (SD) deep blood flow velocity responses showing the baseline and post treatment data from all five groups



6.4.7 Tissue extensibility

In total, six parameters pertaining to the volume (pixel count in kilo pixels) and intensity (colour intensity index) of the 'hard', 'intermediate' and 'soft' tissue types were compared in both four and five group analyses using either a 4*2 (intervention, time) repeated measures ANOVA model or by using Friedman's two-way ANOVA by ranks model depending on the distribution of data (Shapiro-Wilk). No significant main effects, interactions or changes within groups were noted for any of the intervention groups for any time point in either the four-group or the five-group analysis. Figures 6.13 (a–c) shows and compares the mean (SD) group data (measured in arbitrary units) recorded at the two time points for all five groups.

Figure 6.13a: The mean (SD) hardness volume and the mean (SD) hardness intensity measures of the tissues showing the baseline and post treatment data

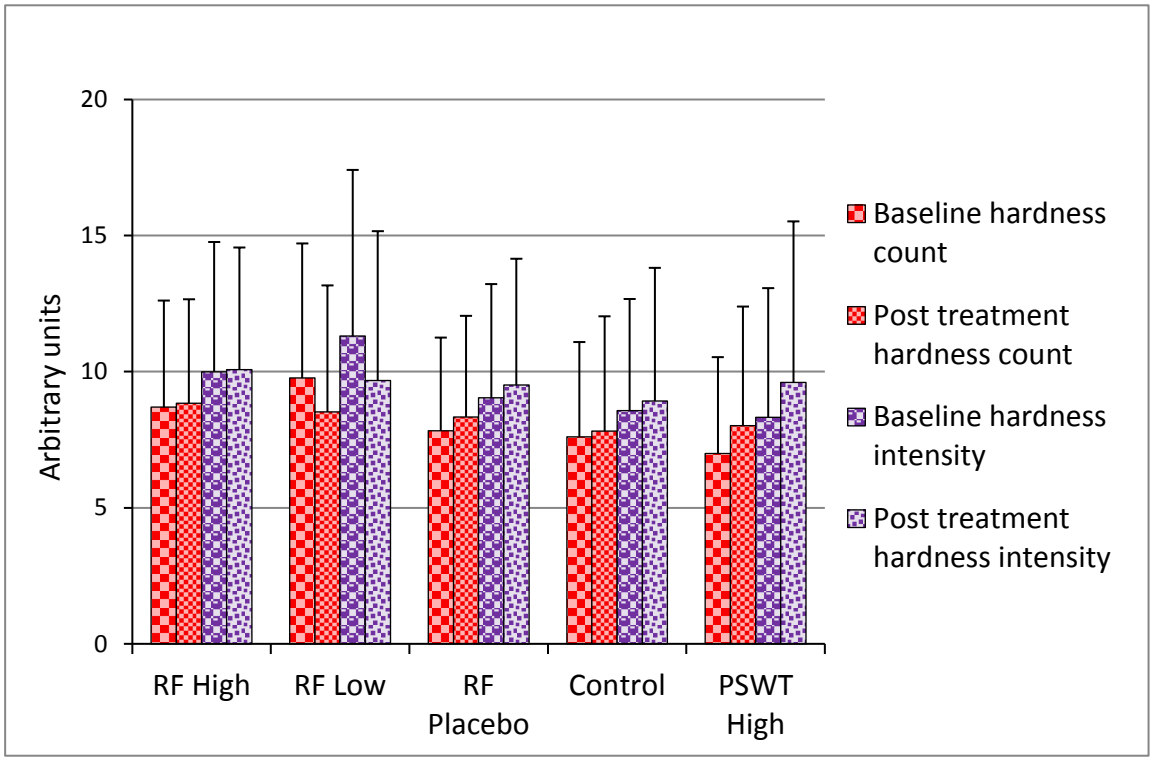


Figure 6.13b: The mean (SD) intermediate tissue volume and the mean (SD) intermediate tissue intensity measures of the tissues showing the baseline and post treatment data

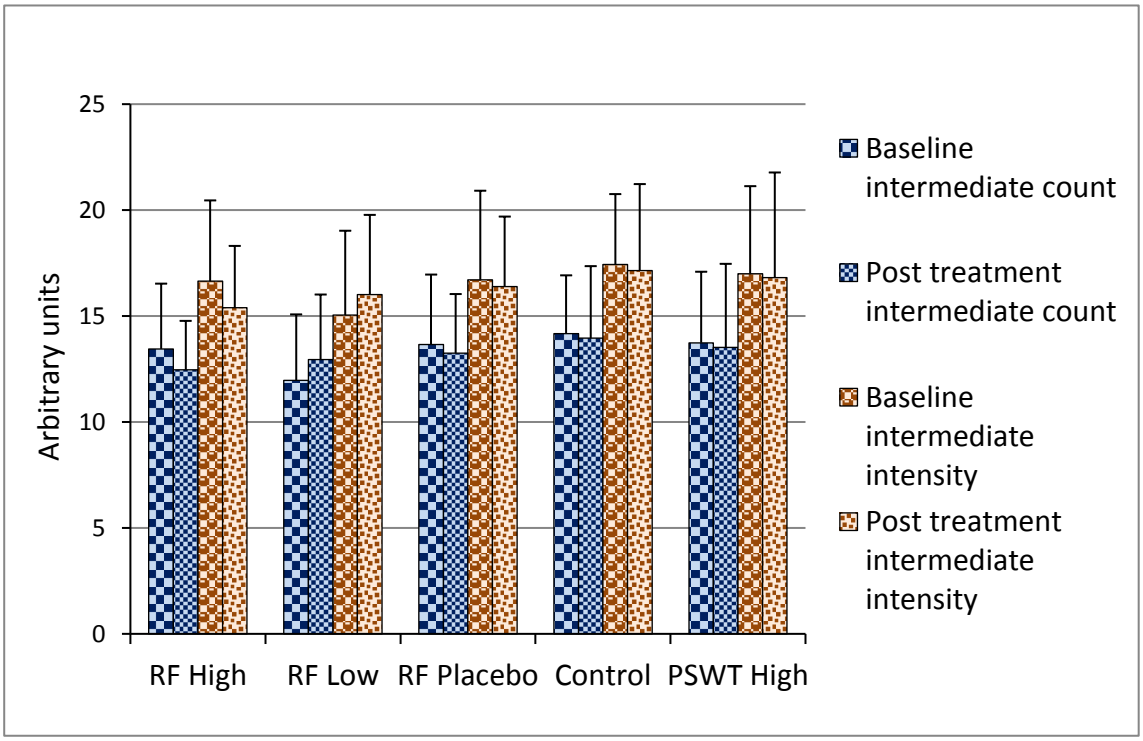
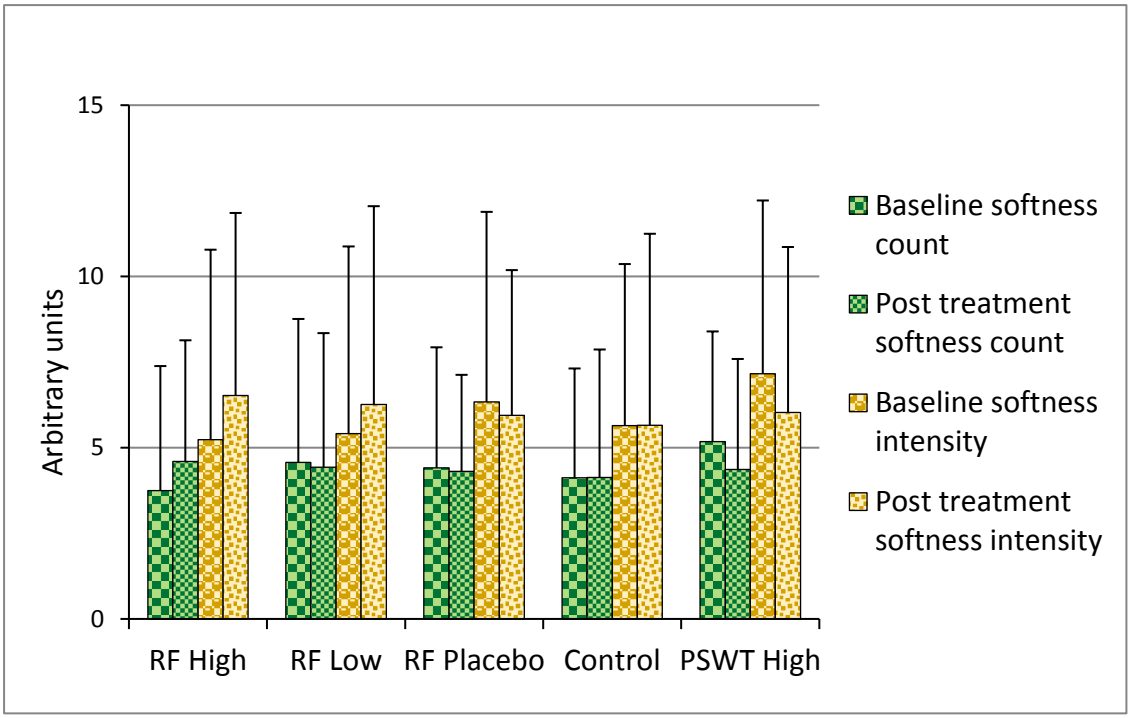


Figure 6.13c: The mean (SD) softness volume and the mean (SD) softness intensity measures of the tissues showing the baseline and post treatment data



6.4.8 Results from the control leg

There were no meaningful changes in the skin physiological results of any of the above parameters from the untreated control leg for any of the five groups. The group mean data are reported in figures 6.14 (a–c).

Figure 6.14a: The mean (SD) SKT responses obtained from the control leg

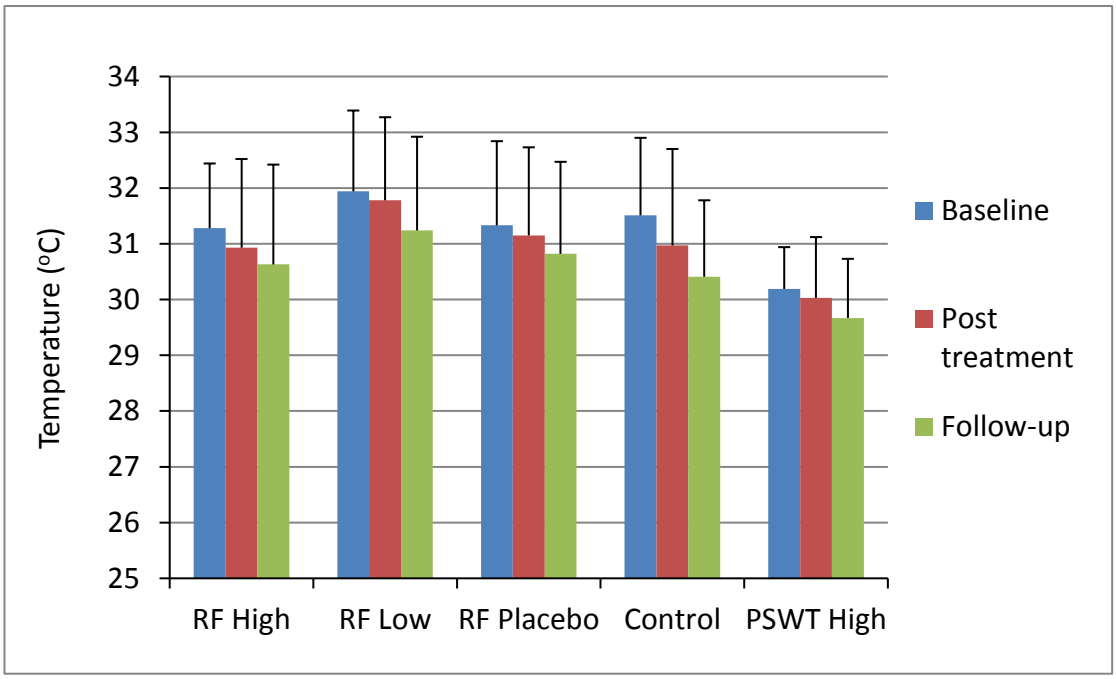


Figure 6.14b: The mean (SD) SBF responses obtained from the control leg

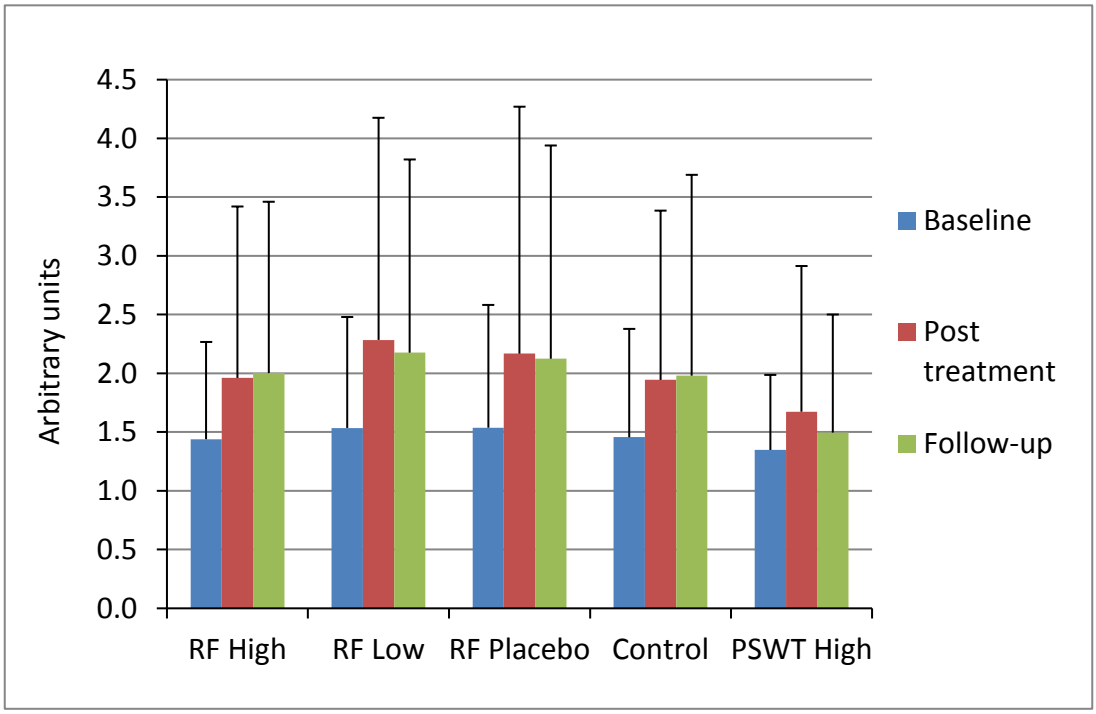
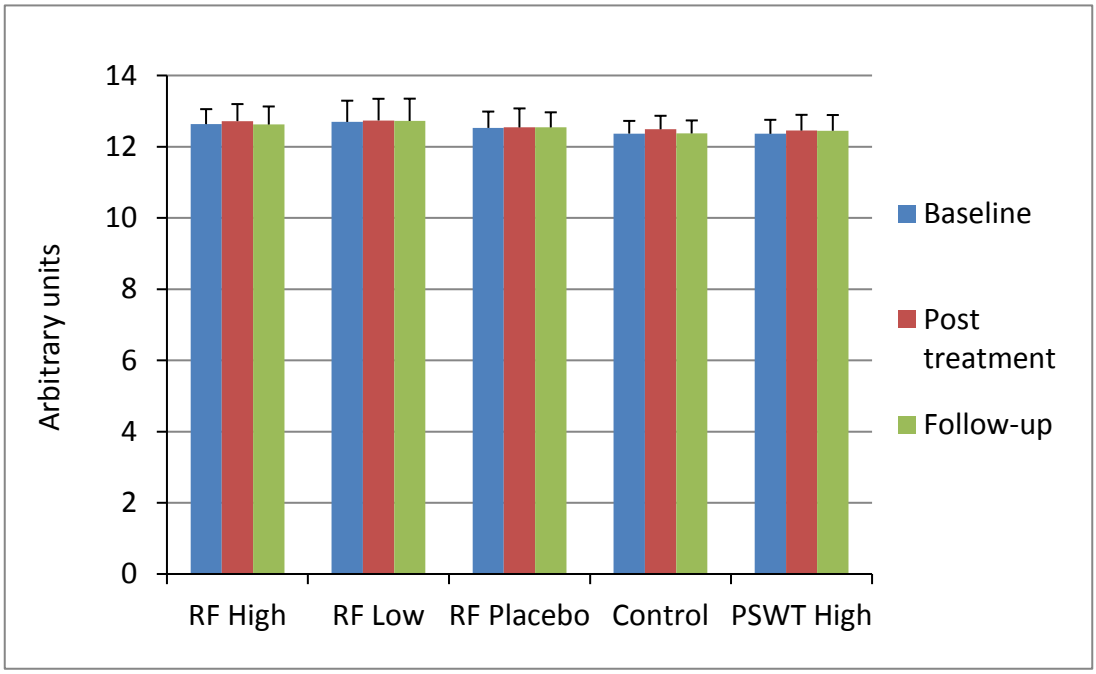


Figure 6.14c: The mean (SD) NCV responses obtained from the control leg



6.4.9 Other results

No statistically significant or meaningful variations were noted in the core temperature, pulse rate or blood pressure of any of the participants during any of the sessions (Table 6.9). The mean (SD) room temperatures varied between 24.3 (±0.56) ^{o}C and 25.53 (±1.11) ^{o}C in the

whole study. All room temperatures were within the thermoneutral zone of humans. The mean (SD) humidity varied between 32.70 (±4.37) % and 41.79 (±6.50)% (Table 6.10).

Table 6.9: The group mean (SD) data for core temperature, BP and PR

	Core temperature (^{o}C)	Cystolic BP (mmHg)	Diastolic BP (mmHg)	PR (per sec)
RF High	36.9 (0.12)	114 (11.27)	67 (7.98)	59 (10.34)
RF Low	36.9 (0.17)	115 (10.83)	67 (7.40)	61 (11.33)
RF Placebo	36.8 (0.26)	112 (11.04)	65 (5.25)	58 (10.14)
Control	36.9 (0.25)	113 (11.40)	65 (5.79)	59 (10.74)
PSWT High	36.8 (0.23)	118 (12.00)	70 (5.47)	59 (10.46)

Table 6.10: The group mean (SD) data for room temperature and humidity

	RF High	RF Low	RF Placebo	Control	PSWT High
Room temperature (^{o}C)	25.1 (1.14)	25.5 (1.11)	25.4 (1.06)	25.2 (1.04)	24.3 (0.56)
Humidity (%)	41 (6.38)	41 (7.40)	40 (6.24)	42 (6.50)	33 (4.37)

6.5 Discussion

The latter half of the past century saw a surge in research activity on the effects of RF-based therapy (within the frequency band of 30 kHz–30 MHz), mainly the continuous and pulsed SWTs. Numerous studies have looked at the RF effects in humans as well as in animal models. At the same time, there is a dearth of evidence to support either the physiological or the clinical effects of RF below shortwave frequencies, as explained in the literature review section. In contrast, numerous studies were identified on the shortwave frequencies.

Following up on the earlier study on the thermal build-up, decay and retention responses to the application of CRMRF (Chapter 5), the current study investigated the thermal, vascular, nerve conduction and tissue compliance responses. It studied both superficial tissue (skin) responses, the vascular responses from tissues up to a depth of 5 cm, and changes in compliance of tissues up to about 2 cm depth from the skin in response to the application of multiple doses of CRMRF therapy. In addition, a high dose application of PSWT was also employed to enable a comparison between the two types of RF treatments.

As mentioned, skin measures relating to blood flow, temperature and nerve conduction closely reflect changes to the body's thermoregulatory system.[1,21,22] Although many similar

physiological studies involving shortwaves have been reported over several decades,[77,80,85,86,187,192] this is the first such study carried out *in vivo* employing RF below the shortwave frequency band. Similarly, measures relating to deep blood flow and tissue compliance closely reflect the body's response to RF energy delivered to deeper tissues, with the RF potentially inducing a hyperthermic effect at depth.[83,194] Although similar studies involving shortwave conducted on either healthy subjects[19,77,91,195] or patients[196-198] have been reported before, this is the first study that employed RF below the shortwave frequency band and that investigated either deep blood flow or tissue compliance.

In contemporary literature, there is an ongoing discourse about the thermal versus non-thermal effects of RF. In this study, the authors did not aim to study the thermal – non-thermal distinction of CRMRF *per se*, but rather, a thermal – sub/minimally thermal difference was investigated. It is challenging to deliver a completely non-thermal dose of RF unless substantially low intensities are selected. This is especially the case with continuous mode RFs due to the prospect of heat accumulation (discussed below). Moreover, many of the physiological/clinical benefits of heating such as reduction of pain and inflammation or increasing tissue extensibility occur when temperatures are raised by 2–4 ^{o}C.[457,462] Although cell metabolism can be affected by changes in temperature that are as small as a fraction of a degree,[6] investigating such effects at the cellular level was beyond the scope of this study.

Traditionally in therapies where RF is used in continuous mode (e.g. CSWT) at relatively higher intensities, a fixed treatment dose is seldom used. Instead, the dosage is adjusted based on the perceived heat reported by the recipient. This is because in continuous mode exposure there is no sufficient 'washout period' to enable the person's circulatory system to drain the accumulated heat away from the area. This is often not the case for pulsed mode therapies (e.g. PSWT), where the 'off cycle' enables the body's circulatory system to dissipate most of the generated heat, thus minimising heat accumulation.[18] For this reason, it is problematic to compare a continuous mode application such as CRMRF with a pulsed mode application such as PSWT. Nonetheless, comparison of these two EPAs was done on the basis that PSWT is the most relevant comparator to CRMRF in contemporary therapy environment. The clinical use of CSWT has decreased significantly in the western world over the recent decades.[56,61]

In agreement with clinical practice, fixed RF doses were not delivered in this study except for PSWT. Data reported in Figure 6.6 shows considerable variation in the amount of energy received by individual participants among the high and low dose groups of CRMRF therapy. They reflect the differences in thermal perception and thermal tolerance among the participants. Although the participants often reported perceived heat from the CRMRF low dose, the treatment protocol allowed the delivery to be controlled so that the heat perception

was not globally apparent ('sub thermal' or otherwise 'minimally thermal' in a clinical context).

Contrary to CRMRF, the PSWT high group received a fixed dose of 47 W (highest MP allowed by the 'Ultramed' device for a 'monode' applicator) throughout the treatment. Although the plan was to reduce the dose if the participants reported undesirable heating, it turned out that the level of heating was only 'mild' at best. One of the potential drawbacks with conventional PSWT devices used in therapy is that there is no attached monitoring system, which can record the actual amount of RF energy delivered to the recipient. Without the need for a special conducting medium, shortwave units are known to emit stray radiations in the air.[18,452] Hence, some of the energy will be lost through scattering, making it difficult to focus the delivery in the area treated.[450,451]

Scattering also makes it challenging to estimate the specific absorption rate (SAR) of radiofrequency energy in the recipient for either intervention. It is challenging also to calculate the SAR for the treated area *per se* since the accurate mass of the area exposed to treatment cannot be determined. If it is assumed that there was zero scattering and that whole of the applied energy was absorbed by the target tissues, the mean (SD) whole body SAR can be estimated to be 0.60 (0.09) W/kg for CRMRF high group, 0.27 (0.07) W/kg for CRMRF low group, 0.04 (0.02) W/kg for CRMRF placebo group and 0.67 (0.10) W/kg for PSWT group. However, although the mean estimated SAR was lower in the CRMRF high group compared to the PSWT high group, its actual SAR is likely to have been higher than PSWT owing to lower scattering.

In therapy-related clinical practice, it is widely accepted that a thermal (high) dose of RF is not advisable for acute clinical conditions.[18] In other words, a substantial rise in tissue temperature is not desirable when there is an acute inflammatory response. For example, in an acute injury where swelling and/or haematoma are present, application of heat may exacerbate the symptoms by causing vasodilatation and thus increasing the interstitial fluid volume.[8] Literature suggests that a mild rise in tissue temperature of about 1 ^{o}C will help to relieve mild inflammation, but an increase of 2–4 ^{o}C is required to decrease pain and increase tissue extensibility.[457,462]

The greater physiological responses obtained from the CRMRF high dose group would make it potentially suitable for treating conditions giving rise to chronic pain and inflammation and in conditions where enhancement in tissue temperature and blood flow are a treatment aim, but unsuitable for application in an acute condition, where neither is recommended. The CRMRF low dose increased the local SKT marginally (yet significantly), but not the local SBF when compared to the placebo or control groups. Although there has been a significant rise in SBF within the low dose group, this is unlikely to have been clinically relevant as a similar change was also noted in the control group. This makes the

low dose application potentially suitable for treatment in acute conditions. Similar effects were also noted with the PSWT dose used in this study, where a mild increase in SKT was obtained without impacting on the SBF significantly. The modest response in SKT obtained from the PSWT high group and/or its lack of sustenance over the follow-up are consistent with the results of several past studies.[80,90,95,105]

Unlike for temperature rise, there are no recommendations in the literature as to what level of rise in blood flow (superficial or deep) will produce clinical benefits. The change in local blood flow secondary to RF application is a thermophysiological response, which is influenced commensurately by the level of rise in the local temperature and its depth of penetration.[8] The differences in deep blood flow responses secondary to exposure by various EPAs are mainly down to the differences in their ability to penetrate tissues. For example, the low penetrative infrared radiation has been shown to increase cutaneous circulation[183] whereas RF-based EPAs are more penetrative and can influence blood flow at various depths.[80,195] It appears from the results of this study though, that a mild increase in SKT of around 1 ^{o}C had no significant or sustained impact on the corresponding blood flow. However, since the measurements were taken only after the end of treatment, it is not known if the blood flow response was greater during the intervention.

Abnormalities in blood flow have an overarching relationship to pathological states and their treatment; hence an accurate measurement of blood flow without interfering with the process itself is imperative. A relative change in the local blood flow can characterise a variety of physiological states, either normal or pathological. For example, an increase in local blood flow may be noticed when there is tissue inflammation.[447] When localised RF treatment is given, monitoring of the blood flow can help in determining how much heating will occur in the skin as well as in the deeper tissues. Hence, it enables a protective mechanism ensuring that the heating is modulated and there is no undue hyperthermia in the tissues.[365]

The blood flow response to tissue heating at depth is more complex than it is to skin heating. Potentially there are multiple mechanisms for the increased human muscle blood flow in response to prolonged external local heating. Heat can cause direct vasodilatation and a reduction in the resistance of arterial walls.[8,341] The response at depth involves a balance between the direct vasodilatory effect of heat as well as the increased blood flow resulting from the increased muscle metabolic activity on one hand, and the vasoconstrictive effect and reduced blood flow induced by thermoregulation on the other hand.[8]

Both active vasoconstriction and vasodilatation can alter heat transfer and blood flow. When there is large alteration in blood flow (such as while exercising) there is also a large effect on heat transfer across the tissues. Anthropometric factors such as the level of subcutaneous fat also play a crucial role.[10,11] In chapter 5 the body fat percentage was shown to have a significant negative correlation to the amount of energy that could be absorbed. Additionally,

various bodily factors (internal factors) such as the efficiency of circulating blood in dissipating the generated heat, the anatomical characteristics of the area treated (size and shape of tissue), the thermal conductivity and thermal capacity of tissues absorbing the energy (impedance), the rate of energy absorption and the rate of metabolism in the treated tissues also determine the thermophysiological response.[8,462]

The size and geometry of treatment electrodes,[18] the thermal properties and conductivity of the coupling medium (in the case of CRMRF) and the strength of the electromagnetic field are the external factors that could influence the RF-tissue interaction. Large circular electrodes measuring 65 mm in diameter that were deemed appropriate for the size of the area treated were used as the active electrodes in this study. While the external factors discussed above remained constant for all five groups, the randomised crossover (repeated measures) design that was employed in this study helped to mitigate the internal factors.

This study shows that a high (thermal) dose of CRMRF can significantly increase the volume and intensity of blood flow in deeper tissues. Although less significant, even a low (minimally thermal) dose of CRMRF can induce increased blood volume at depth, but not the intensity of flow. Either dose of CRMRF failed to significantly increase the velocity of deep blood flow, although there was a 13% increase in velocity in the high dose group. In contrast to CRMRF, the high dose PSWT exposure failed to induce any such effects on the volume, intensity or velocity of blood flow in the deeper tissues. Since similar studies that employed RF at frequencies lower than shortwave have not been undertaken in the past, any comparison from the existing literature was unable to be drawn.

Mixed reports about the deep circulatory effect of PSWT are available from the literature.[19,90] Morrissey (1966)[90] reported that while irradiation of the calf muscles or abdomen using PSWT for 15 min at 40 W did not have any significant influence on the volume of blood flow in the leg, an 80 W exposure to the calf caused a significant increase in the blood flow. Similar increase in calf and foot blood flow after a 20-min abdominal exposure to PSWT at 65 W was reported by Silverman and Pendleton (1968), while a 15 W abdominal exposure did not have any significant impact. Other studies on deep circulatory effects of shortwave were conducted on CSWT.[77,79,88] Comparison between the effects of similar average doses of PSWT and CSWT on deep blood flow is also available.[19] The above results from PSWT studies indicate that when compared to CRMRF, a substantially higher dose of PSWT is required to increase blood flow volume at depth.

Previous research with shortwave has proposed that a tissue temperature rise more than 40 ^{o}C may be necessary to increase muscle blood flow.[96] Since deep tissue temperature was not monitored in this study, any such correlations cannot be drawn for the presented results. However, the tissue temperature in the current study is unlikely to have risen to levels above 40 ^{o}C. Even then a rise in both the volume and intensity of deep blood flow were noted with

the high dose CRMRF, while even the low dose CRMRF increased the volume of flow. Furthermore, the Doppler measurements were only able to be performed about six minutes after the end of the intervention (discussed below), which meant that any deep blood flow responses during and immediately after the treatment were not accounted for. Hence, it is proposed that unlike SWT, the CRMRF can increase and sustain the blood flow at depth at substantially lower tissue temperatures. It may also be proposed that the mechanism underpinning the blood flow response at depth secondary to the application of a low frequency RF such as the CRMRF is not purely thermophysiological, but rather the non-thermal mechanisms may also be involved.

Early work has shown that heat changes the behaviour of collagenous tissue making it more viscoelastic,[75,188] and reduces the spasm in muscles.[457] However, for a notable effect, the tissue temperature will need to be raised at least to the level of 40 ^{o}C.[8] Although not monitored, the deep tissue temperature achieved in this study is unlikely to have reached such high levels (as discussed above for blood flow), and hence failed to demonstrate any changes in tissue compliance when measured using Sonoelastography. However, like the Doppler measurements, Sonoelastography measurements were only able to be done several minutes (eight minutes on average) after the end of treatment (discussed below), thus any effect during or immediately after the intervention should clearly have been missed. Also, the participants were asymptomatic adults who had normal muscle tone, so it is unclear if any further reduction in muscle tone could have been achieved.

As expected the CRMRF high intervention more than doubled the SBF and sustained it significantly over the follow-up phase. Like the SKT results discussed above, the PSWT intervention failed to have any significant impact on the SBF. While this agrees with the suggestions by some earlier studies,[90] they are contrary to some others that had proposed a significant rise in skin and/or muscle blood flow after treatment with PSWT.[19,176] More recently, Al-Mandeel and Watson reported a significant rise in SBF during treatment with PSWT (MP of 24 W). However, the response dropped significantly once the treatment ended.[80] Other shortwave studies that suggested a much higher and/or sustained increase in temperature;[81,96] blood flow;[79,86] and both temperature and blood flow[77,85] were performed using CSWT. Comparison of the effects of similar average doses of PSWT and CSWT on blood flow are also available.[19]

There are not many examples available from the literature to show the influence of low frequency RF on nerve conduction in humans, apart from a handful of studies done using shortwave, which showed mixed results.[78,191,192] No such data on nerve conduction exists for RF below shortwaves. The present study failed to obtain any impact on NCV with either CRMRF or PSWT, although it was anticipated that NCV might change in response to changes in tissue temperature.[80,192]

The Biopac MP150 physiological measurement system and the associated modules used in this study are widely employed in research and has been used previously by the same research group in similar studies involving shortwave.[80,192] The PPG technique to measure SBF has been in use since decades.[404,411] Surface thermistors are a valid and reliable mode of recording local SKT,[350,352] and the Biopac TSD202A thermistor transducer enables real-time SKT monitoring. The system can collect up to 2,000 samples per second.

Once the RF treatment ended, the post-treatment measurements of SKT and SBF were started only after three minutes on average. About two minutes (established in the pilot) were required to clear the skin and re-attach the measurement probes before the recording could be re-started. Once ready, the NCV was recorded first, which lasted 30 seconds for each limb. Then SKT and SBF monitoring were started and continued till the 20-minute follow-up. Although the measurements during the PSWT session could have been started sooner as no skin preparation was required, similar time frame as in the CRMRF was followed to ensure protocol consistency.

It is possible that the study failed to capture the peak responses, which might have occurred during the immediate post-treatment phase (within the first two minutes). Similarly, responses during the intervention phase was also not mapped, unlike in some of the previous PSWT studies where SBF[80] and temperature[83] (invasive study) were monitored during the intervention. The follow-up measurements were not continued beyond 20 minutes owing to time constraints.

It is unsurprising that the core temperature did not change for any of the conditions, since a local application of RF energy is not expected to influence the core temperature.[22] Similar responses were also expected for pulse rate and blood pressure, both of which did not change significantly.[77,80] Also, no significant changes were noted in any of the physiological parameters of the control leg for any of the treatment groups. This suggests that there was no lasting ‘crosstalk’ effect (undesirable effect generated in the neighbouring untreated area), possibly due to the low scattering of RF waves from the CRMRF device. It was not possible to determine if there was any crosstalk effect during the intervention phase since no recordings were performed at the time.

By contrast, SKT of the untreated leg was shown to have risen considerably after PSWT intervention in the previous study by Al-Mandeel and Watson.[80] However, it should be noted that there was a three-minute delay in the post-treatment SKT measurements in this study and it is unclear how much delay (if any) was encountered in their study. In addition, it should be noted that unlike CRMRF, which is delivered using a contact method, PSWT is delivered using a non-contact method potentially causing more scattering of the RF energy through air.

As explained in the methods section, CRMRF was delivered for 15 minutes using the CAP mode first (5 minutes) followed by the RES mode (10 minutes). This sequence and the durations of application were based on recommendations by the manufacturer (Indiba S. A., Spain) rather than on optimum evidence. However, the combined delivery time of 15 minutes was appropriate for a clinical session used in contemporary therapy practice.

Among the two high dose groups in this study the participants described a 'uniform and deep feel' of heating in the CRMRF high intervention, while the feeling of heating was 'mild' at best for the PSWT high group. However, the reported feeling of deep heating should be interpreted with caution because localised thermal perception is based primarily on cutaneous receptors[341] and there remains some controversy as to whether thermal perception at depth is thermal perception *per se* or nociception. In the PSWT high group when asked to rate their perception of heat on a scale of one to four, where one was 'no heat' and four 'high heat', the majority (11 participants out of 15) rated the effect as mild heating. Four participants reported that there was no perceptible heat. This is commensurate with the mild to moderate rise in the mean post-treatment SKT noted in the PSWT high group. These findings agree with some of the previous PSWT studies,[80,105] but at the same time it is interesting to note that those studies had only employed a lower MP dose of PSWT.

At the end of the fourth session the participants were unblinded of their treatment sequence. Prior to this, the participants were asked if they can identify the treatment sessions themselves. About two-thirds identified RF high and control sessions correctly whereas only about a third of the participants could distinguish between RF low and RF placebo sessions. While it is unsurprising that the majority could identify the high dose and control conditions given the nature of intervention, RF low and placebo protocols were closely matched making the blinding reasonably effective.

6.6 Conclusions

The results of this study suggest that a high (thermal) dose as well as low (sub/minimally thermal) dose of CRMRF can significantly enhance and sustain local SKT, while only the high dose has a meaningful impact on SBF. An equivalent high dose of PSWT increased the SKT marginally (yet significantly) but did not sustain it over the follow-up phase. PSWT also failed to show any meaningful effect on the SBF. The results also suggest that the high and low dose treatments of CRMRF can significantly enhance blood flow volume at depth, while only the high dose can significantly enhance both volume and intensity of flow. An equivalent high dose of PSWT failed to show any impact on either of the above parameters.

None of the treatment groups had a statistically significant impact on the velocity of deep blood flow, although the high dose RF increased the velocity marginally. The hardness and softness of tissues, NCV, PR and BP were also not influenced by a local therapeutic

application of either type of RF therapy. The untreated contralateral leg did not show any meaningful change in its physiological responses.

The above findings are based on a baseline, post treatment (2–3 minutes post treatment for skin; 6–8 minutes post treatment for deep) and a 20-minute post treatment follow-up assessment of skin response using surface probes/electrodes and ultrasound Doppler and Elastography. Skin or deep responses during the intervention phase were not measured in this study.

7 Chapter 7 – Section III conclusions: key findings, limitations of the studies and implications for clinical practice and research

In summary, the laboratory study phase of this project investigated an array of physiological responses to cutaneous application of 448 kHz CRMRF in asymptomatic adults. Such research had previously been conducted on RF at or above shortwave frequencies; however, this is the first of its kind on RF below the shortwave frequency range. In addition to the two main studies (described in chapters 5 & 6), a considerable number of pilot experiments were also undertaken leading up to the main research work. Together, the results provide significant insight into the basic principles and some of the physiological effects of CRMRF therapy, which has remained unexplored thus far. Some of the key findings, the potential limitations incurred and the implications and recommendations for future research are summarised in the sections below.

7.1 Key findings

The initial study (Chapter 5) on the thermal response patterns of the two components of CRMRF therapy showed that CAP and RES modes instigate significantly different skin thermal response patterns. The deep thermal effects were not tested but extrapolating from the skin thermal decay patterns observed from either mode, the CAP mode is believed to have effects predominantly superficially and the RES mode deeper into the tissues. The study confirmed that skin temperature can both be raised and sustained significantly by both CAP and the RES modes of CRMRF therapy, although the RES mode thermal retention was significantly more pronounced and longer than that of the CAP mode. Additional data obtained during the above study also showed that at high intensities tissue heating in either mode of treatment was not caused by contact heating from a hot electrode, but rather due to RF-tissue interaction. In fact, the electrode temperatures were consistently lower than the skin temperatures obtained (especially so for the RES mode).

In the second study (Chapter 6), which was a larger experiment, the effects of multiple doses of CRMRF and a high dose PSWT were compared in a randomised crossover trial. The high dose CRMRF was shown to significantly increase and sustain SKT and SBF and significantly increase blood flow volume and intensity at depth (no data was collected on the retention of increased deep blood flow beyond the post treatment measurement). The low dose CRMRF showed similar response on the SKT results, but only increased the blood flow volume at depth (no rise in SBF). The high dose PSWT did increase the SKT significantly but failed to sustain that effect. PSWT also did not have any effect on the other physiological parameters. Tissue extensibility, blood flow velocity, NCV and the other systemic

parameters such as core temperature, BP and PR did not respond significantly to any of the RF treatments.

7.2 Methodological considerations and potential limitations of the studies

The reported effects from the current project and other studies in the past were based on the convention that the participants maintained their treatment position throughout the experiment (mostly lying or sitting). 'Supine lying' was the position adopted for all the studies in this project. Clinically, supine is the most likely position that would be adopted when treating the knee. Also, it will minimise the effects of gravity on the body systems and relax the individual's musculoskeletal system. Moreover, it would have been challenging to maintain another position for similar sustained periods since the experiments lasted for more than an hour. A change in position will trigger a change in the physiological processes. Nonetheless, it is challenging to predict the effect of a change in position upon the observed physiological effects in an experiment. It will be interesting to see how the results of this experiment might change if the positions of the participants are altered. A recently published study demonstrated the changes in skin temperature and potentially the blood flow in the lower limbs in response to different sitting positions.[487] They concluded that the knee and hip positions adopted while sitting have a significant impact on the blood flow and temperature in the lower limbs.

The results obtained in this experiment are likely to have been influenced by external factors such as the size (large; 65 mm in diameter) and geometry (circular) of the treatment electrodes used, the thermal and conductive properties of the cream, and other individual-specific internal factors such as anatomy of the area treated, tissue resistance and the anthropometric factors (e.g. – body fat percentage, BMI). The influence of such individual internal factors on the comparative group results would have been mitigated by the randomised crossover study design and blinded allocation of the treatment order. However, in the main study (Chapter 6) the PSWT session was neither randomised nor blinded, and was always the fifth session for all participants, which was one of the potential limitations of this study.

The magnitude of the generated EMF and the field/current density are influenced by the size of electrode.[18] The electrode size used here was deemed appropriate for the size of the area treated. Potentially, this has helped the homogeneity of field distribution. The large electrodes would have ensured that the field density would not have been disproportionately high under the treatment electrode, but rather, distributed more evenly through the tissues (based on energy dissipation models). The current density and field distribution were not aimed to be analysed in the present study as it is a separate research area. There is no data

currently available on CRMRF based on different electrode sizes or varying CAP/RES mode treatment combinations. The combination of modes used in this project (5 min CAP + 10 min RES) was largely based on manufacturer recommendations, which in turn was based on their in-house research together with user/therapist feedback.

This study did not investigate the temperature changes at depth; however, there is reasonable evidence from the given results that considerable generation and hence absorption of heat may have occurred in the deeper tissues due to CRMRF exposure. Non-invasive methods that are appropriate for temperature measurement at depth were not available in this project. Invasive temperature measurements, like those reported in some of the previous studies, have several potential issues. Where the measurement device (thermocouples or thermistors) was left attached while the RF was delivered (e.g. as in the study by Takahashi et al.[194]), there is a significant possibility that the electromagnetic field might have directly heated the device. This could lead to false temperature readings. In addition, the invasive procedure itself can cause a tissue inflammatory response potentially affecting the local physiological activity (e.g. change in blood flow). Techniques such as magnetic resonance (MR thermometry) and ultrasound (US thermometry) are available for non-invasive temperature measurement at depth. These are gaining ground and are employed in areas like cancer thermotherapy.[490,491] However, such techniques were beyond the scope of this study.

One of the common limitations of laboratory studies is that often the participants may be young adults who are more physically fit than the average population, limiting the generalizability of the results. In all the studies conducted in this project, the participants were reasonably physically fit and active; however, their age ranges were intentionally kept wide, and their activity levels were considerably varied, making the sample more representative of the general population. Besides, the studies were carried out at 'thermoneutral' room temperature conditions for humans. Although the above factors make the presented results more generalizable, it is problematic to extrapolate these results to a patient population because their physiological responses could be different to that of an asymptomatic population.

There was no blinding on the part of the therapist who delivered the interventions and undertook the measurements making this study only single-blind at best. The post treatment assessments were only able to be started at least two minutes after the end of treatment due to the need for skin preparation. No measurements could be performed during the intervention phase. Also, in the second study follow-up assessments were not carried out beyond 20 minutes. Together, these factors somewhat limited the extent to which the physiological responses were understood. However, for the active CRMRF groups there has not been any sharp decline in the responses over the follow-up phase. Hence, extrapolating

from the findings of both studies (Chapters 5 & 6), it is reasonable to expect that the effects would have been sustained significantly for more than 20 minutes. From a clinical perspective, this knowledge is valuable as it provides a reasonable (so-called) 'therapy window' to the treating clinician (assuming similar effects could be reproduced in clinical populations as well).

7.3 Implications for practice and future research

The physiological responses obtained in healthy participants with CRMRF therapy may be indicative of its potential clinical effectiveness. The more pronounced physiological responses obtained from the CRMRF high dose group would make it potentially suitable for treating conditions giving rise to chronic pain and inflammation where enhancement in tissue temperature and blood flow is a treatment aim, but unsuitable for application in an acute condition where a significant rise in either parameter is undesirable. The modest effects of CRMRF low dose on SKT and blood flow would make it potentially suitable for treating acute conditions.

The above suggestions assume that the physiological changes demonstrated in asymptomatic participants can be reproduced similarly in the patient populations as well (potentially leading to clinical benefits), but *per se* the given results cannot be extrapolated to a patient population who could respond differently to the same intervention. As discussed earlier, there is also the possibility that all physiological parameters might have undergone prominent changes during the treatment phase, which will have implications on its choice for clinical applications.

The study did not aim to provide recommendations on CRMRF dosing based on perceived heat or physiological responses; however, they may provide guidance to clinicians for clinical decision making when they may decide to use such therapy. It also provides useful baseline data for further research in the low frequency ranges of RF therapy that has remained largely unexplored. Further studies that explore additional physiological responses by addressing the limitations of this study (as detailed previously) and clinical studies that involve patient groups are therefore necessary. Forthcoming physiological studies should be fully randomised and double-blinded. Longer follow-up periods are also desirable. To find out the full extent of physiological responses future studies should explore the means of monitoring them while the CRMRF intervention is being delivered, minimise the time delay between the end of intervention and the beginning of post treatment measurements, and incorporate temperature measurement at depth into the protocol.

SECTION IV: PHYSIOLOGICAL AND CLINICAL EFFECTS OF CRMRF-BASED THERAPY IN PATIENTS WITH CHRONIC OSTEOARTHRITIS OF THE KNEE – A HOSPITAL-BASED INVESTIGATION

8 Chapter 8 – The effect of CRMRF on pain and function in patients with OA of the knee joint: a randomised controlled trial

8.1 Introduction to osteoarthritis

8.1.1 Epidemiology

Osteoarthritis (OA) is the most common among the various forms of arthritis and a leading condition affecting function and QoL among middle-aged and older adults.[334,492-494] Overall, it is one of the commonest diagnoses made in the older people consulting their general practitioner.[494] Although OA can affect any synovial joint in the body, the condition is more common among the larger joints, the hip and knee being the most prominent.[334,493] Out of the two, OA of the knee[495-498] is more prevalent than OA of the hip.[499-502] Data suggest that in the community as many as 40% of adults who are aged over 65 years (which is a significant proportion of that population) may be affected by either of these conditions. Hence, in most populations of people over 65 years of age OA is the most common cause for long-term disability.[334,503,504] People of all ethnic groups in all geographic locations are affected by OA and women tend to be more prone when compared to men.[505-507]

8.1.2 Global costs

There is a strong positive correlation between advancing age and the incidence of OA, which also means more and more people aged over 40 years are now affected by this condition given the rise in the numbers of older people due to increasing life expectancy.[508] This in turn has significant economic implications commensurate with the growing prevalence of OA and the profound effects it has on the QoL of people. Although OA is currently a major worldwide cause for economic loss due to its direct as well as indirect costs, there is a lack of global estimates regarding its overall economic burden.[334,509]

Chen et al. (2012)[509] reported in their review on the global economic impact of OA that there is only limited evidence available from the eastern countries of the world regarding the economic cost of OA. Besides, they further reported that although studies have been conducted about the costs in the west, clarity was lacking making the results inconclusive. It is alleged that cost-related studies frequently fail to separate the cost of OA from under the rubric of ‘musculoskeletal conditions’, leading to many gaps in the OA economic data.[333] Nonetheless, in the USA alone, it has been estimated that over 10 million QoL years are lost annually due to knee OA.[510]

8.1.3 Classification of OA

The most common type of OA is primary or idiopathic OA. In this type, there is no known cause for joint degeneration.[511,512] Another type of OA called the secondary OA, which is less common, develops from joint degeneration due to causes such as injuries to the joint or other pathologies that have an impact on the joint. These pathologies can be developmental, hereditary, inflammatory, metabolic or neurological disorders, or even a combination of such factors.[511,512] While primary OA seldom occurs in people younger than 40 years, secondary OA may occur in younger or older adults.[513-515] Patients with idiopathic OA may also present themselves with a predisposing cause such as a genetic predisposition or biomechanical stress to the joint accelerating the degenerative process.[334]

8.1.4 Pathophysiology and symptoms of OA knee

OA-related knee pain is the commonest cause for physical disability in older adults.[494] The disease and its symptoms start from the degeneration of the synovial joint, either tibio-femoral or patello-femoral, or both and affect the periarticular tissues. It is an active process involving progressive degeneration of the articular cartilage, which is accompanied by its attempted repair, sclerosis and thickening of the subchondral bone and possibly the formation of osteophytes and subchondral bone cysts.[512,516] The clinical syndrome is presented with chronic knee pain and inflammation, tenderness, restriction of movement, stiffness of the joint, effusion and weakness. The pain can be during activity, during rest or at night, and is often described as a poorly localised deep aching discomfort, the level of which may increase with an increase in physical activity and a drop in atmospheric temperature. As the condition progresses, the functional ability and hence the QoL diminish and the individual may develop physical deformities leading to psychological and social isolation.[334,492,494]

Reflecting on accepted clinical practice, the guidelines published by the American College of Rheumatology classified OA as a clinical syndrome in older adults who are presented with knee pain, morning stiffness and crepitus,[517-519] although such classification may not be devoid of shortcomings.[520] Radiographs of the knee joint have traditionally been the corner stone for diagnosis of OA knee; however, the history and clinical assessment of the symptoms also play a crucial role. This is because; up to a third of older adults may show radiographic evidence of joint degeneration, half of whom are not presented with the pain and associated symptoms of OA.[495,498,521,522] Conversely, half of such people who are presented with the pain and other symptoms of OA fail to show definite arthritic evidence in their radiograph.[497] Hence clinical decision making may depend on radiograph, history and symptoms.

8.1.5 Current best treatment for OA knee

Since there is no cure for OA available, current management plans are aimed at reducing the symptoms, improving function and enhancing QoL.[331,523-527] Where possible, slowing down the progression of the joint degeneration is also important in order to avoid or delay expensive invasive procedures such as total knee replacement (TKR).[330] Conservative treatment for OA (all non-surgical treatment methods) has several pathways: medical management, intra-articular injections, physical medicine and rehabilitation and promoting self-management by educating the patient about the condition.[524] With the rapidly growing evidence-base for OA management, updated clinical practice guidelines have been published by many societies recently.[525-527] The predominant theme across all these guidelines is the emphasis placed on the non-drug non-surgical management options. There is an increasing urge to focus on patient-driven self-management rather than clinician-centred passive interventions,[330] although rehabilitation is recommended widely and is even considered the core treatment of OA knee in key guidelines.[525-528]

8.1.6 Physiotherapy interventions for OA knee

Physiotherapy for OA knee combines the broad base of non-drug, non-surgical treatment options. It mainly includes patient education on self-help, activity modification, biomechanical correction where needed (e.g. using orthotics), exercise therapy in various forms (land-based or aquatic), manual therapy, electrophysical agents and acupuncture. Exercise is recommended as a key treatment for OA knee by all clinical guidelines.[331,525-527,529-531] This recommendation is justified by the fact that a recent updated Cochrane review[529] on 44 RCTs concluded that there is high quality evidence to suggest that a land-based exercise programme is significantly beneficial for OA knee when compared to no exercise, with the beneficial effects such as reduction in pain sustained up to six months after the end of formal treatment.

Exercise may involve both regular physical activity by the patients themselves (activities involving skeletal muscle activity that requires energy expenditure)[525,527,532,533] and exercise therapy using prescribed therapeutic exercises usually delivered by a physical therapist (planned and structured physical activity).[534,535] In OA knee, exercise intervention of either type is aimed at improving the joint ROM, muscle strength, soft tissue compliance, proprioception and aerobic performance. Nonetheless, although exercise-based rehabilitation is a key part of OA knee management there is no consensus on the optimal content of an exercise-programme.[528,535] Rather, in current practice the exercise intervention is tailored to fulfil the specific needs of the individual besides accommodating their limitations and comorbidities. Without tailoring the exercises to the clinical presentation, the clinical effects may attenuate and not reach the optimum benefit level.[330,526]

Although exercise therapy is at the forefront of conservative OA knee management, there is no evidence to suggest that exercise alone is adequate to improve the condition in the long term. Adherence to and benefits from exercise may diminish over time especially given the relatively modest effect sizes for pain (0.39 – 0.49) and function (0.31 – 0.52) proposed by several studies.[529,536-539] Based on this, there is a need to improve the overall treatment effects by facilitating the sustenance of treatment effects. The physical therapists may combine exercise intervention with manual therapy (MT) techniques aimed at alleviating the symptoms and restoring function.[537,540] Although some authors have reported the benefits of MT for OA knee,[541-544] the available evidence was not deemed strong enough to warrant recommendation in clinical guidelines.

Another area being advocated in the management of OA knee is the use of physical agents (including electrophysical agents). The NICE guidelines for the care and management of OA in adults states that the use of thermotherapy (therapeutic heat) should be considered along with the other treatments.[545] Half of all non-pharmacological interventions suggested by 'European League against Rheumatism (EULAR)' as potential treatments for the management of OA knee are electrophysical agents.[546] These agents are: acupuncture (including electroacupuncture), low level laser therapy (LLLT), transcutaneous electrical nerve stimulation (TENS, including interferential therapy (IFT)), ultrasound (US) and pulsed electromagnetic fields (PEMF, including shortwave therapy (SWT)).[547] In a review Bjordal and colleagues[547] questioned the lack of recommendation given to physical agents by EULAR for OA knee management despite them demonstrating the same level of evidence as certain analgesics such as paracetamol, opioids and coxibs. The review went on to conclude that LLLT, TENS and PEMF exhibited statistically significant effects over placebo within 1 – 4 weeks, while the evidence for acupuncture was mixed. The outcome on TENS, which had the most number of studies in their review, was also supported by other reviews.[548]

In agreement with the above report, the effect of SWT on OA knee was demonstrated by the comprehensive review of literature undertaken in this project, which has also been supported by other researchers in the past.[137] Twenty-six SWT studies on OA[55,256,258-264,266-282] and four studies on OA using RF devices operating at frequencies below the shortwave frequency range[194,249-251] were identified. Overall, it was concluded that there is moderate evidence to support the use of PSWT in OA knee. Based on this evidence and the available data for OA knee, it was recommended that a mean PSWT power dose at or above 14.5 W, 8–12 sessions over 4–6 weeks, and 15–20 minutes per session may be necessary for the treatment to be beneficial. With only four studies identified, currently there is no substantive evidence available to support the use of RF below the shortwave frequency band for the management of OA knee.

8.2 Rationale for the study

A lack of research emphasis has been particularly evident on the non-shortwave RF band, where only a small number of studies were identified in the literature review. This warrant emphasis in this area especially since EPAs delivering non-shortwave RF are already in clinical use and that the studies published so far have reported encouraging results. Purely based on the reported results of the studies identified, such low frequency RF may be beneficial in delivering useful therapeutic effects. However, the paucity of controlled trials and the poor methodological quality of available studies suggest that more studies need to be conducted in this area before such therapy can be considered.

It should be noted that the studies conducted on asymptomatic adults strongly indicated a significantly more pronounced physiological response from CRMRF as against PSWT. It is anticipated that such physiological response may lead to more pronounced clinical benefits. Since OA knee is a pressing health issue that warrants conservative management and since RF interventions such as PSWT has proven to be effective in its management, it is prudent to investigate the potential clinical benefits of 448 kHz CRMRF in a similar population of patients affected by chronic OA of the knee joint(s).

8.3 Key aims of the study

The main aims of this study were to investigate:

1) Whether 448 kHz CRMRF treatment can reduce symptoms and significantly improve function in patients affected by chronic OA of the knee joint(s).
2) Whether any such potential clinical benefit is significantly better than a placebo treatment or the current standard treatment for OA that is based on exercise and advice.

8.4 The study design

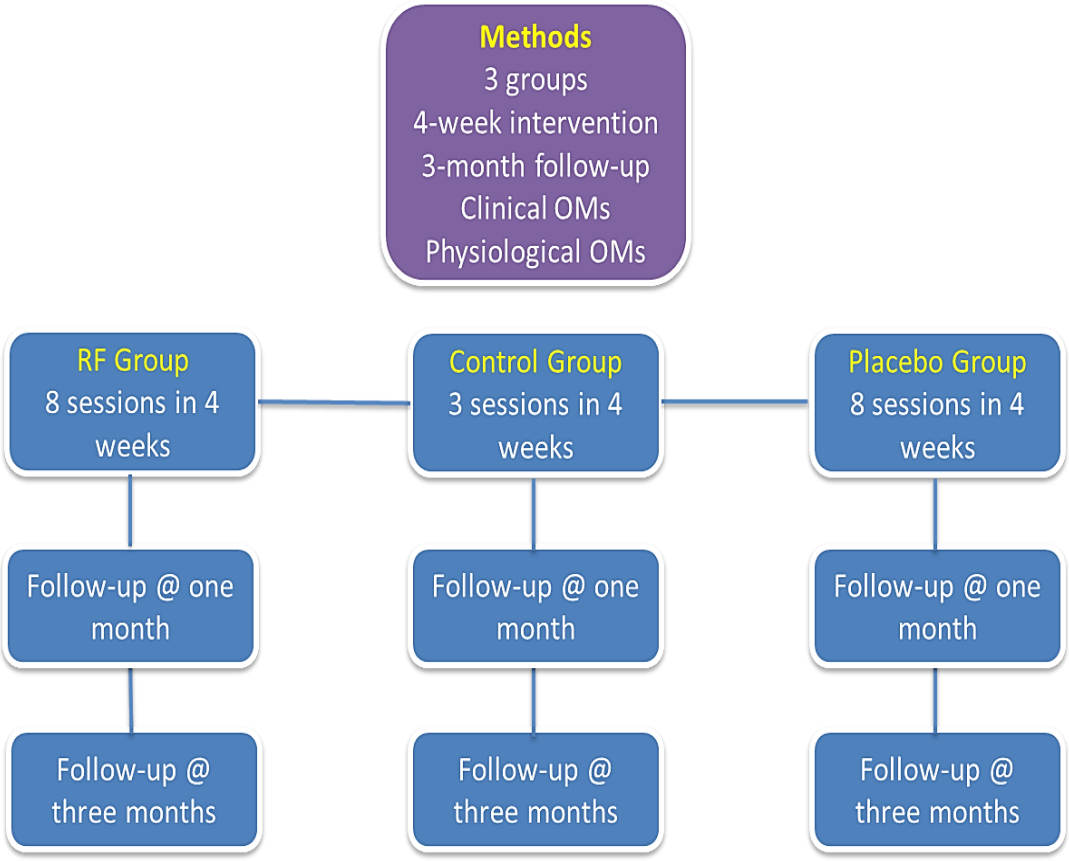
A placebo-controlled RCT was employed to address the above aims of the study. The three-group study lasted four months (one-month intervention period and three months' follow-up) and involved an experimental group, control group and a placebo group. Participants in each group were assessed using clinical outcome measures at four time points stated below, to examine the effects of the intervention:

1) Before the start of the intervention (pre-treatment)
2) After the intervention ended (post treatment)
3) One month after the intervention ended (one-month follow-up)
4) Three months after the intervention ended (three-month follow-up)

The RCT design is considered the best research design for primary clinical studies investigating the efficacy of interventions.[549,550] An RCT with experimental, control and placebo groups enable the researcher to statistically weigh the effect of the experimental intervention in question against a 'control' condition where any changes would have happened not by the influence of the experimental intervention; and against a 'placebo intervention' to assess the potential for the so-called 'placebo effect'.[549,550] It is generally accepted that certain types of treatments can induce placebo effect on the patients (for example, placebo medications) for up to 40%.[551-553]

The basic study design is illustrated in Figure 8.1. The groups, outcome measures and interventions are explained in detail in the following sections.

Figure 8.1: The study design for the clinical trial



8.5 Materials and methods

8.5.1 The CRMRF device

The CRMRF treatment device and its operating principles have been described in detail in chapter 4. As explained, it had active and placebo settings.

8.5.2 Outcome measures

Four clinical outcome measures, which were valid and reliable and widely used in clinical practice and OA research, were used to assess the response obtained towards CRMRF treatment over the course of the study. They are explained below.

8.5.2.1 Self-reported pain

Average pain experienced by the participants over the preceding 24 hours was rated using a self-administered visual analogue scale (VAS) (Appendix 8.1). At every assessment, the level of pain was self-reported by the participants as 'pain over the last 24 hours' on a 10 cm VAS. On this scale, the pain is rated from 0 – 10, where a score of '0' meant no pain at all and '10' meant the worst imaginable pain. While administering, the participants were asked to mark on the scale what they believed their pain level was. The distance to this mark on the scale was measured from zero using a ruler. The obtained value, which was between '0' and '10' (inclusive), was taken as the pain score for that assessment. It was assumed that the participants were blinded to their previous score.

Subjective assessment of pain using VAS is a quick and easy to administer measuring tool that can reflect real change in patients' pain symptoms, and which is commonly used in clinical research.[554,555] VAS is proven to be valid, reliable and responsive for a variety of clinical conditions including musculoskeletal disorders.[554-564] A reduction in pain by a score of around 1.9 – 2.0 out of 10 (19 – 20%) is generally accepted as a minimum clinically important difference (MCID) for VAS.[565-567]

8.5.2.2 WOMAC osteoarthritis index

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Appendix 8.2) was used for the assessment of functional ability of the participants throughout the study.[568-570] The WOMAC is a questionnaire that assesses the levels of pain, stiffness and physical function in patients with OA of the hip/knee. The index consists of 24 items based on symptoms and physical function, divided into three subscales as given below:

1) Five items on pain
2) Two items on stiffness
3) Seventeen items on the level of physical function

The items can be scored by marking on a 10 cm VAS or on a five-point Likert scale (both forms are equally valid) with the answers ranging from 'none' to 'extreme' where the patients indicate their level of problem by marking in the appropriate box.[569] The five-point Likert type questionnaire was used in this study as the researcher had previous experience with this form of WOMAC. Once the questionnaire is completed, the assessor scores each item from 0 – 4 depending on the responses given (severity of the problem), as follows:

1) Score 0 for ‘none’.
2) Score 1 for ‘mild’.
3) Score 2 for ‘moderate’.
4) Score 3 for ‘severe’.
5) Score 4 for ‘extreme’.

Hence, the three subscales of pain, stiffness and physical function can score a maximum of 20, 8 and 68 respectively.[571] The higher the score, the higher is the severity of the problem and vice versa. The WOMAC global score can be calculated by totalling the scores of the three individual subscales. Hence, the maximum WOMAC global score that can be achieved by a participant at any assessment is 96. A 16% reduction from the baseline WOMAC global score can be considered as its MCID.[572]

The questionnaire is among the most widely used outcome measures in OA research with proven psychometric properties,[570,571,573-580] and is officially available in over 65 language formats in addition to English.[581] WOMAC has also been validated for telephonic[582] and computerized/electronic administration.[583,584] In this study all participants administered the questionnaire ‘in person’ during their visits to the clinic.

8.5.2.3 Walking ability

The walking ability of the participants was assessed using the Timed Up and Go (TUG) test.[585] The test measures the time (in seconds) taken by the person to rise from sitting from a standard arm chair, walk three metres in a straight line, turn around, walk back to the chair and sit down again. The participants were given standard instructions on how to perform the task at their ‘normal speed’ when the assessor asks them to ‘start’. They could use their walking aid if they needed it. The researcher assessed the walking time in seconds using a timer while the participants performed the task. They wore their regular footwear during the assessment.

The performance on TUG is linked to multiple factors such as balance, strength and agility. It is also linked to age, cognitive ability and the type of footwear used.[586-589] TUG is widely used in clinical and research settings to get valuable information on the risk of falls among the elderly and frail, and to assess the functional decline among different clinical populations such as fractures, OA knee/hip, COPD, cancer and various neurological conditions affecting gait and balance such as stroke.[590-594] Although originally developed for the assessment of elderly population, it is also used widely in the arthritic population and has proven psychometric properties.[585,595-601] The MCID of TUG test has been reported to be 3.4 seconds.[602]

8.5.2.4 Knee joint range of movement

The knee joint active ROM was measured by the assessor using a universal goniometer with the participant in supine, supported by pillows. The measurement was always performed at the lateral aspect of the treated knee joint, since the participant was always to be positioned with the treated side facing the assessor. The participant was asked to bend/straighten their knee to the best they can, within the level of pain. The assessor measured the knee flexion/extension using the greater trochanter, lateral condyle of the femur, head of the fibula and lateral malleolus as bony landmarks.[603,604]

For the analysis, ROM was regarded as the flexion and extension movement ranges combined, by adding the two values together. Where the knee was not extending fully to 180 degrees, a negative value was assigned to the extension ROM depending on the level of lag from 180 degrees. Where the extension was beyond 180 degrees owing to joint hypermobility or deformity from OA knee the extension ROM was a positive value. The flexion ROM was always a positive value. The extension ROM had positive and negative values. Combining the flexion and extension scores eliminated all negative scores.

Reduction in the knee ROM is one out of the numerous factors proposed to be contributing to the reduced level of physical function among people affected by OA knee.[605-608] Reduced knee ROM is also one of the clinical signs used in the diagnosis of OA knee.[609,610] Hence it is prudent to assess the ROM as an outcome measure in OA research since any improvement in ROM is directly indicative of an improvement in the symptoms. Universal goniometry is widely used in research and clinical practice to obtain instant measure of joint ROM since several decades, and is established to be a valid and reliable tool for manual administration.[604,611-615]

8.5.3 The study setting, Ethics approval, trial registration and key dates

This study was carried out at the outpatient physiotherapy wing of the Safari Therapy Unit in the Hemel Hempstead General Hospital, Hemel Hempstead, Hertfordshire. The centre operates under the ‘Hertfordshire Community NHS Trust’. The ethics approval for the study was granted on 25 June 2015 by the ‘NRES Committee North West - Greater Manchester South’ under the Research Ethics Service of the NHS Health Research Authority (HRA) (REC reference: 15/NW/0529; Protocol number: HSK/PG/NHS/00312; IRAS project ID: 173691) (Appendix 8.3). Participant recruitment was started in December 2015. The first participant visit was on 04 January 2016. The last participant was recruited at the end of June 2016. The study was formally completed on 28 October 2016 with the final set of assessments completed. The study was registered with the ISRCTN registry (Registration number: ISRCTN10995065) and with the National Institute of Health Research (NIHR) Clinical Research Network (CRN) (Portfolio) (study ID: 20264).

8.5.4 The study population and sample recruitment

The study population was formed by the communities under the care of Safari Therapy Unit, Hemel Hempstead General Hospital, Hemel Hempstead under the Hertfordshire Community NHS Trust. Patients who were on the waiting list for physiotherapy treatment after being diagnosed with OA knee and referred by their general practitioners (GP) or the concerned specialist consultants, were invited in writing seeking their willingness to take part in the study if they met the following criteria (inclusion criteria):

1) Clinical and/or radiological diagnosis of OA knee, meeting the American College of Rheumatology clinical criteria for OA knee.[517]
2) OA symptoms present since a minimum of six months.
3) Over 18 years of age.

The patients were sent an invitation package containing an invitation letter (Appendix 8.4) a participant information sheet (Appendix 8.5), a return form (Appendix 8.6) to indicate whether they wish to be considered for the study and postage paid return envelope. Where the patients were willing to be considered for inclusion, they were contacted by the researcher by phone to collect further details about their condition. Subsequently, they were recruited if they did not meet any of the below criteria (exclusion criteria):

1) RF-based treatment contraindicated for any of the following reasons:
    a) Pregnancy
    b) Active cancer/malignancy
    c) Active tuberculosis
    d) Metal implant in the affected knee
    e) Pacemaker or another sensitive electronic implant present
2) Significant comorbidities such as neurological impairment precluding them from study participation
3) Any active skin lesions/conditions around the affected knee joint
4) Known hypersensitivity to heat
5) Any recent invasive procedures to the affected knee within the last three months
6) Any invasive procedures planned during the potential study period
7) Inability to attend the hospital for intervention/assessments
8) Inability to provide written consent

8.5.5 Sample size and power calculation

No baseline data was available concerning the use of CRMRF therapy on patients affected by OA knee. Based on a Minimal Clinically Important Difference (MCID) of 16 – 20% reduction on the WOMAC global score (Effect size of 0.5),[572,616,617] a total of 42 participants (in three groups) was required to demonstrate a statistically and clinically significant difference with 95% confidence and 80% power (G*Power 3.1). Allowing for a maximum drop-out of 20%, it was anticipated that 17 participants per group would be needed to achieve a sufficiently powered study. Hence, the estimated overall sample required was 51.

8.5.6 The study groups

After screening, those patients who satisfactorily passed the inclusion/exclusion criteria were recruited into the study. The patients were randomly allocated to one of the three study groups at the time of recruitment. The randomisation was performed with concealed envelopes, which were prepared *a priori* using a computer-generated randomisation chart (Appendix 8.7) (IBM SPSS Statistics, Version 20), and blinded from the participants. The three study groups were as given below (Figure 8.1).

1) ACTIVE GROUP – Received CRMRF therapy + Current standard treatment for OA knee. Received eight sessions of treatment in four weeks.
2) PLACEBO GROUP – Received placebo CRMRF therapy + Current standard treatment for OA knee. Received eight sessions of treatment in four weeks.
3) CONTROL GROUP – Received current standard treatment for OA knee only. Received three sessions of treatment in four weeks, commensurate with normal departmental practice.

In this study, whichever group the participant was randomly allocated to, the ‘current standard treatment’ they would have received even if they were not a participant in this study was continued to be delivered uninterrupted. This was important from an ethical standpoint because no patient was disadvantaged because of their participation in the study. On the other hand, those participants who were randomised into the active or placebo groups received additional CRMRF or placebo CRMRF treatment sessions. Since the active and control groups received dissimilar number of treatment sessions, it raises the issue of non-equivalence between the groups. However, if the number of sessions for the control group was increased to match that of the active group it would not have reflected standard clinical practice. Similarly, the active group number of sessions could not be reduced to match that of the control group because that would have meant too few CRMRF sessions delivered.

8.5.7 Interventions

8.5.7.1 The CRMRF intervention

A high dose of CRMRF that generated a 'moderate' skin thermal sensation employing the same method and principle used for delivering the 'CRMRF high' intervention in the physiological study (Chapter 4) was used for the active group of this study. The intensity of delivery was therefore not fixed but adjusted according to patient feedback on their perception of moderate heating. Fifteen minutes of treatment (5 minutes CAP + 10 minutes RES) was delivered twice a week for four consecutive weeks providing a total of eight sessions. The treatment was delivered to the knee joint area covering the lower aspect of the quadriceps femoris muscle, around the patella and the medial and lateral joint lines. However, emphasis was given to the areas of the joint reported by the patients as more symptomatic. The return plate electrode was placed under the calf one-fourth way down the distance between the fibular head and the lateral malleolus (like the laboratory study), which was the standardised position adopted.

8.5.7.2 The CRMRF placebo intervention

The device mode was set to the placebo setting (treatment option '1') on the dial prior to the start of the treatment. The treatment was delivered using the exact techniques as in the active group except that no verbal feedback was sought from the participants since there was no energy delivery. The intensity was raised as for the real treatment, until the output display was at around similar levels to those of real treatments delivered to the active group. From the participant perspective, the treatment procedures and machine appearance were identical in active and placebo interventions.

8.5.7.3 Current standard treatment

By default, all patients in all three groups received the current standard care offered to the patients undergoing physiotherapy treatment for OA knee in the UK. This included advice and education regarding OA knee and exercises (home/gym-based exercise programme). Both components were tailored to suit individual participants. All participants in all three groups were given this intervention on their first visit. Subsequently, they were reviewed and re-emphasised at the fourth visit for the participants in the CRMRF and placebo groups, and at the second visit for the control group (the control group participants only received three sessions in four weeks).

The exercise programme included open and closed chain knee ROM exercises, open and closed chain knee strengthening exercises, and mild-to moderate gym-based tasks such as exercising on a static bike. The advices included restricting the activities that place excessive load and shear forces on the affected knee joint. This included cutting down on

walking briskly on hard/uneven surfaces, cutting down on kneeling, crouching and stair climbing where possible. The patients were also urged to use footwear that provides proper support to the limb while walking. The standard treatment protocol was designed based on departmental practice and current best evidence.

8.5.8 Procedure

On the first day of the study, an informed consent (Appendix 8.8) was signed by both parties (researcher and participant) before the start of the proceedings. Subsequently, the participant's 'skin thermal sensitivity' and the ability to distinguish between warm and cold temperatures was tested using test tubes filled with water at approximately three different temperatures (±0.5 ^{o}C): 45 ^{o}C (warm), 35 ^{o}C (neutral) and 25 ^{o}C (cold). After screening, a brief clinical assessment including the history of the condition, duration, and the past and present treatment history was carried out and recorded. A brief description about the assessment and treatment procedure was provided depending on their group allocation. Then, the clinical assessment data was collected in the following order:

1) Demographic and anthropometric data
2) TUG test at the designated area outside the treatment room
3) VAS and WOMAC
4) Knee ROM

To start the treatment session the participants in the active/placebo groups positioned themselves in supine on a treatment plinth, fully supported with pillows. The CRMRF intervention was delivered using the methods explained earlier. After the treatment, the standard care package with exercises and advice was delivered. Participants of the control group only received the standard care package as mentioned. A standardised application of treatment relevant to the allocated group was ensured for all participants. At the end of the first session, subsequent treatment sessions were booked. The control group participants were asked to attend two more sessions two weeks apart and all others were asked to attend twice weekly for the next four weeks ensuring a uniform gap between the sessions during the week (two days gap between sessions was ensured).

If any RF treatment sessions were missed due to an unforeseen reason, the intervention durations were extended till all planned sessions were completed. However, if more than two RF sessions were missed (> 25% of the total number of sessions) the intervention was considered invalid. If any control group participant missed their second session, they were contacted by phone to discuss any concerns and to reinforce the message about exercises and self-care. At sessions 2 – 7, the active/placebo participants attended the clinic to receive their 15-minute RF intervention only. At session 8, participants in all three groups underwent

the clinical assessments 2 – 4 mentioned above before being treated. The assessment was done before treatment to avoid the immediate impact of the intervention on the participants' performance. For example, the pain from the exercise (if any) can influence all the above assessments.

At the end of eight sessions, two follow-up visits were booked (first one after one month and the second after three months from the 8th session). All participants were advised to continue with the home exercises and self-care programme at least until the second follow-up. At the follow-up sessions, the clinical assessments 2 – 4 mentioned above were repeated.

8.5.9 Analysis of data

All data was processed and analysed using Microsoft Office Excel Version 2010 (Microsoft Corporation, USA) and IBM SPSS Statistics Version 20 (IBM Corporation, USA). To ascertain whether there were any statistically significant differences within the treatment groups or between the groups, the group data were compared on an intention to treat (ITT) basis using a mixed model analysis of variance (ANOVA) at four within-group time points (baseline, post treatment, one-moth follow-up and three months follow-up) and three between-group conditions (active, placebo and control). Where the data demonstrated deviation from normality, and/or inequality of variances, data transformation was performed using the square root function before conducting the ANOVA. Additionally, correlational analyses were performed involving the percentage changes in outcomes, dosage parameters (mean CRMRF dose and SAR in the active group) and the demographic and anthropometric data using either Pearson correlation or Spearman's rho depending on the distribution of data. The statistical significance was set at $p \leq 0.05$ (0.8 P, 95% CI).

8.6 Results

The flow of participants through the study is shown in Figure 8.2. Two participants from the control group and one participant from the placebo group withdrew from the study during the intervention phase (due to losing interest in one case and a lack of progress/deterioration of symptoms due to unrelated reasons in two cases). There were no withdrawals from the active group. Hence a total of 42 participants (93%) completed the interventions and all the assessments. All types of interventions and assessments were tolerated well and there were no reports of any adverse events that might be a consequence of the intervention, including any issues due to potential CRMRF-induced overheating.

The demographic and the mean (SD) anthropometric data from all 45 participants are reported in Table 8.1. There were no significant differences between any of the three groups in any characteristic.

Figure 8.2: The flow of participants through the clinical trial

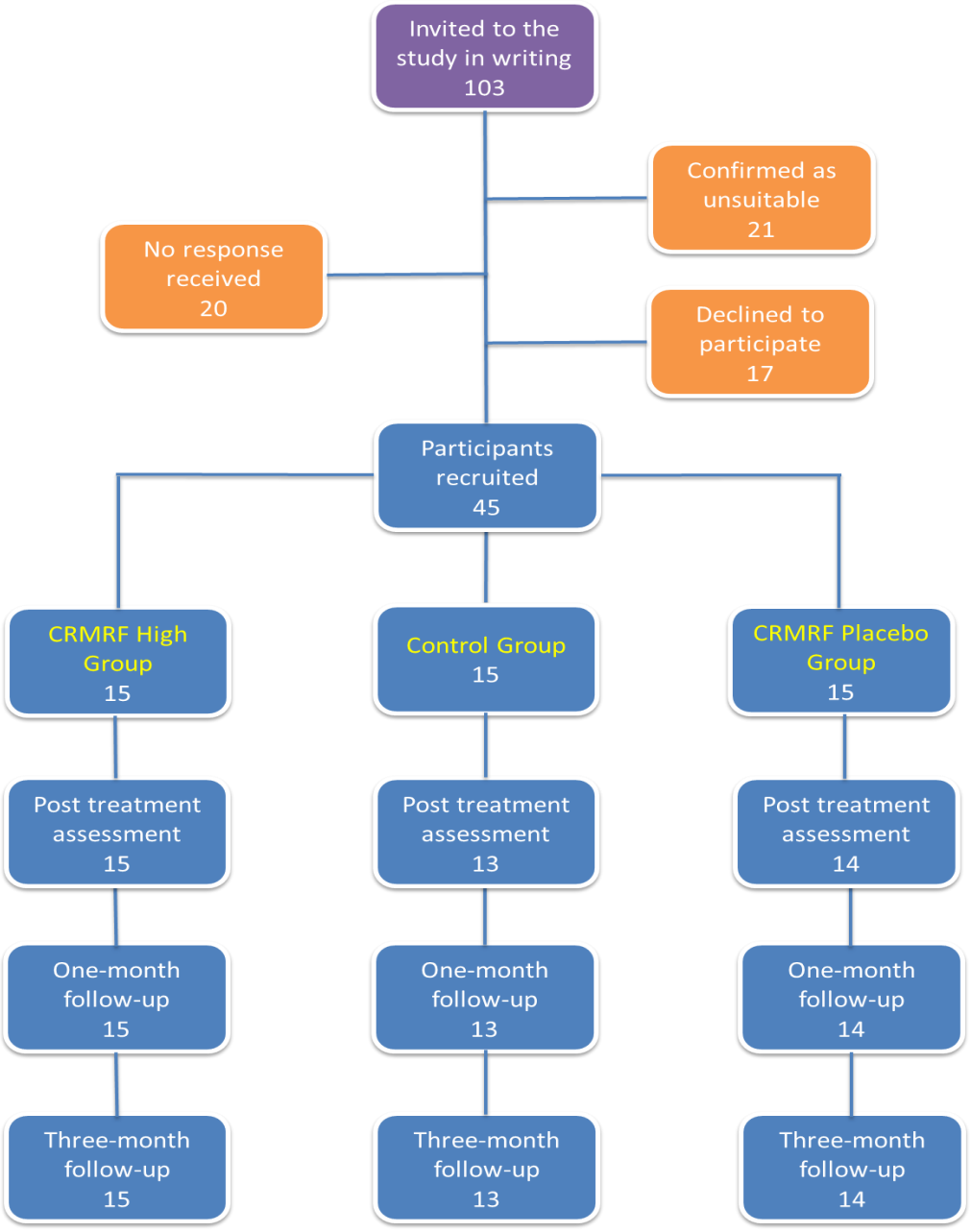


Table 8.1: Demographic and the mean (SD) anthropometric data

Study Group	Demographic data			Mean (SD) anthropometric data				
	Mean (SD) age (years)	Males	Females	Mean (SD) duration (years)	Height (m)	Weight (kg)	Body fat (%)	BMI
CRMRF High	63.33 (9.93)	6	9	5.57 (4.14)	1.67 (0.10)	87.79 (16.71)	39.15 (7.55)	31.33 (3.77)
CRMRF Placebo	62.60 (10.38)	6	9	4.30 (3.85)	1.63 (0.09)	81.77 (16.77)	38.01 (12.58)	30.53 (5.64)
Control	59.67 (6.21)	6	9	5.97 (5.73)	1.67 (0.07)	95.51 (16.08)	42.18 (8.53)	34.22 (5.66)

Fixed treatment doses were not delivered to the active group (like the laboratory study, chapter 6). The overall mean (SD) CAP and RES doses received by the participants in the

active group over the eight sessions were 17.29 (1.37) W and 60.56 (6.00) W respectively. The overall mean (SD) total dose (CAP + RES) over the eight sessions was 46.13 (4.26) W. Figure 8.3 shows the individual mean doses (CAP, RES, total) over the eight sessions for 15 participants. Figure 8.4 shows the mean (SD) total doses from sessions 1 – 8. The mean doses delivered over the eight sessions did not vary significantly. As explained before, the differences in the treatment dose among participants were due to the doses being adjusted based on the participants' thermal perception and verbal feedback.

Figure 8.3: The mean CRMRF doses of all eight sessions

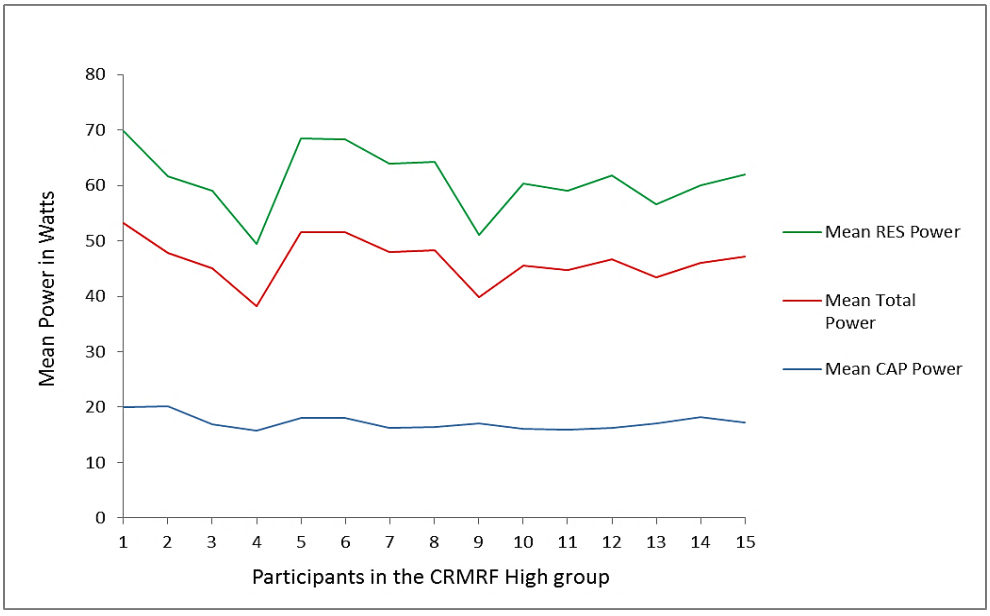
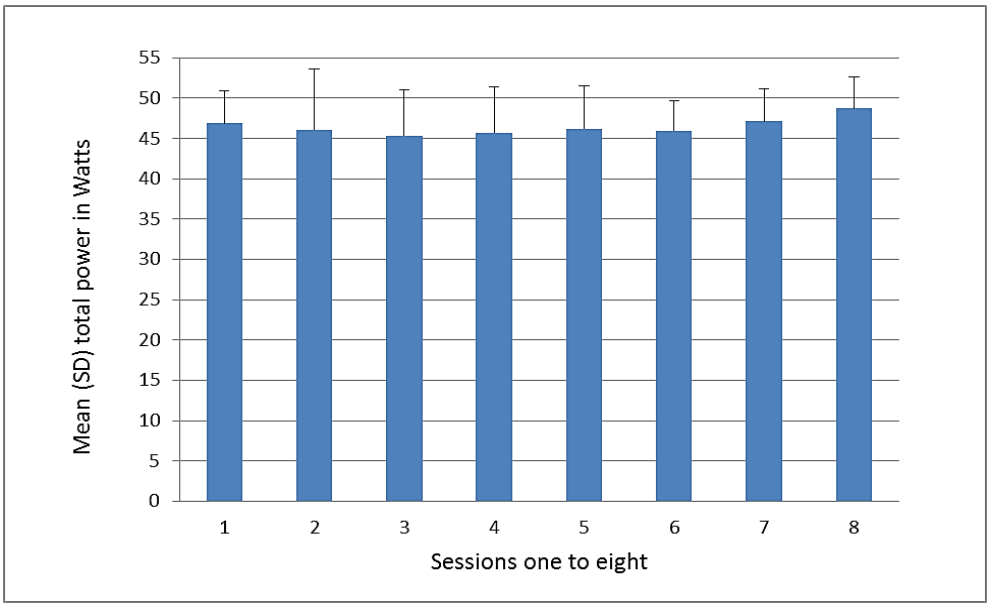


Figure 8.4: The mean (SD) CRMRF doses delivered to the active group participants over the eight sessions



The results of all four clinical outcome measures based on the four time points are given below. The post treatment results are based on the effects of seven treatment sessions instead of eight (except the control group) since the post treatment outcomes were obtained prior to delivering the last treatment session. This was done to avoid the immediate impact of treatment influencing the outcomes, especially TUG and knee ROM.

8.6.1 Self-reported pain

The group wise mean (SD) 24-hour pain rated by the participants at each assessment point is plotted in Figure 8.5. Figure 8.6 shows the percentage changes of mean from the baseline. The statistical analysis (4*3 mixed methods ANOVA (time, group)) revealed a significant main effect for the time (within-group change) ($F(2.086, 87.602) = 15.918$, $p < 0.001$) and a significant interaction between the group and time ($F(4.172) = 5.172$, $p = 0.001$). Therefore, the type of intervention made a significant difference to the reported pain scores and there was a significant overall difference between the pre, post and the one-month and three-month follow-up scores. There was no significant difference between the baseline pain scores of the three groups. Whilst the change in the mean VAS score of the active group reached accepted MCID levels when compared between the baseline and all the other time points, MCID was not attained for placebo and control groups.

Results of the pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was significant) are reported in Tables 8.2 & 8.3. All significant effects and interactions have been highlighted. For the between-group pairwise comparisons it is evident that the active group differed significantly from both placebo and control groups at post treatment (time point two) while there was no difference between the placebo and control groups. However, at the one-month follow-up (time point three) the significant difference was limited to between active and control groups. Further, no groups differed from each other at the three-month follow-up (time point four). Within the active group, there was a highly significant reduction in the pain scores from baseline to post treatment, which was sustained significantly over the follow-up phase. No such meaningful changes where noted within the other two groups, except between the baseline and one-month follow-up in the placebo group.

Figure 8.5: The mean (SD) pain scores

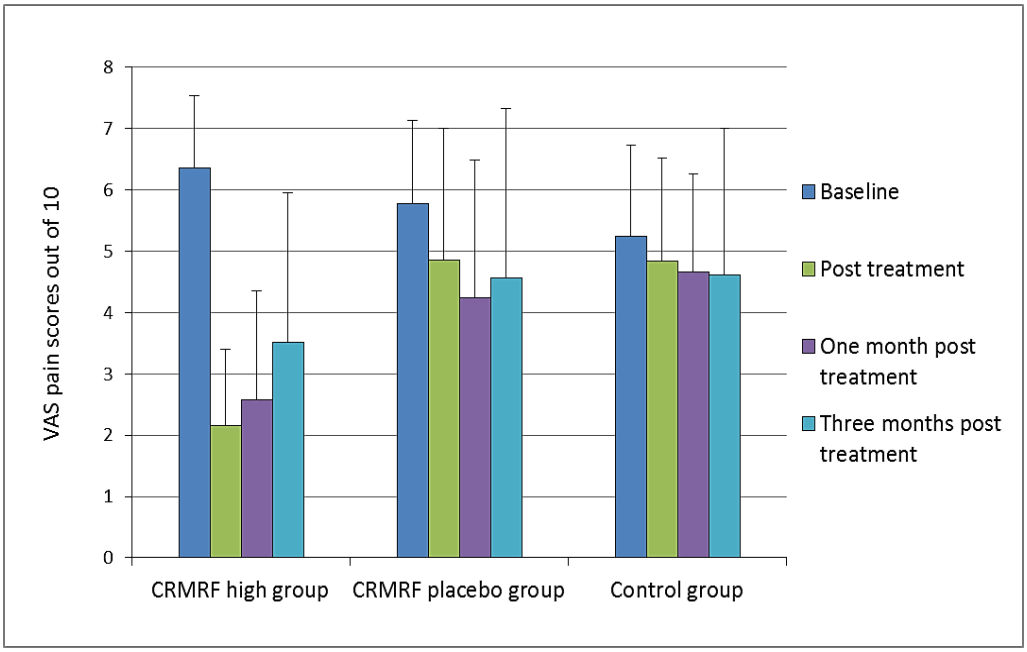


Figure 8.6: Percentage change in the mean pain scores from the baseline

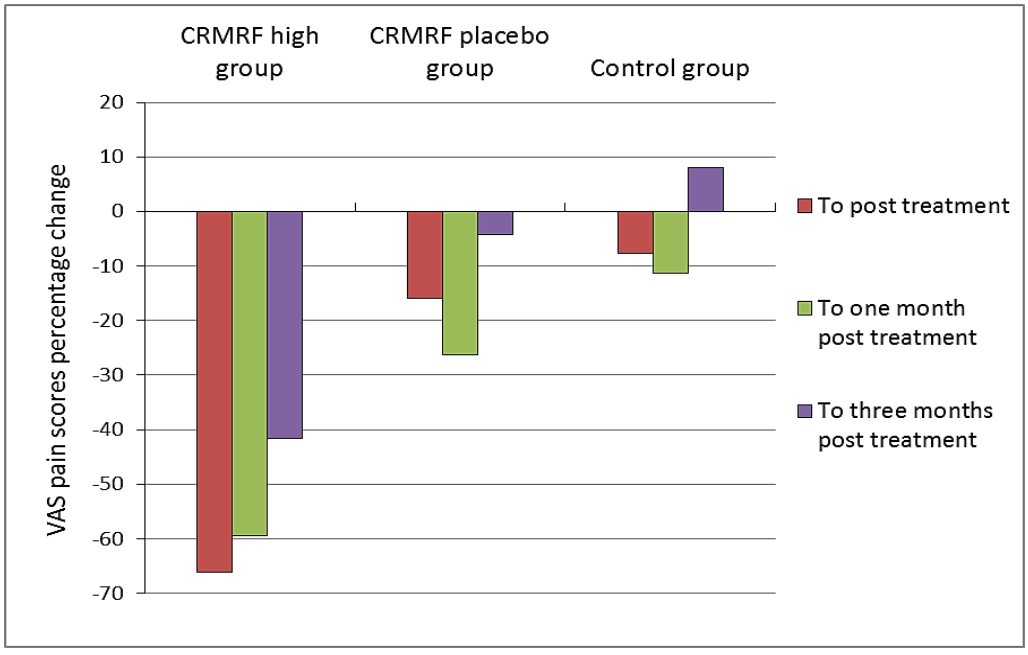


Table 8.2: Within-group pairwise comparisons for the pain scores

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	1.168*	.129	.000	2.46
		3	1.068*	.159	.000	1.92
		4	.762*	.208	.004	1.41
	2	1	-1.168*	.129	.000	
		3	-.100	.080	1.000	
		4	-.407	.181	.180	
	3	1	-1.068*	.159	.000	
		2	.100	.080	1.000	
		4	-.307	.173	.503	
	4	1	-.762*	.208	.004	
		2	.407	.181	.180	
		3	.307	.173	.503	
RFP	1	2	.253	.129	.339	
		3	.440*	.159	.049	0.79
		4	.432	.208	.266	
	2	1	-.253	.129	.339	
		3	.188	.080	.147	
		4	.180	.181	1.000	
	3	1	-.440*	.159	.049	
		2	-.188	.080	.147	
		4	-.008	.173	1.000	
	4	1	-.432	.208	.266	
		2	-.180	.181	1.000	
		3	.008	.173	1.000	
CTR	1	2	.109	.129	1.000	
		3	.150	.159	1.000	
		4	.303	.208	.923	
	2	1	-.109	.129	1.000	
		3	.042	.080	1.000	
		4	.194	.181	1.000	
	3	1	-.150	.159	1.000	
		2	-.042	.080	1.000	
		4	.152	.173	1.000	
	4	1	-.303	.208	.923	
		2	-.194	.181	1.000	
		3	-.152	.173	1.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Table 8.3: Between-group pairwise comparisons for the pain scores

Time	Group		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
1	RFH	RFP	.126	.106	.730	
		CTR	.242	.106	.084	
	RFP	RFH	-.126	.106	.730	
		CTR	.116	.106	.842	
	CTR	RFH	-.242	.106	.084	
		RFP	-.116	.106	.842	
2	RFH	RFP	-.790*	.200	.001	1.29
		CTR	-.817*	.200	.001	1.49
	RFP	RFH	.790*	.200	.001	
		CTR	-.028	.200	1.000	
	CTR	RFH	.817*	.200	.001	
		RFP	.028	.200	1.000	
3	RFH	RFP	-.502	.232	.108	
		CTR	-.676*	.232	.017	1.10
	RFP	RFH	.502	.232	.108	
		CTR	-.174	.232	1.000	
	CTR	RFH	.676*	.232	.017	
		RFP	.174	.232	1.000	
4	RFH	RFP	-.204	.305	1.000	
		CTR	-.217	.305	1.000	
	RFP	RFH	.204	.305	1.000	
		CTR	-.013	.305	1.000	
	CTR	RFH	.217	.305	1.000	
		RFP	.013	.305	1.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

8.6.2 WOMAC osteoarthritis index

The group wise mean (SD) WOMAC global scores obtained from the questionnaires at each assessment point are plotted in Figure 8.7. Figure 8.8 shows the percentage changes of mean from the baseline. The statistical analysis (4*3 mixed methods ANOVA (time, group)) of the WOMAC global scores revealed a significant main effect for the time (within-group change) ($F(2.168, 91.075) = 18.206$, $p < 0.001$) and a significant interaction between the group and time ($F(4.337) = 2.712$, $p = 0.031$). Therefore, the type of intervention made a significant difference to the reported scores and there was a significant overall difference between pre, post, one-month follow-up and three-month follow-up WOMAC global scores. There was no significant difference between the baseline scores of the three groups. The changes in the WOMAC global scores reached the MCID levels for all three time points in both active and placebo groups, although the difference was almost two-fold in the active group. In the control group, the MCID level was attained only by the one-month follow-up, which was also sustained at the three-month follow-up.

Results of the pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was significant) are reported in Tables 8.4 & 8.5. All significant effects and interactions have been highlighted. In the between-group pairwise comparisons the only significant difference was found between the active group and control group at post treatment (time point two). No other groups differed significantly from each other at any other time point. Within the active and placebo groups, there was a significant reduction in the WOMAC global scores from baseline to post treatment, which was sustained significantly over the follow-up phase. Nonetheless, the improvement in the outcome was much more pronounced in the active group compared to the placebo. No such meaningful changes where noted within the control group.

Figure 8.7: The mean (SD) WOMAC global scores

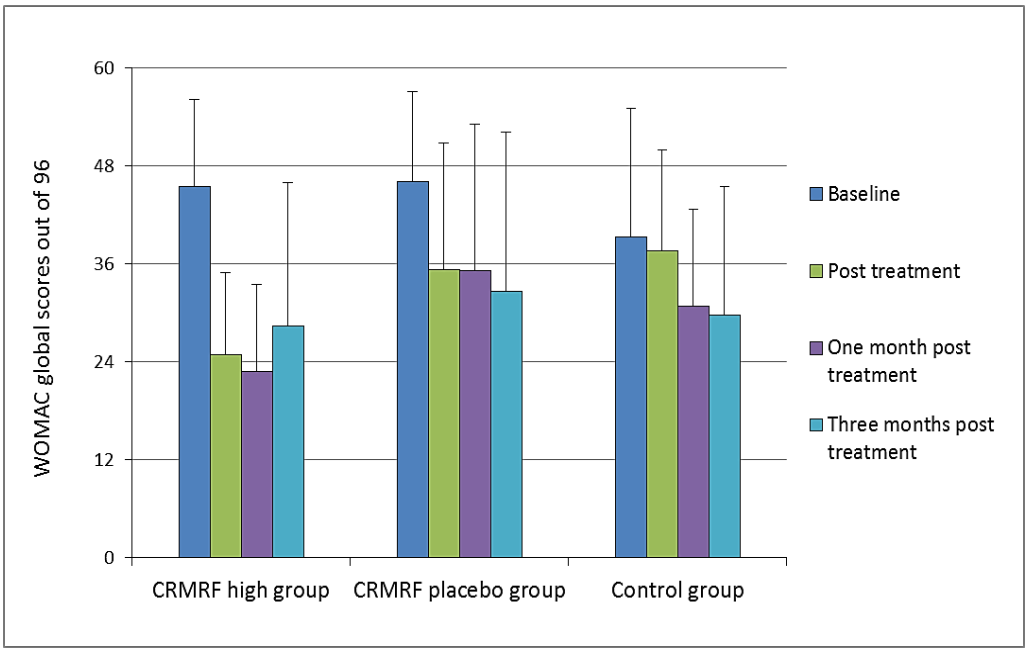


Figure 8.8: Percentage change in the mean WOMAC global scores from the baseline

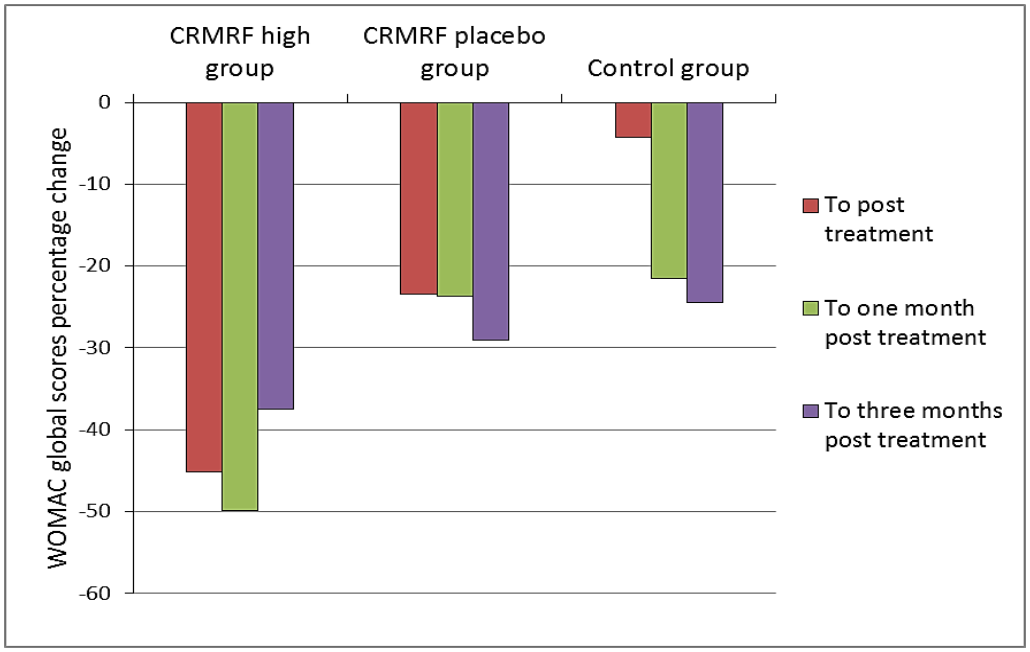


Table 8.4: Within-group pairwise comparisons for the WOMAC global scores

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	1.940*	.297	.000	1.53
		3	2.163*	.343	.000	1.72
		4	1.670*	.455	.004	1.16
	2	1	-1.940*	.297	.000	
		3	.222	.203	1.000	
		4	-.270	.428	1.000	
	3	1	-2.163*	.343	.000	
		2	-.222	.203	1.000	
		4	-.492	.414	1.000	
	4	1	-1.670*	.455	.004	
		2	.270	.428	1.000	
		3	.492	.414	1.000	
RFP	1	2	.977*	.297	.012	0.79
		3	1.093*	.343	.016	0.74
		4	1.412*	.455	.021	0.84
	2	1	-.977*	.297	.012	
		3	.116	.203	1.000	
		4	.434	.428	1.000	
	3	1	-1.093*	.343	.016	
		2	-.116	.203	1.000	
		4	.318	.414	1.000	
	4	1	-1.412*	.455	.021	
		2	-.434	.428	1.000	
		3	-.318	.414	1.000	
CTR	1	2	.094	.297	1.000	
		3	.711	.343	.265	
		4	1.056	.455	.151	
	2	1	-.094	.297	1.000	
		3	.617*	.203	.025	
		4	.962	.428	.180	
	3	1	-.711	.343	.265	
		2	-.617*	.203	.025	
		4	.345	.414	1.000	
	4	1	-1.056	.455	.151	
		2	-.962	.428	.180	
		3	-.345	.414	1.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Table 8.5: Between-group pairwise comparisons for the WOMAC global scores

Time	Group		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
1	RFH	RFP	-.038	.369	1.000	
		CTR	.558	.369	.414	
	RFP	RFH	.038	.369	1.000	
		CTR	.596	.369	.341	
	CTR	RFH	-.558	.369	.414	
		RFP	-.596	.369	.341	
2	RFH	RFP	-1.001	.510	.169	
		CTR	-1.288*	.510	.046	0.94
	RFP	RFH	1.001	.510	.169	
		CTR	-.287	.510	1.000	
	CTR	RFH	1.288*	.510	.046	
		RFP	.287	.510	1.000	
3	RFH	RFP	-1.107	.572	.178	
		CTR	-.893	.572	.377	
	RFP	RFH	1.107	.572	.178	
		CTR	.214	.572	1.000	
	CTR	RFH	.893	.572	.377	
		RFP	-.214	.572	1.000	
4	RFH	RFP	-.297	.733	1.000	
		CTR	-.056	.733	1.000	
	RFP	RFH	.297	.733	1.000	
		CTR	.241	.733	1.000	
	CTR	RFH	.056	.733	1.000	
		RFP	-.241	.733	1.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

8.6.3 Walking ability

The group wise mean (SD) TUG scores obtained at each assessment point are plotted in Figure 8.9. Figure 8.10 shows the percentage changes of mean from the baseline. The statistical analysis (4*3 mixed methods ANOVA (time, group)) of the TUG scores revealed a significant main effect for the time (within-group change) (F (2.022, 84.917) = 15.199, p < 0.001); however, there was no significant interaction between the group and time. Therefore, the type of intervention did not make a significant difference to the reported TUG scores, but there was a significant overall difference between pre, post, one-month follow-up and three-month follow-up TUG scores for all groups. There was no significant difference between the baseline scores of the three groups. All three group results failed to reach the MCID levels.

Results of within-group pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was significant) are reported in Table 8.6. All significant effects and interactions have been highlighted. All three groups demonstrated a significant improvement in walking time from baseline to post treatment and from baseline to one-month follow-up; however, there was no significant difference between the baseline and the three-month follow-up.

Figure 8.9: The mean (SD) TUG scores

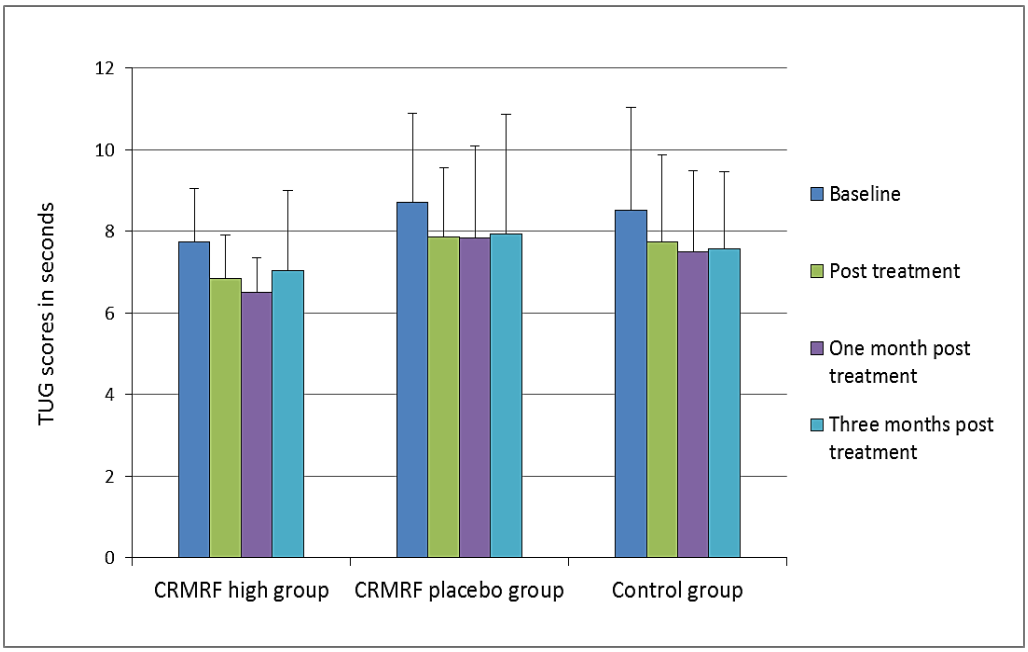


Figure 8.10: Percentage change in the mean TUG scores from the baseline

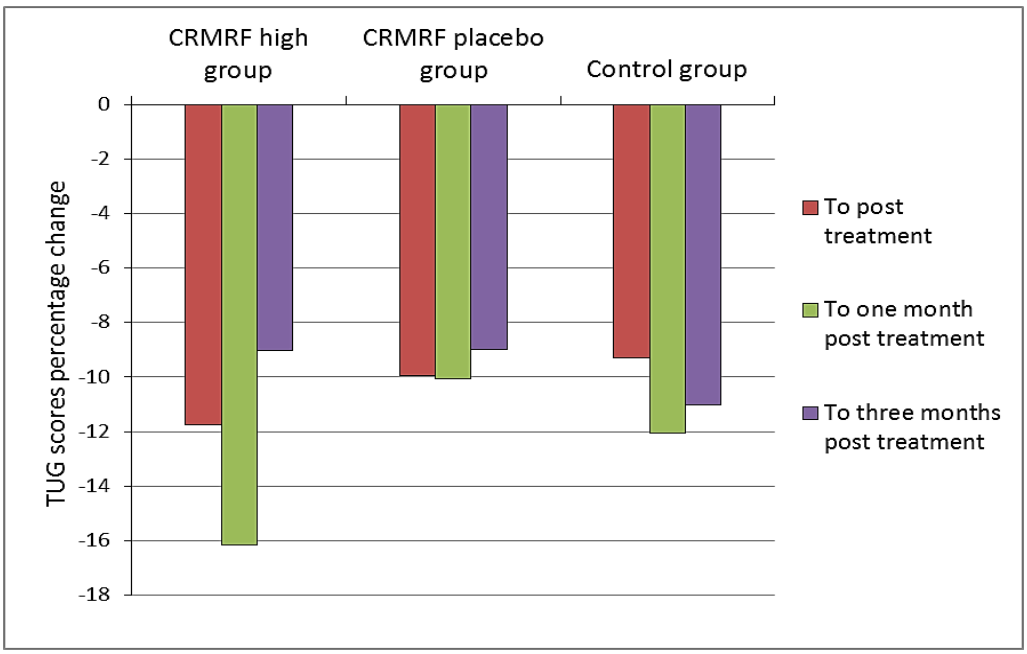


Table 8.6: Within-group pairwise comparisons for the TUG scores

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	.166*	.043	.002	0.72
		3	.230*	.050	.000	1.09
		4	.139	.067	.274	
	2	1	-.166*	.043	.002	
		3	.064	.030	.213	
		4	-.027	.064	1.000	
	3	1	-.230*	.050	.000	
		2	-.064	.030	.213	
		4	-.091	.050	.448	
	4	1	-.139	.067	.274	
		2	.027	.064	1.000	
		3	.091	.050	.448	
RFP	1	2	.145*	.043	.009	0.41
		3	.156*	.050	.020	0.39
		4	.150	.067	.188	
	2	1	-.145*	.043	.009	
		3	.011	.030	1.000	
		4	.005	.064	1.000	
	3	1	-.156*	.050	.020	
		2	-.011	.030	1.000	
		4	-.006	.050	1.000	
	4	1	-.150	.067	.188	
		2	-.005	.064	1.000	
		3	.006	.050	1.000	
CTR	1	2	.136*	.043	.017	0.33
		3	.176*	.050	.006	0.45
		4	.158	.067	.143	
	2	1	-.136*	.043	.017	
		3	.040	.030	1.000	
		4	.023	.064	1.000	
	3	1	-.176*	.050	.006	
		2	-.040	.030	1.000	
		4	-.018	.050	1.000	
	4	1	-.158	.067	.143	
		2	-.023	.064	1.000	
		3	.018	.050	1.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

8.6.4 Knee joint ROM

The group wise mean (SD) knee ROM obtained at each assessment point are plotted in Figure 8.11. Figure 8.12 shows the percentage changes of mean from the baseline. The statistical analysis (4*3 mixed methods ANOVA (time, group)) of the knee ROM revealed a significant main effect for the time (within-group change) ($F(3, 126) = 9.070$, $p < 0.001$) and a significant interaction between the group and time ($F(6) = 2.553$, $p = 0.023$). Therefore, the type of intervention made a significant difference to the observed knee ROM and there was a significant overall difference between the pre, post, one-month follow-up and three-month follow-up knee ROM. There was no significant difference between the baseline values of the three groups.

Although there was a significant main effect for the interaction between time and group, the pairwise comparisons did not reveal any significant interactions between any of the groups

for any of the time points and are hence not reported here. Results of the within-group pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was significant) are reported in Table 8.7. All significant effects and interactions have been highlighted. Within the active group, there was a highly significant improvement in the observed knee ROM values from baseline to post treatment, which was sustained significantly over the one-month follow-up phase. No such meaningful changes were noted at any time point within the other two groups.

Figure 8.11: The mean (SD) knee ROM

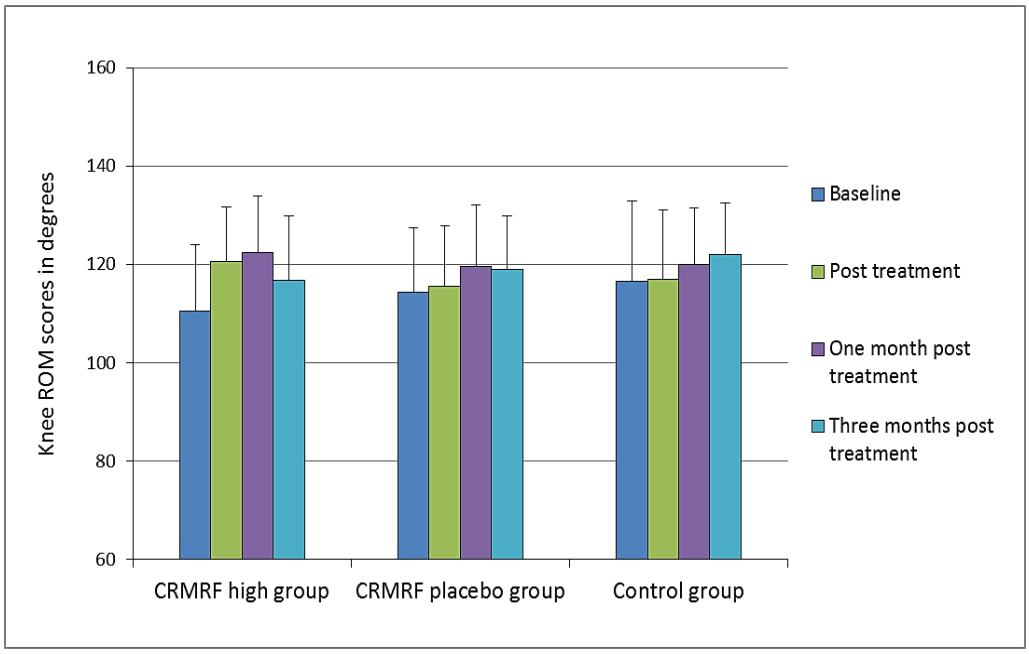


Figure 8.12: Percentage change in the mean knee ROM from the baseline

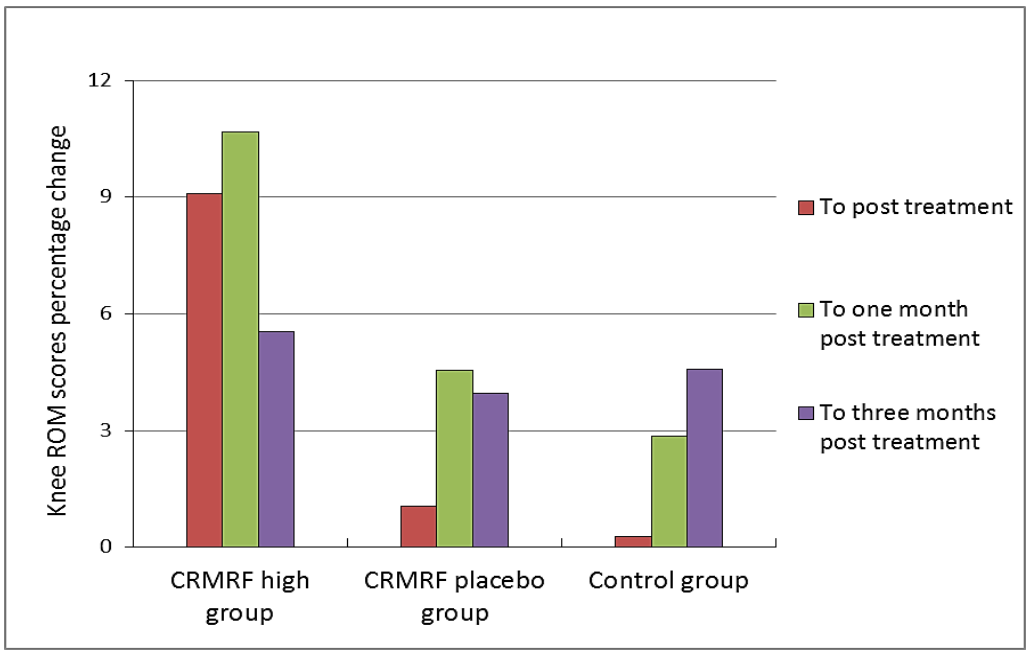


Table 8.7: Within-group pairwise comparisons for the knee ROM

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	-.475*	.114	.001	0.81
		3	-.553*	.130	.001	0.91
		4	-.289	.126	.162	
	2	1	.475*	.114	.001	
		3	-.077	.094	1.000	
		4	.186	.105	.501	
	3	1	.553*	.130	.001	
		2	.077	.094	1.000	
		4	.263	.100	.069	
	4	1	.289	.126	.162	
		2	-.186	.105	.501	
		3	-.263	.100	.069	
RFP	1	2	-.058	.114	1.000	
		3	-.242	.130	.420	
		4	-.215	.126	.577	
	2	1	.058	.114	1.000	
		3	-.185	.094	.341	
		4	-.157	.105	.849	
	3	1	.242	.130	.420	
		2	.185	.094	.341	
		4	.027	.100	1.000	
	4	1	.215	.126	.577	
		2	.157	.105	.849	
		3	-.027	.100	1.000	
CTR	1	2	-.021	.114	1.000	
		3	-.166	.130	1.000	
		4	-.259	.126	.278	
	2	1	.021	.114	1.000	
		3	-.145	.094	.787	
		4	-.238	.105	.170	
	3	1	.166	.130	1.000	
		2	.145	.094	.787	
		4	-.093	.100	1.000	
	4	1	.259	.126	.278	
		2	.238	.105	.170	
		3	.093	.100	1.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

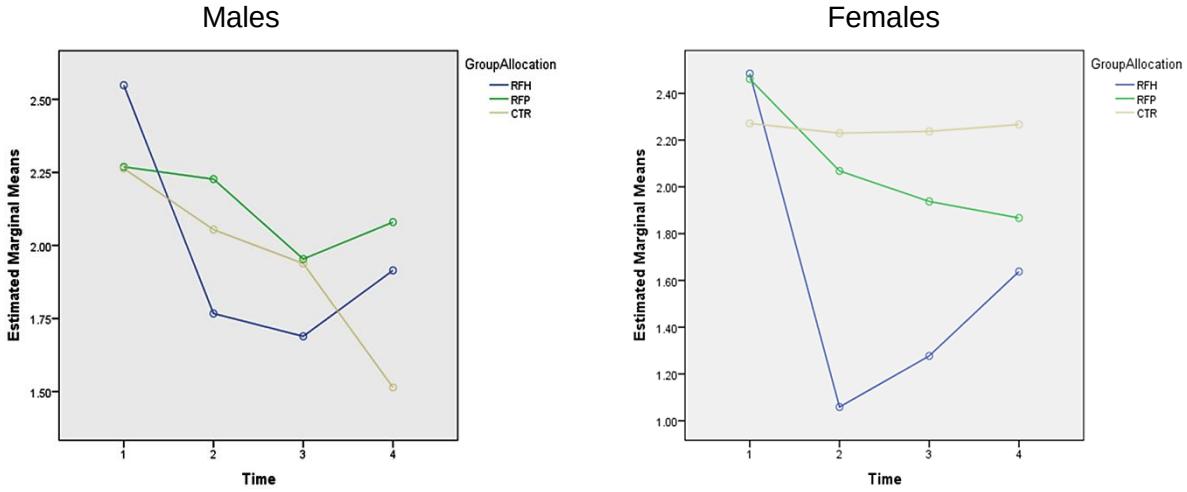
8.6.5 Subgroup analyses and correlations

Subgroup analyses were performed using gender as a grouping variable in the main ANOVA alongside group allocation to examine if men and women responded differently to the interventions in each group. Additionally, correlational analyses (Pearson correlation / Spearman's rho) were performed using a group wise split file command in the SPSS software for age, BMI, OA duration and the mean CRMRF dose / SAR (active group only), with the percentage changes in the four outcome measures at three stages – from baseline to post treatment, from baseline to one-month follow-up and from baseline to three-month follow-up. This analysis examined if the outcomes within the groups were influenced by any of the above factors. Additionally, correlations were also tested using the same parameters, but with group and gender wise split file command to test if the outcomes in men and women in each group correlated differently to the parameters given above. The results are explained below.

8.6.5.1 Subgroup analyses

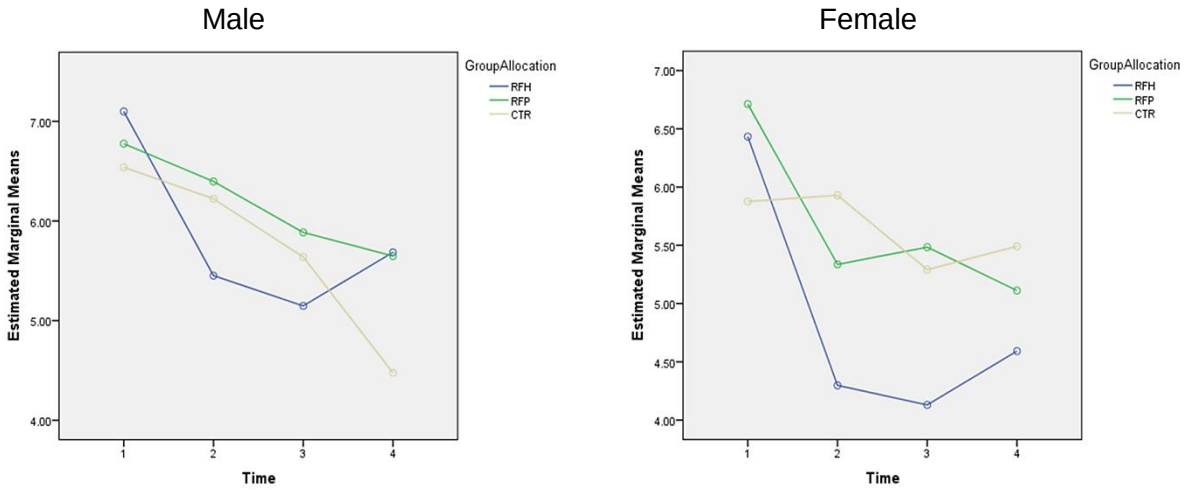
For self-reported pain, there was no overall significant effect of gender in the main ANOVA for any of the interactions. However, there were significant differences between groups at post treatment and one-month follow-up based on gender. While males did not show any differences between groups at any time point, females in the active group demonstrated highly significant reduction of their pain scores compared to the other two groups at post treatment (both $p \leq 0.001$) and compared to control group at the one-month follow-up ($p = 0.009$). In the pairwise within-group comparisons based on gender, the females in the active group demonstrated a more pronounced reduction in pain compared to that of males at post treatment ($p = 0.014$) although both genders achieved significant improvements over time. Figure 8.13 shows male and female pain responses separately (plot as obtained from SPSS.

Figure 8.13: Pain scores – males versus females (Y – axis: estimated marginal means of the square root transformed pain data; X – axis: four time points)



For the WOMAC global scores, there was no overall significant effect of gender in the main ANOVA for any of the interactions. However, there were significant differences between groups at post treatment based on gender. While males did not show any differences between groups at any time point, females in the active group demonstrated a significant reduction in their WOMAC global scores compared to the control group at post treatment ($p = 0.046$). In the pairwise within group comparisons, there were no significant differences between the genders at any time point in any group; however, females in the active group demonstrated a greater improvement in function over time although both genders achieved significant improvements within the groups. Figure 8.14 shows the changes in the male and female WOMAC global scores separately.

Figure 8.14: WOMAC global scores – males versus females (Y – axis: estimated marginal means of the square root transformed WOMAC global data; X – axis: four time points)



For TUG and knee ROM scores there were no noteworthy effects of gender on the outcome, except that there was a greater improvement in the knee ROM among the females in the active group to post treatment and to one-month follow-up while males showed no improvement.

8.6.5.2 Correlations

No significant correlations were observed between age, BMI, mean CRMRF dose / SAR of the active group or OA duration and the percentage changes of the four outcomes from baseline to any of the time points in any of the three groups. This may suggest that age, BMI, treatment dose (within the active group) or duration of OA did not significantly influence the patients' response to treatment in this study regardless of the intervention or outcome measure. Similarly, there was no significant influence of gender in the above correlational analyses in any of the groups. This may suggest that there was no significant difference in the way how either gender correlated with age, BMI, mean CRMRF dose / SAR of the active group or duration of OA for any of the four outcomes in any of the three groups in this study.

8.6.6 Post-hoc power and sample size calculation

All power and sample size calculations were conducted using G*Power (Version 3.1). The observed power and the computed sample sizes required for a power of 0.8 for all ANOVA main effects and interactions are given below in Table 8.8. The data suggests that with a total sample of 45 in the study, the power and sample size requirements have been met.

Table 8.8: Power and sample size for the main effects and interactions

Outcome measures	Parameter	Observed power	Total sample required for 0.8 P
VAS pain score	Main effect for time	1.00	18
	Time*Group interaction	0.99	24
WOMAC osteoarthritis index	Main effect for time	1.00	18
	Time*Group interaction	0.85	42
TUG test score	Main effect for time	1.00	18
	Time*Group interaction	Non significant	
Knee ROM	Main effect for time	0.98	27
	Time*Group interaction	0.83	45

8.7 Discussion

The study investigated the effects of 448 kHz CRMRF on the clinical outcomes of patients affected by chronic OA of the knee. To the researcher's knowledge this is the first such study conducted using RF at this operating frequency level and energy type.

The results revealed significant improvements in OA-related pain and function in participants treated with active CRMRF in addition to exercise and advice, when compared to those who were treated with exercise and advice only. The fact that the placebo group also improved at a greater rate than the control group (although much less pronounced than the active treatment) indicated the presence of a placebo effect. This is unsurprising given the fact that placebo effect of up to 40% has been shown to exist in various forms of treatments.[551-553] The study participants included 20% more females than males, which reflect the fact that the condition affects females more than males.[505] Interestingly, the response of female participants to the CRMRF intervention was significantly more pronounced than that of male participants in this study for the measured outcomes. Whilst the outcome was influenced by the gender, other parameters such as age, BMI, the CRMRF dose / SAR within the active group or the duration of OA did not influence the outcome significantly.

Self-reported pain on a 10 cm VAS was used in this study as it is a simple, straight-forward and easy to administer measure of the participants' subjective perception of pain. Although it is a valid and reliable measure to be used in clinical research (described in the methods section), VAS has been criticised for failing to reflect the elements of multidimensional pain construct (e.g. the cognitive and behavioural elements).[618] However, VAS is so commonly used to evaluate the level of pain in clinical practice that almost all participants were already familiar with this scale and had administered it previously while receiving care. It is also

worth noting at this point that the use of WOMAC meant that some other aspects of the pain experience of the participants were evaluated.

The participants were asked to rate 'the average pain over the last 24 hours' considering all their activities and instances when they did experience more pain or less pain in their knee, to reflect on their whole day's symptoms. Another option was to rate 'pain now', which however was considered unsuitable since various factors could have influenced a sudden spike or reduction in their pain. For example, the hospital building where the study was carried out is situated on a hilly terrain. The participants may have come by walking, by car or by public transport (such external factors could not be controlled), which would have exerted varying levels of stress on the knee and hence could have reflected on their pain scores. Taking a 24-hour average of the pain was therefore considered a more robust option. The VAS pain measurement could be suitably used for the assessment of the current level of pain or for recall of the average pain over a period.[619-621]

The literature has suggested that the MCID of VAS vary according to the level of pain[622] and the type of condition.[623] On average, a reduction in pain by a score of around 1.9 – 2.0 out of 10 (19 – 20%) is generally accepted as MCID.[565-567] In this study, the active group reported 66.11% reduction in pain from baseline to post treatment, 59.50% reduction from baseline to one-month follow-up and 44.60% reduction from baseline to three-month follow-up. In contrast, the control group reported 7.75% reduction in pain from baseline to post treatment, 11.31% reduction from baseline to one-month follow-up and 12.20% reduction from baseline to three-month follow-up. The changes in the placebo group to the same time points were 15.84%, 26.36% and 20.92% respectively. It should be noted that the pain results in only the active group attained the MCID levels, which was sustained significantly throughout the study.

The pain results clearly demonstrated that the active CRMRF treatment had an immediate treatment effect that was over four times more pronounced than that of the placebo while it was close to 10 times more pronounced than that of the control intervention. A significant proportion of this effect was sustained even after three months from the intervention. This study did not employ any follow-up assessments longer than three months. The rate of decline could slow with time, which means some of the clinical effects could be retained for longer than three months. However, it is difficult to predict when the decline might reach a plateau.

Like the VAS pain, studies have reported different levels of MCID for the WOMAC global score. Recently, Hmamouchi et al. (2012)[572] suggested that a 16% reduction from the WOMAC global baseline score can be considered as MCID, while Angst et al. (2001)[624] had earlier recommended that a change of 12% would be sufficient. In this study, the active group reported 45.16% reduction in the WOMAC global score from baseline to post

treatment, 49.85% reduction from baseline to one-month follow-up and 37.54% reduction from baseline to three-month follow-up. In contrast, the control group reported 4.24% reduction in the WOMAC global score from baseline to post treatment, 21.53% reduction from baseline to one-month follow-up and 24.41% reduction from baseline to three-month follow-up. The score changes in the placebo group to the time points were 23.44%, 23.73% and 29.09% respectively. The changes in WOMAC scores for the active treatment group can therefore be considered highly clinically significant.

The above WOMAC percentage changes suggest that (as stated in the results) while all groups demonstrated clinically meaningful changes within, the change in the active group was significantly more pronounced when compared to that in the other two groups although not these interactions attained statistical significance. Whilst the benefit of exercise and advice became evident in the control group only after eight weeks from the start (as shown by their reduced WOMAC global scores), the placebo group gained potential additional benefits sooner, possibly due to two reasons. Firstly, the higher number of treatment sessions they received in the first four weeks and secondly, the presence of placebo effect. However, it should be noted that by the one-month follow-up and thereafter the WOMAC scores of both placebo and control groups were closely matched.

The feedback received from the participants who gained a greater reduction in pain and hence a greater improvement in physical function suggested that they could enjoy a more functionally active life. Nonetheless, interestingly in many instances this increase in function led to a return of symptoms in the weeks following the end of treatment. Besides the CRMRF treatment effect wearing off, the above reason might be partly responsible as to why the symptoms started to increase towards the three-month follow-up phase in many participants. Specifically, there were some participants from the active group who complained about the symptoms going back to usual pre-intervention levels after they had undertaken spells of unaccustomed functional tasks that they normally would not have undertaken (potential ‘bounce back’ effect). This feedback was part of informal discussions with the participants, which did not form part of the outcome measures.

The two other outcome measures on walking ability (TUG) and the knee ROM only provided limited information regarding the usefulness of CRMRF for OA knee. TUG produced evenly matched results in all three groups with no significant difference between them although the overall trend was that of significant improvements within all three groups. However, none of them reached the proposed MCID levels, and there might be an issue with the level of reliability of the TUG results since the participants potentially wore different types of footwear during the tests. It was not realistically possible to ensure that the participants wore the same pair of footwear for all four assessments. The knee ROM results were highly significant within the active group, but not within the other two groups. The overlap between

the group variances at the post treatment and the follow-up assessment were possibly too high in relation to their mean difference making their interactions insignificant.

The findings from this study are limited to a ‘high dose’ CRMRF application that generated a ‘moderate’ thermal response in the participants. The dosage delivery in the active group was adjusted based on the verbal feedback from the participants. The overall mean (SD) total (CAP + RES) dose of 46.13 (4.26) W delivered over the eight sessions generated moderate thermal sensation in the tissues. It is unlikely that the participants would have been able to tolerate treatment doses that were any higher since it would have caused thermal discomfort. On the other hand, it is likely that the clinical effects demonstrated might have been linked to the applied dose (dose-response relationship); however, this can only be confirmed with studies that employ contrasting doses of this treatment. Subtle changes in the applied dose between participants within the active group did not correlate with a change in the clinical outcome. A dose-response relationship for contrasting doses of CRMRF was demonstrated in the laboratory study on asymptomatic adults (Chapter 6), hence it remains a realistic possibility in clinical populations too.

The patients who received the active treatment reported experiencing good pain relief for close to two days after a treatment session (informal verbal feedback). Many also described that after receiving the treatment they felt like ‘having extra cushion’ in the knee. This pain relief is unlikely to have been a mere counterirritant effect, although little is known about the potential effect of CRMRF on the joint tissues affected by OA. Since lasting pain relief and commensurate improvements in function were noted in the actively treated group on a short to medium term, it is proposed that the CRMRF energy may potentially have promoted a lasting anti-inflammatory effect in the arthritic joint structures and/or the periarticular tissues. However, the wearing off the effects (although not completely) within a few weeks after treatment suggests that any such benefits might not have been permanent, but rather due to reversible changes that were induced in the tissues.

Future research should investigate whether providing periodic follow-up treatment sessions (maintenance dose) would enhance and/or consolidate the obtained benefits. Further research should also investigate on the optimum intervention duration, duration of individual sessions, spacing between sessions and optimum dosing. To understand the potential changes to the articular and periarticular tissues in response to CRMRF treatment, future studies should consider employing outcome assessments that can monitor the changes in deeper tissues. Additionally, studies in animal models can help to histologically analyse the tissue changes resulting from CRMRF exposure.

The study only experienced less than 7% dropout (3 out of 45) from the beginning to the end. While all 15 participants in the active group completed all the intervention and assessment sessions, there were two dropouts from the control group. One participant

withdrew after the first session citing lack of interest and the second participant withdrew prior to his second session citing inability to attend because of an aggravation in symptoms (due to an unrelated cause) as the reason. There was one withdrawal from the placebo group after completing six treatment sessions. This person did not give a reason, but the researcher recollects that he was unsatisfied about a lack of improvement in the symptoms to the level he expected.

Data from all three participants who dropped out were included in the analysis based on an intention-to-treat basis, carrying forward their last set of data for the subsequent assessment points. The remaining 42 participants progressed through their sessions in an uneventful manner completing all segments of the study as expected. There were few instances of protocol violations where a scheduled treatment session had to be cancelled and rearranged due to extenuating circumstances. No participant missed more than one scheduled session in this manner.

On the final visit, all participants were asked to identify the study group they were allocated to, based on their perception about the treatment they received. Four participants (27%) in the active group were ‘unsure’ what treatment they received. The remaining 11 participants were ‘certain’ they received the active CRMRF intervention. Eight participants (53%) from the placebo group could not identify their treatments correctly. The others said they thought they had received the placebo mainly due to their lack of improvement in the symptoms. Ten participants out of 15 (67%) in the control group were unaware which group they belonged to. The above numbers suggest that blinding was achieved to a fair extent, which surpassed the expectations of the researcher. It was assumed that the active intervention would be easy to identify because of the explicit heating sensation and hence the low blinding rate for the group was as expected. In contrast, the fact that most people in the control group could not correctly identify their group allocation was surprising.

As explained in the literature section of this thesis only four previous studies on OA knee were identified that employed RF-based intervention below the shortwave frequency range.[194,249-251] Three of those studies were RCTs.[249-251] Only two studies employed RF interventions whose frequencies were close to the frequency of CRMRF (448 kHz).[249,250] Taverner and colleagues[250] used 480 kHz transcutaneous pulsed radiofrequency (TPRF) therapy against a placebo on patients awaiting total knee replacement (TKR). Significant reduction in the pain scores at one and four weeks post treatment was reported by the active group participants compared to the placebo group. The scope of this study was limited, because pain was the only outcome recorded and there were no follow-up assessments beyond four weeks. Their four-week follow-up results were consistent with the findings in the current study.

Comparable results were also obtained by Alcidi and colleagues,[249] who tested a similar type of 500 kHz RF against TENS in patients with OA knee. The RF therapy yielded a greater and longer lasting reduction in pain compared to the TENS. However, the study failed to employ appropriate duration of treatment with TENS to make a valid comparison. Moreover, TENS is shown to induce more effective pain relief during treatment as opposed to post-treatment.[255] Additionally, the study did not follow-up the participants beyond one month, further limiting the scope of the findings.

Nelson and colleagues[251] reported that 15 participants when treated with an active 6.8 MHz pulsed electromagnetic field (PEMF) device showed a three-fold improvement in the pain scores compared to 19 placebo-treated participants. There were no follow-up assessments, and pain was the only outcome measured, which like the above studies, limited the validity and relevance of the findings. Similarly, 12 patients presenting with OA knee were treated using an 8 MHz RF applicator by Takahashi and colleagues[194] in a pilot study. Hyperthermia was induced inside the knee joints and significant pain relief was obtained. However, as above there were no follow-up assessments of the outcome in this study.

The current study included adult participants regardless of age or gender and did not exclude participants based on OA in their other joints (e.g. hip, ankle) like in many other OA knee studies.[625-627] On one hand, such broad inclusion criteria may have acted as a confounder, but on the other hand it has potentially made the study more reflective of real clinical world where patients are often presented with associated problems. The randomised study design would have mitigated such confounders to a large extent.[628,629] Besides, the groups were not significantly different in terms of mean age, BMI, OA duration, or the baseline scores of any of the outcome measures.

One of the potential problems faced in this study was ensuring the proper diagnosis of OA in the prospective participants. Patients referred to physiotherapy directly from GP were often not diagnosed fully. Instead, the patients were referred by simply stating ‘knee pain’. Also, not all patients had previously undergone radiological evaluation at the time of or after contacting their GP. Hence, screening such patients using a comprehensive assessment system such as the criteria set out by the American College of Rheumatology[517,518] was crucial to ensure that only those patients who were diagnostically suitable for the study were being recruited. The American College of Rheumatology criteria consider the clinical picture besides the radiological findings. Under these criteria radiological evaluation is therefore not necessary in all cases. The patients referred by the specialist consultants had already undergone full diagnostic evaluation including radiographs in almost all cases. The patients referred by GPs were not sent for radiological evaluation solely for this study.

8.8 Conclusions

A four-week high dose CRMRF intervention (that produced a moderately thermal response) delivered alongside exercises and advice about self-management of OA knee induced a statistically significant and clinically meaningful reduction of pain as well as improvement of function in patients affected by chronic OA in their knee joints. The effects were significantly greater compared to those obtained using the current standard care comprising exercises and advice. A placebo CRMRF intervention when delivered in addition to standard care, also induced significant clinical benefits when compared to the standard care alone; however, the size of the effect was significantly smaller than that obtained with the active CRMRF treatment. The study only experienced less than 10% dropout of participants. A post-hoc power calculation revealed that the obtained power of the ANOVA main effects of time and group-time interactions (where the interactions were significant) in all four outcomes were over 80%.

Although the sample size might not have been big enough to conduct comprehensive subgroup analyses, overall the responses obtained from female participants were more pronounced than those obtained from male participants. The effects among either gender was not influenced by the age or BMI of the participants, or the duration of their OA. Overall, the treatment effects obtained with CRMRF appeared to wear off substantially after three months from the end of the intervention, which suggests that the treatment might be beneficial in the short to medium term. Whether a longer intervention period and/or periodic follow-up treatment sessions (maintenance doses) will enhance the outcomes further, is unknown but could be usefully investigated with future research. Future clinical studies should identify the optimum dosage and intervention parameters and investigate the dose response relationship by employing varying doses of CRMRF.

9 Chapter 9 – Skin and deep physiological effects of CRMRF treatment in patients with OA of the knee joint: a single-blind randomised controlled trial

9.1 Introduction

Chapter 8 explained how patients affected by OA in their knee joints responded to a four-week intervention comprising high dose CRMRF and standard care, when compared to a standard care only intervention or a placebo CRMRF and standard care intervention. Statistically significant (and clinically meaningful) improvements were obtained in pain and function with the addition of CRMRF. The second aim of the clinical study was to investigate the physiological effects of CRMRF on patients with OA knee and compare them with that of asymptomatic adults, which were obtained in the laboratory study (Chapter 6). However, a direct comparison between the two was deemed problematic since some of the methods that were used in the laboratory study had changed in the clinical segment. These changes will be explained in the methodology section of this chapter.

The laboratory study on asymptomatic adults revealed significant gains in SKT, SBF, deep blood flow volume and intensity of flow secondary to application of high dose CRMRF. The low dose CRMRF and high dose PSWT groups that were part of the laboratory study did not feature in the study on patients with OA knee, since this was a three-group RCT featuring only a high dose CRMRF intervention alongside a placebo CRMRF and control condition with no CRMRF intervention. The physiological measures were carried out at the first session of the clinical trial alongside the clinical outcome measures. Repeat measurement of the physiological parameters was unable to be performed during subsequent sessions since it would have involved substantially more patient time and was hence deemed unethical. From the pilot work, there was no evidence that repeated applications gave rise to different results and thus a single recording session for the physiological parameters was adopted.

9.2 Materials and methods

9.2.1 Changes to the experimental protocol

The physiological measurement protocol used for the patients was like that used in the laboratory study on asymptomatic adults, with the exceptions below.

1) The measurements from the skin were obtained from the medial joint line instead of lower medial thigh.
2) The NCV and tissue extensibility, which did not demonstrate any significant change in the laboratory study were unavailable in the patient study.

3) Instead of the Biopac system and the MyLab70 ultrasound device, equivalent portable measurement devices were used in the patient study. The ultrasound probe was not changed.

4) No skin measurements were obtained from the untreated contralateral limb owing to time constraints and the lack of effects obtained from the laboratory study.

9.2.2 Apparatus

The following devices, which have already been described in detail in chapter 6, were used for the experiment. Except Items two and three, all devices are the same as those used in the laboratory studies.

1) Indiba Activ 902 CRMRF device (Indiba S. A., Spain) was used for CRMRF delivery.

2) The FlexComp Infiniti system (SA7550), a heart rate/blood volume pulse (HR/BVP) sensor (P/N: SA9308M), and a skin temperature sensor (P/N: SA9310M) (Thought Technology Ltd., Montreal, Canada) were used for SBF and SKT monitoring.

3) Esaote MyLab25 ultrasound scanning device and an Esaote LA523 ultrasound probe (Esaote S.p.A, Genoa, Italy) were used for deep blood flow monitoring.

4) An infra-red (IR) tympanic thermometer (Braun ThermoScan IRT 4520, Braun GmbH, Kronberg, Germany) was used for core temperature measurement.

5) Blood pressure (BP) and pulse rate (PR) were monitored using a digital upper arm BP monitor (Omron M2, Omron Healthcare Europe B.V., Hoofddorp, Netherlands).

6) A body composition monitor (Omron BF508, Omron Healthcare Europe B.V., Hoofddorp, Netherlands) was used to obtain the weight, body fat percentage, visceral fat and the body mass index (BMI) measurements of the participants.

9.2.3 Sample and groups

The three groups of participants in this experiment have been described in the previous chapter. Forty-five patients affected by OA knee were randomly allocated into a CRMRF high, CRMRF placebo and control groups, with 15 in each as described. The only difference in the method of this experiment compared to the laboratory study was that this experiment did not employ a crossover (two-way repeated measures) design. Hence, each participant was tested only in one session.

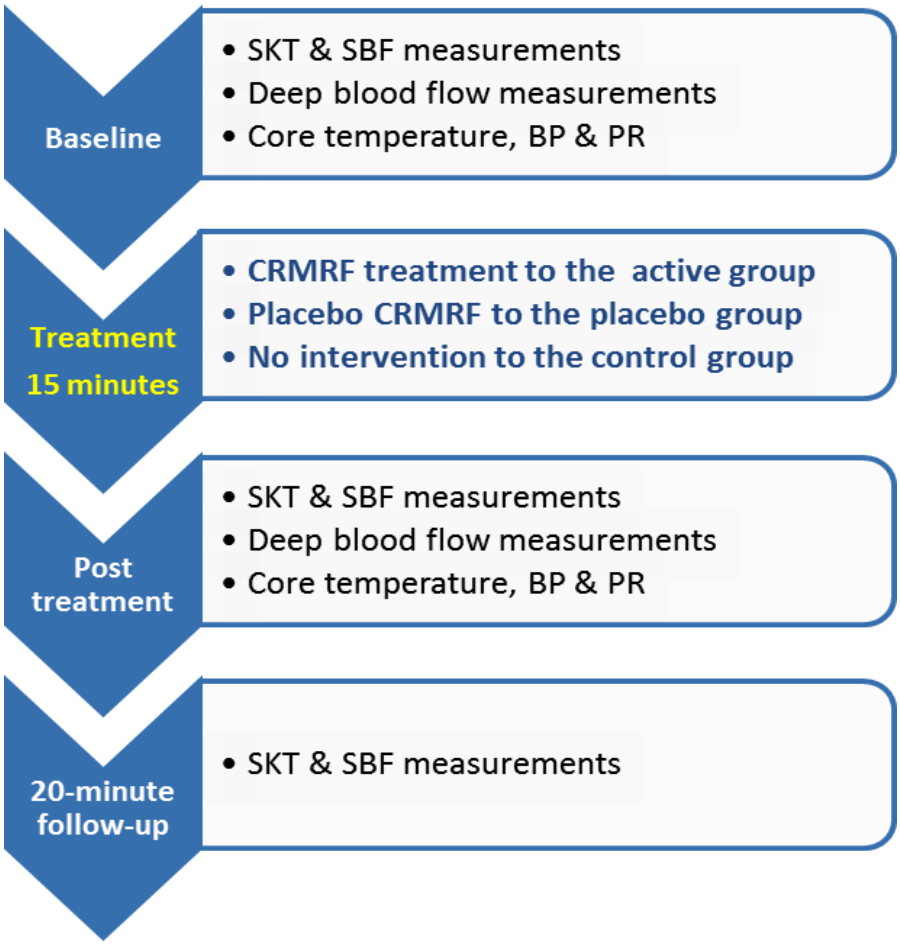
9.2.4 Experimental procedure

Like the laboratory study, on the day of the study the participants were asked to attend the session by avoiding food, beverages and strenuous exercises within one hour before the start. This was to ensure that their physiological condition remained stable during the

sessions.[80,455,456] A similar experimental procedure to that of the laboratory study was employed, with the exceptions stated earlier in this chapter. Signing of the consent form, participant screening using an eligibility questionnaire, testing of skin thermal sensitivity and the ability to distinguish between warm and cold temperatures and the collection of demographic and anthropometric data have been explained in the previous chapter.

To start the experiment the participants positioned themselves in supine on a treatment plinth and were fully supported using pillows. Skin over the medial aspect of the affected knee joint and lower medial thigh was prepared and was marked with tape to deliver the treatment and obtain the physiological measurements. Skin temperature was recorded from the middle of the medial joint line. This was repeated every two minutes until stabilised. The stabilised temperature was considered the baseline temperature. The core (tympanic) temperature was also monitored at the same time. All data, except those from the FlexComp Infiniti and Doppler were entered manually into a participant data collection form (Appendix 9.1). The experimental timeline and measurements are illustrated in Figure 9.1.

Figure 9.1: The experimental timeline for the physiological study on patients



9.2.5 Data acquisition

9.2.5.1 Skin physiological measurements

All skin physiological measurements of SKT and SBF were performed pre-treatment, immediately post treatment and 20-minute post treatment for all three groups. The PPG and SKT probes from the FlexComp Infiniti data acquisition system were attached to the predetermined marked areas on the medial joint line. The probes were positioned within the treatment zone and attached using Micropore™ (3M™) tape. All the probes and connecting leads were removed from the skin prior to the RF treatment and reattached for post treatment measurements. This was done to avoid potential signal interference, probe damage and tissue irritation, as explained in chapter 4 (pilot experiments). Reliability of probe and electrode placements had been established during the laboratory study by extensive pilot works.

The sampling rate and settings on the FlexComp Infiniti device were pre-set by the manufacturer on the appropriate software menu. The FlexComp Infiniti system is battery powered and was not required being set up to run well in advance before the start of the experiment like Biopac, to ensure proper baselining of the data streams. As determined previously, since the SKT took 20 minutes for baselining, the FlexComp system was also set up to run for 20 minutes prior to the start. Both SKT and PPG data were collected for 80 seconds at each of the three measurements (device pre-set). The core (tympanic) temperature, BP and PR were also concurrently monitored at the three time points.

9.2.5.2 Deep physiological measurements

The deep blood flow measurements were performed pre-and post intervention only, unlike the skin measurements. For each participant, blood flow was identified by manoeuvring the ultrasound probe over the lower anteromedial aspect of the quadriceps femoris muscle. Once the most prominent pulsatile (arterial) flow was identified, skin markings were used to establish the accuracy of probe placement and ensure repeatability. Prior to this study, the intra-rater reliability for both Doppler and Sonoelastography measurements was established in a separate pilot study that involved 12 healthy adult participants (explained in chapter 4, pilot experiments). For all participants, the machine settings remained the same for both pre-treatment and post treatment measurements, and like those used in the laboratory experiment. Colour Doppler recordings for velocity of flow were performed first followed by power Doppler for volume and intensity of flow. Up to five seconds of blood flow data clips were recorded during each measurement, which was then broken down into image frames for analysis.

9.2.6 The CRMRF intervention

The interventions have been explained in detail in the previous chapter. For the active and placebo groups, all physiological measurements were performed prior to delivering the standard care intervention. For the control group, the intervention was sandwiched between the pre-and post measurements.

9.2.7 Analysis of data

All data was processed and analysed using Microsoft Office Excel Version 2010 (Microsoft Corporation, USA) and IBM SPSS Statistics Version 20 (IBM Corporation, USA). To ascertain whether there were any statistically significant differences within the treatment groups or between the groups, the group data were compared using a mixed model analysis of variance (ANOVA) at three within-group time points (baseline, post treatment and follow-up) and three between-group conditions (active, placebo and control). Where the data exhibited deviation from normality and/or inequality of variances, data transformation was performed before performing the analysis using the square root function. To enable a comparison between the patient data and the asymptomatic participant data, a similar mixed model ANOVA was carried out between the two 'CRMRF high' groups. Since the two sets of data were not directly comparable due to the reasons stated earlier, data normalization was carried out by taking the baseline scores as 'zero' and the 'percentage changes from baseline' as the subsequent points. The two sets of data were compared based on their face validity as the equivalence between the two sets of devices (Biopac and FlexComp, and the two ultrasound devices) was not able to be tested in this project. The statistical significance was set at $p \leq 0.05$ (0.8 P, 95% CI).

9.3 Results

All 45 participants completed the physiological measurements session. As stated in the previous chapter, all types of treatments and measurements were well tolerated and there were no reports of any adverse events that might be a consequence of the intervention, including any issues due to potential RF overheating. The demographic and the mean (SD) anthropometric data from the participants are reported in the previous chapter. There were no significant differences between any of the three conditions in either characteristic. The details of the CRMRF dosage delivered to the active group participants are also reported in the previous chapter. The results of each physiological parameter obtained from the study groups are reported below.

9.3.1 Skin temperature results

Figures 9.2 & 9.3 shows the mean (SD) SKTs recorded at three time points and the percentage changes of mean respectively. The statistical analysis (3*3 mixed methods

ANOVA (time, group)) revealed a highly significant main effect for time (within-group change) (F (1.377, 57.817) = 155.643, $p < 0.001$) and a highly significant interaction between group and time (F (2.753) = 238.511, $p < 0.001$). Therefore, the type of intervention made a significant difference to the reported SKT values and there was a significant overall difference between the pre, post and 20-minute follow-up SKT. There was no significant difference between the baseline values of the three groups.

Results of the pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was relevant and meaningful) are reported in Tables 9.1 & 9.2. All significant effects and interactions have been highlighted. For the between-group pairwise comparisons it is evident that the active group differed significantly from both placebo and control groups at all time points while the difference between the placebo and control groups might have been due to the drop in SKT in the placebo group due to the cold nature of the coupling medium. Within the active group, there was a highly significant increase in the SKT from baseline to post treatment, which was sustained significantly over the follow-up phase. The control group also showed a significant rise in SKT within-group; however, this was much less pronounced than that of the active group.

Figure 9.2: The mean (SD) SKTs from the three groups

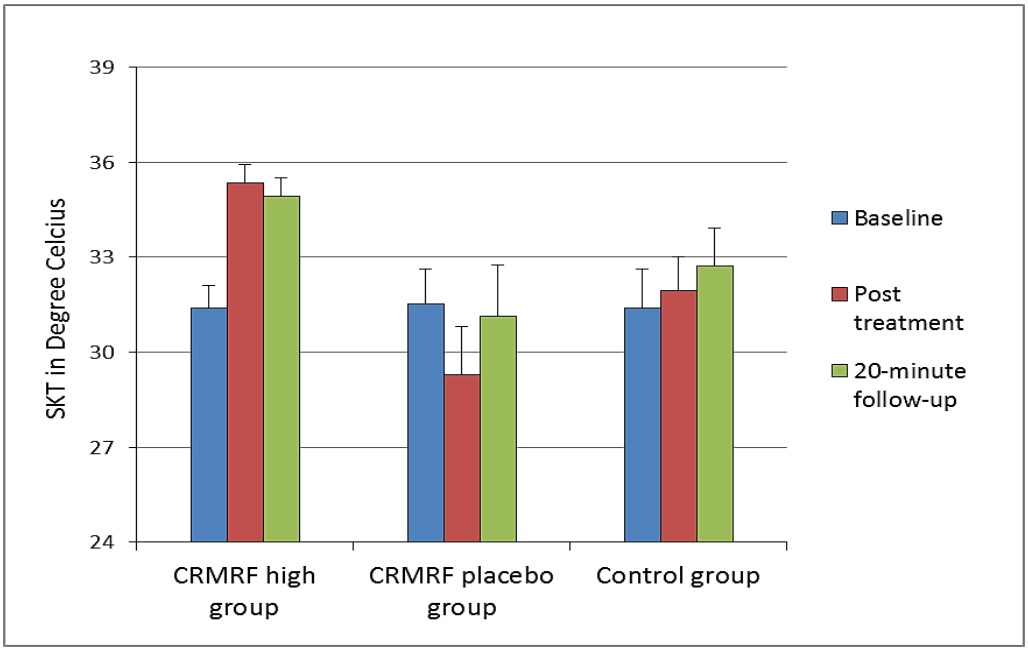


Figure 9.3: Percentage change in the mean SKTs from the baseline

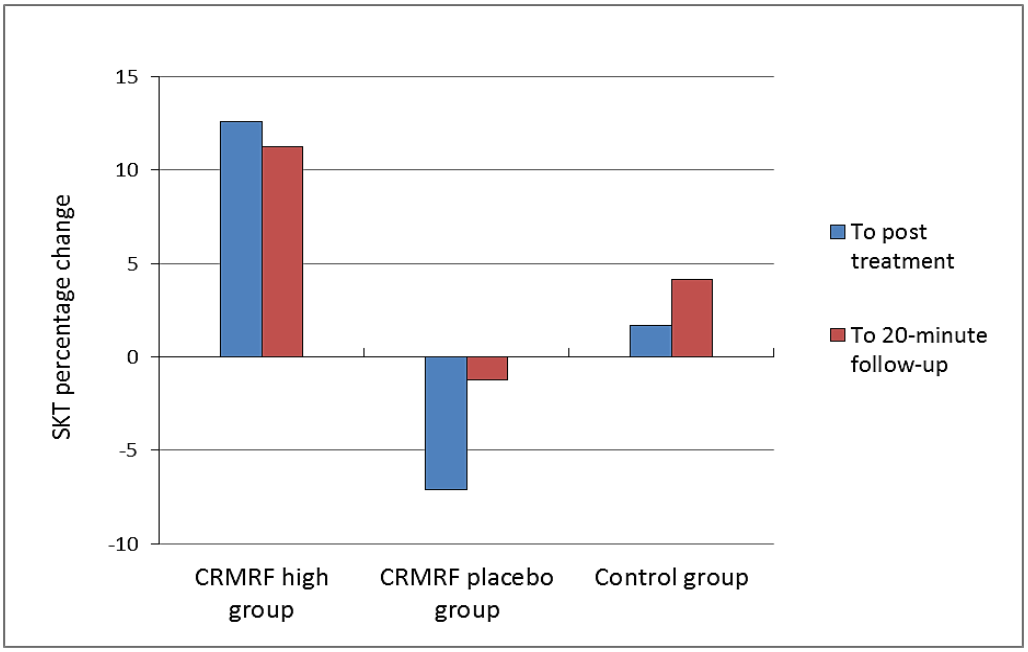


Table 9.1: Within-group pairwise comparisons for SKT

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	-.342*	.013	.000	5.99
		3	-.307*	.016	.000	5.46
	2	1	.342*	.013	.000	
		3	.035*	.008	.000	0.58
	3	1	.307*	.016	.000	
		2	-.035*	.008	.000	
RFP	1	2	.204*	.013	.000	
		3	.035	.016	.088	
	2	1	-.204*	.013	.000	
		3	-.169*	.008	.000	
	3	1	-.035	.016	.088	
		2	.169*	.008	.000	
CTR	1	2	-.047*	.013	.003	0.48
		3	-.115*	.016	.000	1.06
	2	1	.047*	.013	.003	
		3	-.067*	.008	.000	0.68
	3	1	.115*	.016	.000	
		2	.067*	.008	.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Table 9.2: Between-group pairwise comparisons for SKT

Time	Group		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
1	RFH	RFP	-.010	.034	1.000	
		CTR	-.001	.034	1.000	
	RFP	RFH	.010	.034	1.000	
		CTR	.009	.034	1.000	
	CTR	RFH	.001	.034	1.000	
		RFP	-.009	.034	1.000	
2	RFH	RFP	.536*	.037	.000	4.91
		CTR	.294*	.037	.000	3.88
	RFP	RFH	-.536*	.037	.000	
		CTR	-.242*	.037	.000	1.98
	CTR	RFH	-.294*	.037	.000	
		RFP	.242*	.037	.000	
3	RFH	RFP	.331*	.039	.000	2.87
		CTR	.191*	.039	.000	2.16
	RFP	RFH	-.331*	.039	.000	
		CTR	-.140*	.039	.003	1.04
	CTR	RFH	-.191*	.039	.000	
		RFP	.140*	.039	.003	
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

9.3.2 Skin blood flow results

Figures 9.4 & 9.5 shows the mean (SD) SBFs recorded at three time points and the percentage changes of mean respectively. The statistical analysis (3*3 mixed methods ANOVA (time, group)) revealed a highly significant main effect for time (within-group change) ($F(1.554, 65.285) = 21.793$, $p < 0.001$) and a highly significant interaction between group and time ($F(3.109) = 45.058$, $p < 0.001$). Therefore, the type of intervention made a significant difference to the reported SBF and there was a significant overall difference between the pre, post and 20-minute follow-up SBF. There was no significant difference between the baseline values of the three groups.

Results of the pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was relevant and meaningful) are reported in Tables 9.3 & 9.4. All significant effects and interactions have been highlighted. Any change in SBF over time was only noted in the active group, which was also significantly higher than that of the other two groups. Between post treatment and the 20-minute follow-up there was a drop in the obtained SBF within the active group; however, the retained SBF was still significantly higher than that of baseline. There was no difference between the placebo and control groups at any time.

Figure 9.4: The mean (SD) SBFs from the three groups

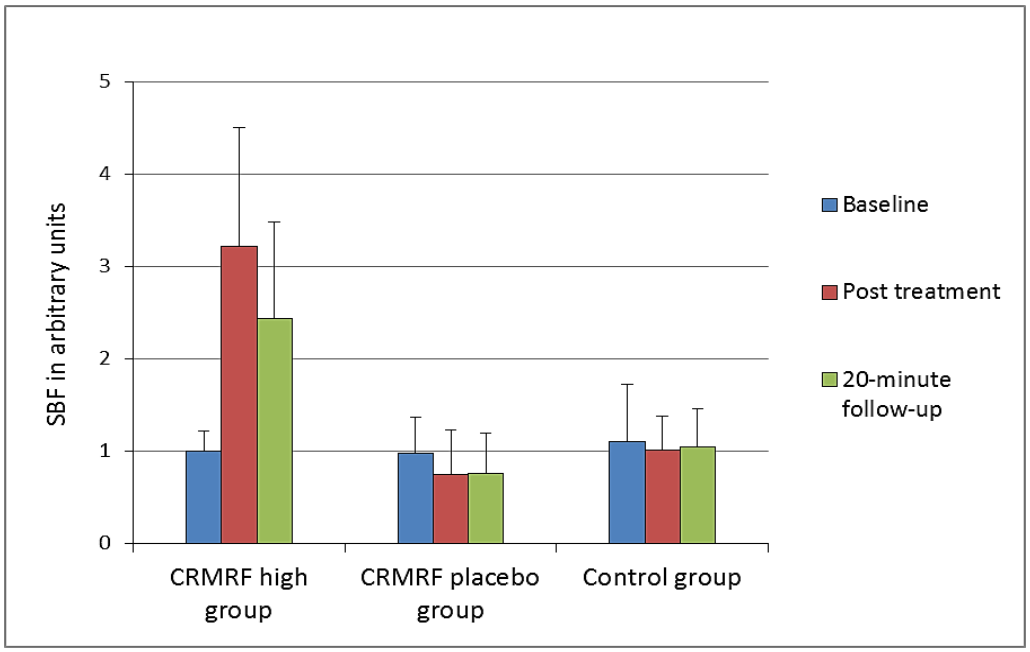


Figure 9.5: Percentage change in the mean SBFs from the baseline

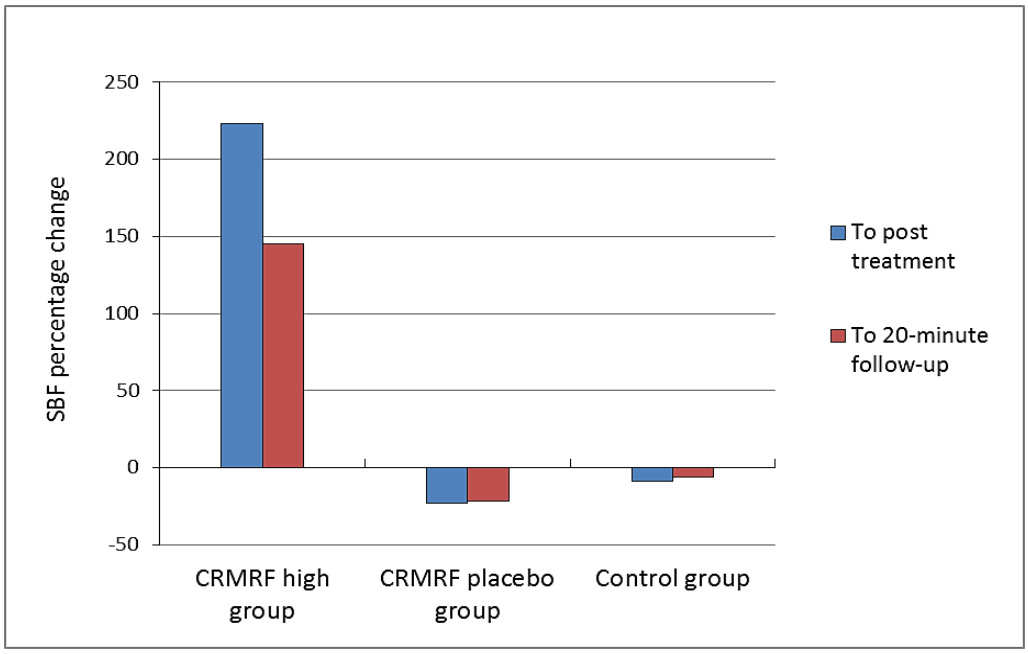


Table 9.3: Within-group pairwise comparisons for SBF

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	-.766*	.061	.000	2.81
		3	-.540*	.060	.000	2.26
	2	1	.766*	.061	.000	
		3	.226*	.037	.000	
	3	1	.540*	.060	.000	
		2	-.226*	.037	.000	
RFP	1	2	.135	.061	.095	
		3	.123	.060	.135	
	2	1	-.135	.061	.095	
		3	-.012	.037	1.000	
	3	1	-.123	.060	.135	
		2	.012	.037	1.000	
CTR	1	2	.029	.061	1.000	
		3	.016	.060	1.000	
	2	1	-.029	.061	1.000	
		3	-.012	.037	1.000	
	3	1	-.016	.060	1.000	
		2	.012	.037	1.000	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Table 9.4: Between-group pairwise comparisons for SBF

Time	Group		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
1	RFH	RFP	.022	.071	1.000	
		CTR	-.027	.071	1.000	
	RFP	RFH	-.022	.071	1.000	
		CTR	-.049	.071	1.000	
	CTR	RFH	.027	.071	1.000	
		RFP	.049	.071	1.000	
2	RFH	RFP	.923*	.099	.000	3.00
		CTR	.767*	.099	.000	2.63
	RFP	RFH	-.923*	.099	.000	
		CTR	-.155	.099	.367	
	CTR	RFH	-.767*	.099	.000	
		RFP	.155	.099	.367	
3	RFH	RFP	.685*	.090	.000	2.50
		CTR	.529*	.090	.000	1.98
	RFP	RFH	-.685*	.090	.000	
		CTR	-.156	.090	.269	
	CTR	RFH	-.529*	.090	.000	
		RFP	.156	.090	.269	

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

9.3.3 Blood flow volume

Figures 9.6 & 9.7 shows the mean (SD) deep blood flow volume recorded using power Doppler ultrasound pre-and post treatment and the percentage changes of mean respectively. The statistical analysis (2*3 mixed methods ANOVA (time, group)) revealed a highly significant main effect for time (within-group change) ($F(1, 42) = 57.081$, $p < 0.001$) and a highly significant interaction between group and time ($F(2) = 75.930$, $p < 0.001$). Therefore, the type of intervention made a significant difference to the reported blood flow volumes and there was a significant overall difference between the pre-and post results. There was no significant difference between the baseline values of the three groups.

Results of the pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was relevant and meaningful) are reported in Tables 9.5 & 9.6. All significant effects and interactions have been highlighted. Like SBF, any change in blood flow volume over time was only noted within the active group, which was also significantly higher than that of the other two groups. There was no difference between the placebo and control group results in either within or between group pairwise comparisons.

Figure 9.6: The mean (SD) blood flow volumes from the three groups

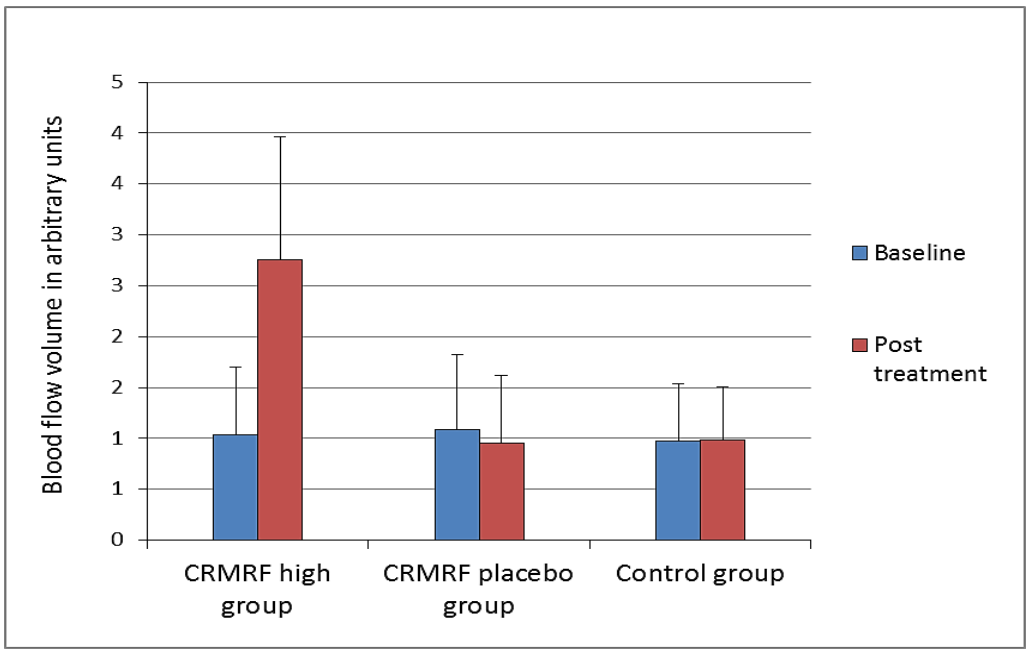


Figure 9.7: Percentage change in the mean blood flow volumes from the baseline

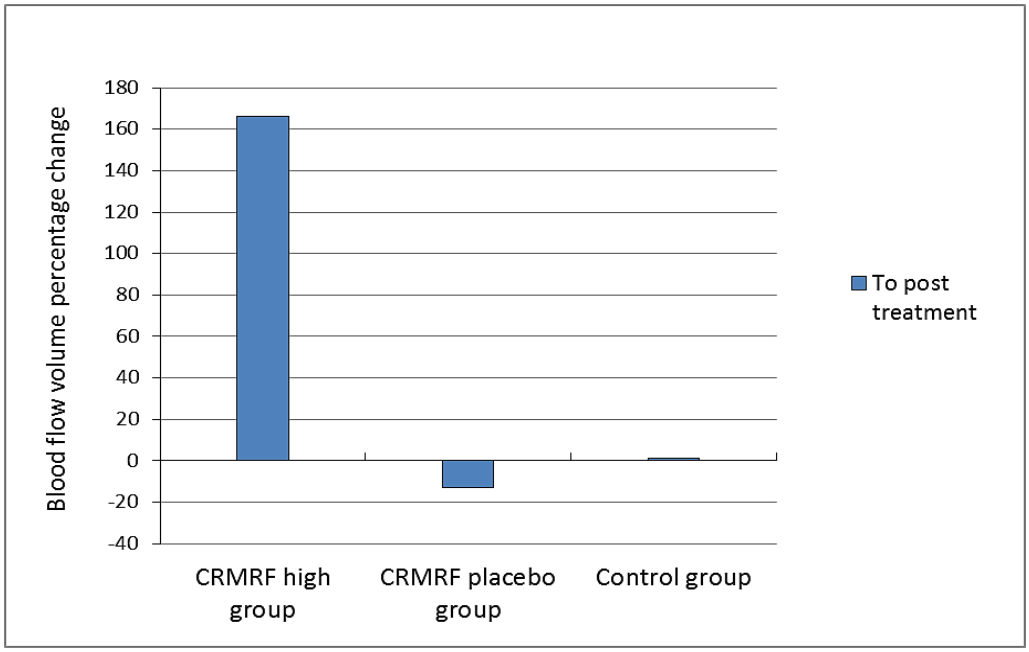


Table 9.5: Within-group pairwise comparisons for blood flow volumes

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	-.647*	.045	.000	1.75
	2	1	.647*	.045	.000	
RFP	1	2	.067	.045	.145	
	2	1	-.067	.045	.145	
CTR	1	2	-.009	.045	.848	
	2	1	.009	.045	.848	
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

Table 9.6: Between-group pairwise comparisons for blood flow volumes

Time	Group		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
1	RFH	RFP	-.024	.116	1.000	
		CTR	.021	.116	1.000	
	RFP	RFH	.024	.116	1.000	
		CTR	.045	.116	1.000	
	CTR	RFH	-.021	.116	1.000	
		RFP	-.045	.116	1.000	
2	RFH	RFP	.690*	.122	.000	1.88
		CTR	.659*	.122	.000	1.89
	RFP	RFH	-.690*	.122	.000	
		CTR	-.031	.122	1.000	
	CTR	RFH	-.659*	.122	.000	
		RFP	.031	.122	1.000	
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

9.3.4 Blood flow intensity

Figures 9.8 & 9.9 shows the mean (SD) deep blood flow intensity recorded using power Doppler ultrasound pre-and post treatment and the percentage changes of mean respectively. The statistical analysis (2*3 mixed methods ANOVA (time, group)) revealed a highly significant main effect for time (within-group change) ($F(1, 42) = 25.578$, $p < 0.001$) and a highly significant interaction between group and time ($F(2) = 43.744$, $p < 0.001$). Therefore, the type of intervention made a significant difference to the reported blood flow intensities and there was a significant overall difference between the pre-and post results. There was no significant difference between the baseline values of the three groups.

Results of the pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was relevant and meaningful) are reported in Tables 9.7 & 9.8. All significant effects and interactions have been highlighted. Like SBF and blood flow volume, any change in blood flow intensity over time was only noted within the active group, which was also significantly higher than that of the other two groups. There was no difference between the placebo and control groups.

Figure 9.8: The mean (SD) blood flow intensities from the three groups

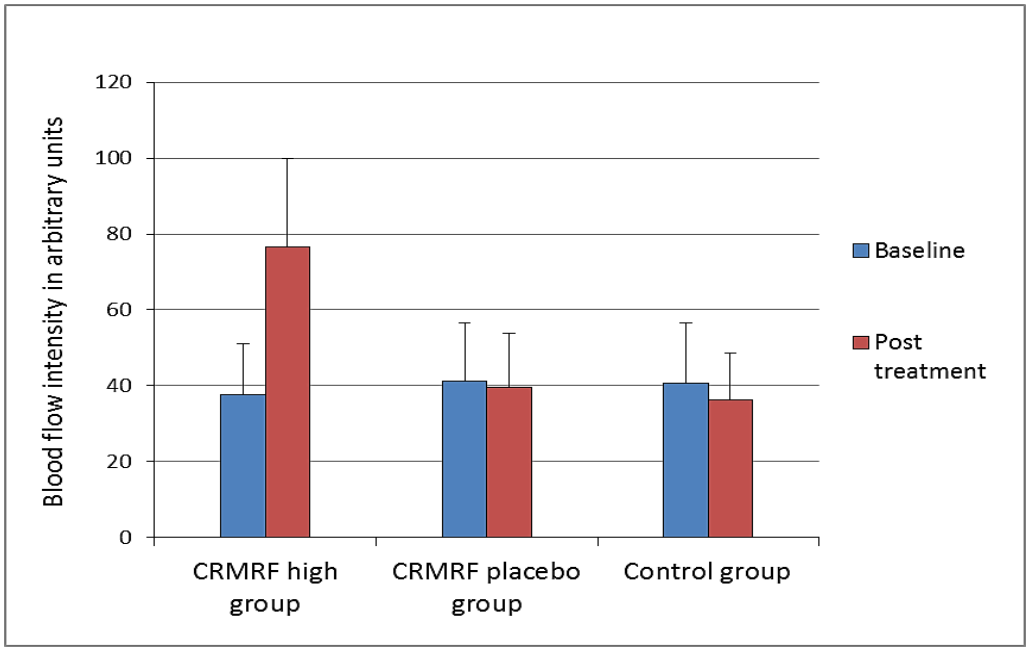


Figure 9.9: Percentage change in the mean blood flow intensities from the baseline

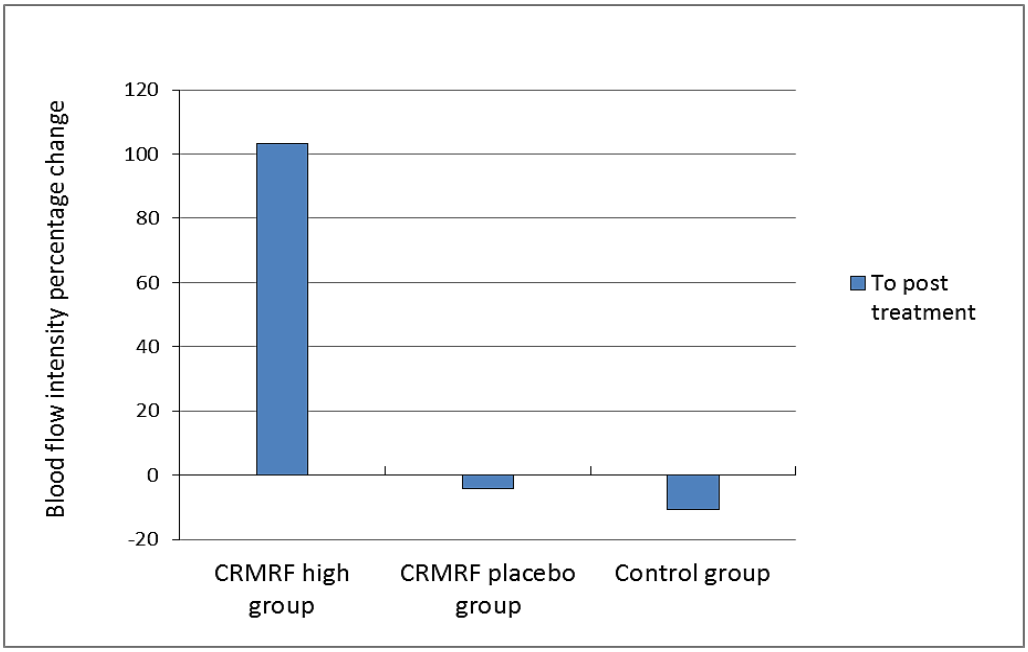


Table 9.7: Within-group pairwise comparisons for blood flow intensities

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	-2.611*	.248	.000	2.17
	2	1	2.611*	.248	.000	
RFP	1	2	.131	.248	.599	
	2	1	-.131	.248	.599	
CTR	1	2	.311	.248	.216	
	2	1	-.311	.248	.216	
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

Table 9.8: Between-group pairwise comparisons for blood flow intensities

Time	Group		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
1	RFH	RFP	-.280	.417	1.000	
		CTR	-.204	.417	1.000	
	RFP	RFH	.280	.417	1.000	
		CTR	.077	.417	1.000	
	CTR	RFH	.204	.417	1.000	
		RFP	-.077	.417	1.000	
2	RFH	RFP	2.462*	.405	.000	2.05
		CTR	2.718*	.405	.000	2.34
	RFP	RFH	-2.462*	.405	.000	
		CTR	.257	.405	1.000	
	CTR	RFH	-2.718*	.405	.000	
		RFP	-.257	.405	1.000	
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

9.3.5 Blood flow velocity

Figures 9.10 & 9.11 shows the mean (SD) blood flow velocity recorded using colour Doppler ultrasound pre-and post treatment and the percentage changes of mean respectively. The statistical analysis (2*3 mixed methods ANOVA (time, group)) did not reveal any significant main effect for time (within-group change); however, there was a small yet significant interaction between group and time ($F(2) = 3.976$, $p = 0.026$). Therefore, the type of intervention made a significant difference to the reported blood flow velocities although there was no significant overall difference between the pre-and post results. There was no significant difference between the baseline blood flow velocities of the three groups.

Results of the pairwise comparisons (adjustment for multiple comparison: Bonferroni), their significance values and their effect sizes (where the interaction was relevant and meaningful) are reported in Tables 9.9 & 9.10. All significant effects and interactions have been highlighted. The active group demonstrated a small yet significant increase in the blood flow velocity, which was also significantly different from the placebo group. Neither placebo nor control group changed significantly within group.

Figure 9.10: The mean (SD) blood flow velocities from the three groups

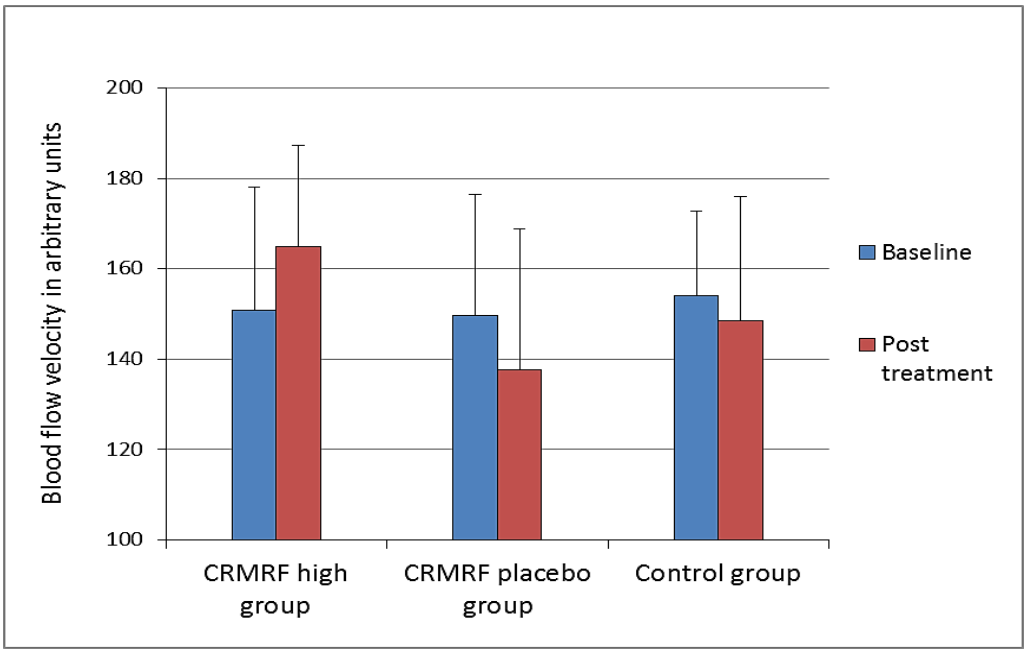


Figure 9.11: Percentage change in the mean blood flow velocities from the baseline

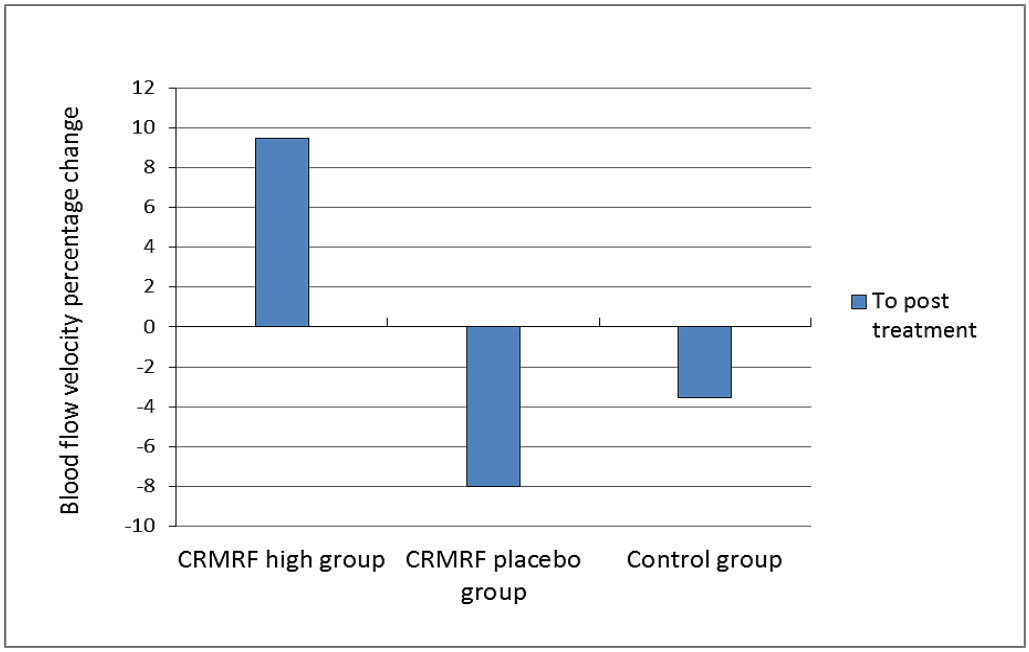


Table 9.9: Within-group pairwise comparisons for blood flow velocities

Group	Time		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
RFH	1	2	-.591*	.291	.049	0.54
	2	1	.591*	.291	.049	
RFP	1	2	.521	.291	.080	
	2	1	-.521	.291	.080	
CTR	1	2	.251	.291	.393	
	2	1	-.251	.291	.393	
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

Table 9.10: Between-group pairwise comparisons for blood flow velocities

Time	Group		Mean Difference	Std. Error	Sig.[b]	Effect size (Hedges's g)
1	RFH	RFP	.044	.384	1.000	
		CTR	-.168	.384	1.000	
	RFP	RFH	-.044	.384	1.000	
		CTR	-.211	.384	1.000	
	CTR	RFH	.168	.384	1.000	
		RFP	.211	.384	1.000	
2	RFH	RFP	1.156*	.418	.025	0.99
		CTR	.675	.418	.341	
	RFP	RFH	-1.156*	.418	.025	
		CTR	-.482	.418	.766	
	CTR	RFH	-.675	.418	.341	
		RFP	.482	.418	.766	
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

9.3.6 Core temperature, blood pressure and pulse rate

Like the laboratory study, no significant variations were noted in any of the groups for the mean core temperature, mean PR or mean BP.

9.3.7 Comparison between the normative and patient data

The statistical analysis (3*2 mixed methods ANOVA (time, group)) revealed a significant interaction between the group and time for all physiological outcomes when the asymptomatic population data was compared to the patient data. This meant that the normative (asymptomatic) population responded differently to the patient population at time points two (post treatment) and three (20-minute follow-up) for all outcomes. The responses were significantly more pronounced among the patients. Key results are reported in Table 9.11.

Table 9.11: Main interactions and pairwise comparisons between the normative and patient physiological data

Physiological measure	Parameter	F statistic	*p* value
Skin temperature	Time*Group interaction	5.167	0.013
	Post treatment		NS
	20-minute follow-up		0.004
Skin blood flow	Time*Group interaction	5.663	0.012
	Post treatment		0.012
	20-minute follow-up		NS
Deep blood flow velocity	Time*Group interaction	NS	
	Post treatment		NS
Deep blood flow volume	Time*Group interaction	7.768	0.009
	Post treatment		0.009
Deep blood flow intensity	Time*Group interaction	12.966	0.001
	Post treatment		0.001

NS - Not significant

9.4 Discussion

This chapter presented the results of the last part of this research project that overall carried out a series of studies relating to the physiological and clinical effects of RF-based treatment in asymptomatic adults as well as adult patients affected by chronic OA of the knee joint. In this study, the skin and deep physiological measures that increased significantly after exposure to a high dose of CRMRF when studied on asymptomatic adults were repeated on patients to enable a comparison. The physiological testing was carried out concomitantly with the clinical RCT on the same study groups that examined the benefits of CRMRF on

pain and function in OA knee. All the relevant measurements were carried out during the first treatment session of the four-month long clinical trial. However, all experimental groups from the laboratory study were not able to be replicated in the patient physiological study owing to time constraints and the fact that priority was given to the clinical outcomes study that involved three groups only.

No similar physiological studies conducted on patients employing RF below the shortwave frequency range have been reported so far. Hence the author is unable to draw any direct comparisons from the literature. To the contrary, considerable numbers of SWT studies have been reported in the last several decades, which have been covered in detail in the section II of this thesis. In one such study on the physiological effect of PSWT on patients with OA knee, Al-Mandeel (2004)[192] reported more pronounced skin physiological responses such as SKT and SBF among the patients when compared to those obtained from asymptomatic adults. Similar MP doses of PSWT were used for both groups of participants. The study also suggested that in either group of participants, the key factor that may have determined the extent of physiological effect might be the applied dose of RF, with a significantly low MP dose of PSWT proving only as good as a placebo.[192]

From the results of the current study it is obvious that the physiological responses obtained from the patients were significantly more pronounced than those obtained from the asymptomatic adults; however, the patients received a significantly higher average treatment dose (p = 0.013) in comparison to the earlier laboratory study. In contrast, the SAR in the two groups was not significantly different from each other, which effectively negates the effects of a difference in the overall dose (SAR was marginally lower for patients). The mean (SD) CRMRF doses delivered in the laboratory study and the first session of the clinical study were 42.37 (4.64) W and 46.87 (4.08) W respectively, which means the mean dose (and hence the total energy) was about 10% higher in the clinical study. While the percentage change in SKT after CRMRF intervention was commensurately higher among patients, the skin and deep blood flow responses (except blood flow velocity) were more than twice as greater among the patients. However, agreeing to the laboratory study, no significant changes were noted in the core temperature, BP or PR in any group at any time.

One of the differences between the laboratory study and the clinical study was that the laboratory provided a more controlled environment in terms of room temperature, humidity and any potential noise due to interference from other fields. The room temperature was always monitored during the laboratory study and maintained within the thermoneutral zone for humans. However, it was not possible to alter the room temperature in the hospital, although it was periodically monitored. Also, there was no provision to monitor the humidity levels in the hospital treatment room. The mean (SD) room temperatures for the CRMRF high dose groups in the laboratory and clinical study were 25.12 (1.14) ^{o}C and 24.27 (0.93)

^{o}C respectively. Ultimately, there was no indication from either study that room temperature and/or humidity correlated significantly with the physiological responses from the participants.

The study had its limitations like the laboratory study segments. There was no blinding on the part of the therapist who delivered the interventions and performed the assessments making this study only single-blind at best. The post treatment skin measurements could only be started with a delay of a minimum of two minutes after the end of treatment due to skin preparation time. The start of deep blood flow measurements was delayed even further, by at least five minutes after the end of treatment. Further, like the laboratory study, temperature from the deeper tissues were not measured. No measurements could be performed during the intervention phase and the follow-ups of skin measurements could not be continued for longer than 20 minutes.

Together, the above factors have affected the validity of the findings on the physiological responses of CRMRF in patients to some extent. Nonetheless, like the laboratory study results, there has not been any sharp decline in the responses of the active intervention over the follow-up phase. Hence, it is proposed that the effects would have been sustained significantly for more than 20 minutes providing a longer therapy window. The reported effects from the current clinical study are based on the convention that the participants maintained their treatment position throughout the experiment (lying in supine).

9.5 Conclusions

The high dose CRMRF delivered to participants affected by OA knee yielded highly significant gains in SKT, SBF, deep blood flow volume and intensity of flow, and a marginal yet significant increase in the deep blood flow velocity over the placebo and control interventions. Core temperature, BP and PR did not change significantly at any time in any group. The findings were generally more pronounced than that obtained from the asymptomatic adults in the laboratory study; however, the patients had received a higher average dose of CRMRF (hence a higher amount of energy) compared to those in the laboratory study. The SAR was not significantly different between the two. The results confirm that the physiological effects of CRMRF in an asymptomatic population can be reproduced in a patient population potentially in a more pronounced manner, and *per se* the effects may indicate the presence of clinical benefits such as those observed in the patients affected by OA knee (previous chapter).

10 Chapter 10 – General discussion and key messages

10.1 Introduction

Radiofrequency-based treatment in therapy-related clinical practice has become less common in the contemporary therapy environment in the Western world. This fashionable shift in practice became more evident in the recent decades, concomitant with a shift in emphasis towards other forms of physical therapy and newer trends in EPAs. However, RF-based EPAs are still used reasonably widely as revealed by the literature review although the clinical application and research are largely limited to the shortwave frequency range. The use and research of microwave therapy (microwave diathermy) have also diminished. The RF frequencies below the shortwave range (such as the CRMRF employed in this research) are not used as commonly as shortwave RF frequencies and little is known about their underpinning mechanisms, effects and efficacy due to a scarcity of research in the area. Nonetheless, their clinical use and commercial presence have not diminished. It is interesting to note that EPAs such as the CRMRF have close resemblance with longwave diathermy, an EPA that had been in clinical use decades ago (a complex EPA, the clinical use of which diminished owing to practical reasons), although the resemblance is limited to the base frequency of RF employed.

The research described in this thesis was primarily aimed at addressing the shortcomings in the knowledge base relating to 448 kHz CRMRF. Three segments of work involving a detailed review of therapy-related RF literature, multi-stage laboratory studies on asymptomatic adults and hospital-based clinical investigation on patients affected by chronic OA of the knee joint were completed. The clinical trial on patients also incorporated the key elements of the laboratory-based physiological study. The results of all study segments were discussed in detail and the summary findings were laid out in the preceding chapters. As a concluding section, this chapter will aim to draw on the main findings and key arguments from all segments of this project.

10.2 Radiofrequency evidence base

10.2.1 Main findings

The results of the comprehensive review of literature presented in section II has confirmed that the research on RF-based EPAs in therapy practice is largely centred on the shortwave frequency range. The quality of the research and its reporting remained poor across the whole spectrum of clinical studies, especially the studies published in the earlier decades. Often the results proved contradictory, with no clear association between the methodological quality score of a study (Downs and Black score) and its reported outcome. The outcomes mostly appeared to follow a dose-response relationship.

As explained in chapter 2, an all-inclusive approach followed in the literature review and the diverse nature of the identified studies precluded a systematic review. If the assumptions of a systematic review were to be imposed, only a handful of studies on the effect of SWT on OA knee would have met the inclusion criteria. Besides, it should be noted that several systematic reviews on the effect of SWT on OA knee have already been published. Among the other conditions, sufficient number of qualifying studies were not identified to enable a systematic review. In the future, in the event of more studies being published on conditions other than OA knee, systematic reviews should be undertaken. These reviews should follow stricter inclusion criteria on the methodological aspects such as the RF doses used, the use of standardized outcome measures and baseline comparability of the group data.

Based on the available evidence from the shortwave studies, it is proposed that the only clinical conditions where RF-based therapy may be beneficial are chronic OA of the knee, chronic LBP, acute postoperative pain and acute postoperative wound healing. Within these conditions only OA knee had a reasonable number of studies reported. Except for OA knee no recommendations for treatment doses could be made for any of the conditions. It is entirely possible that it is the lack of quality studies and hence the lack of quality evidence for the other conditions that has lead the researcher to making such a conclusion. It should be noted that a 'lack of evidence' is not necessarily an 'evidence of lack'. In this era of evidence-based practice, good quality research studies that comply with the required levels of methodological robustness and completeness of reporting should continue to be reported and reviewed before any claims about efficacy can be proved or disproved.

The complete lack of studies on the CRMRF frequency range provided the researcher no understanding about the effects, efficacy and the theoretical underpinning of this type of RF energy. Hence there was little information from the literature review that could be carried forward to the next phase in a manner that informed and influenced the later stages of CRMRF research in this project.

10.2.2 Key messages

In summary, based on the available literature the three key take home messages reached from the literature review are given below.

1) Shortwave therapy delivered at the appropriate dosage parameters can help to alleviate pain, reduce inflammation and improve tissue healing in certain conditions.
2) There is insufficient information available on the effects, efficacy and theoretical underpinning of RF-based therapy operating below the shortwave frequency range.
3) The effects of RF in tissues are largely thermophysiological, although no definitive information is available for frequencies lower than shortwaves.

10.3 Experiments on physiological effects of RF

10.3.1 Asymptomatic adults

The lack of information available on the effects of low frequency RF-based therapies and the indication from the literature that *per se* the predominant biological effect of RF is thermophysiological, led the focus on to investigating tissue temperature, tissue extensibility and blood flow responses in the laboratory studies. As identified previously, the changes in these parameters reflect the body's response to thermophysiological stimuli. However, due to a lack of published studies, it was unclear if the physiological responses to CRMRF would have any association to that of SWT. Multiple doses of CRMRF were employed to study the level of variation in response and the potential dose response relationship. PSWT is not known to cause extremely high thermophysiological responses due to a washout of the heat energy from the tissues during its "off cycle". The inclusion of a high dose PSWT group in the study enabled a comparison of its thermophysiological responses with that of CRMRF.

10.3.1.1 Main findings

The laboratory study involving asymptomatic adults confirmed that a high dose of CRMRF can significantly increase and sustain SKT and skin and deep blood flow changes, significantly more than a comparable high dose of PSWT. In fact, the effects induced by PSWT were only as big as those induced by a low 'minimally/sub thermal' dose of CRMRF. More importantly, the skin physiological effects induced by PSWT were not sustained over the follow-up assessment phase. By contrast, the low dose CRMRF despite only inducing a similar minimal skin thermal perception both significantly enhanced and sustained SKT and SBF. It also significantly increased the blood flow volume at depth. These findings are interesting from the perspective of a 'therapy window' effect where only the CRMRF interventions provided a longer lasting effect, to be of clinical use.

Considering the responses from the two contrasting doses of CRMRF, it is proposed that CRMRF is potentially capable of inducing a sustained influence on the physiological processes relating to SKT and local blood flow with mechanisms that are either thermal or nonthermal or both. While the significantly pronounced effect of high dose CRMRF on blood flow may clearly have been due to a significant rise in tissue temperature (effect being predominantly thermal), the low dose CRMRF also produced significant rise in blood flow (although the 'effect size' was smaller) despite a lack of commensurate rise in tissue temperature. This might potentially have been a combined thermal and nonthermal effect.

As discussed, previous research with shortwave has proposed that a tissue temperature rise more than 40 ^{o}C may be necessary to increase deep blood flow.[96] Deep tissue temperature was not monitored in the current study, and *per se* any such correlations cannot be drawn for the presented results; however, the tissue temperature is unlikely to have risen to levels

above 40 ^{o}C in this study. Still, a rise in both the volume and intensity of deep blood flow were noted with the high dose CRMRF, while even the low dose CRMRF increased the volume of flow. In contrast, a high dose of PSWT that generated a similar small rise in SKT as the low dose CRMRF failed to have any impact on the blood flow suggesting its lack of notable effect in the absence of significant tissue heating. In other words, unlike CRMRF the current study did not reveal any evidence for a potential nonthermal impact of PSWT on blood flow.

Considering the above argument, it is implied that compared to CRMRF a substantially higher dose of treatment and hence a substantially higher amount of energy (potentially generating a high thermal response) may be needed for PSWT to produce effects like that of CRMRF. PSWT was in fact designed to deliver pulsed RF energy to provide physiological benefits without an undue rise in tissue temperature like that observed in CSWT. It appears from this study that a low dose CRMRF can potentially achieve the same benefits more effectively than PSWT without unduly raising the tissue temperature and despite being a continuous mode RF therapy. Therefore, it is assumed that the type of applied energy might also be a critical factor beside the temperature change, in deciding the level of tissue response.

10.3.1.2 Dose response relationship and SAR

The high dose CRMRF inducing a more pronounced physiological response than the low dose CRMRF indicates a dose-response relationship between groups. The mean dose delivered to the high dose group was twice as big as that of the low dose group. In addition, there were small variations in dosage within the groups itself since a fixed dose was not delivered to everyone in the group (dosing varied based on their thermal perception and thermal tolerance).

Similarly, the physiological responses within the groups varied between participants. However, the dose variations within the groups did not concomitantly correlate to this variation in the level of physiological responses within the groups. A correlational analysis was performed between the applied dose and the percentage change in each physiological measure in each group to confirm this. Similarly, no significant correlations were found within group between the estimated whole-body SAR and any of the physiological parameters. The points given below summarises the above arguments.

- A dose response relationship was observed between the high and low dose CRMRF groups.
- There was no dose response relationship within the groups although the participant doses and physiological responses were varied.

- The difference in physiological outcome among the participants in a group was not related solely to their differences in the overall dose or SAR.

It is problematic to calculate the SAR for the local treated area since the exact volume of tissues that was exposed to the RF energy cannot be determined. In addition, there are issues with potential scattering of the RF waves, which means not all the applied energy may reach the target tissues. This means that both parameters that are required to calculate an accurate SAR – received energy and the mass of tissue exposed cannot be determined accurately. However, the whole-body SAR can be calculated from the total body mass of the person and the total applied energy. Hence, if it is assumed that the energy loss due to scattering or other causes was zero, the mean (SD) estimated whole body SAR was 0.60 (0.09) W/kg for the CRMRF high dose group and 0.27 (0.07) W/kg for the low dose group. Since the PSWT group had received a higher MP dose of RF energy, the mean (SD) SAR was marginally higher at 0.67 (0.10) W/kg. Therefore, it appears that CRMRF can achieve more pronounced physiological responses than PSWT when estimated whole body SAR levels are considered.

Since only two doses of CRMRF were studied in this research project based on the subjective perception of the participants, the minimum required dose for the optimum response in any physiological parameter could not be identified. It has also not been possible to identify why some participants were able to receive a higher dose of RF when compared to the others. It was thought that the BMI of the individual may positively correlate with the level of energy uptake; however, no such correlation or even a trend towards such a correlation was observed in the data. As a result, it was noted that the higher the BMI, the lower was the SAR. It is therefore proposed that the thermal sensory perception of the individual may have been solely responsible for the level of energy uptake. The thermal perception is a normally distributed phenomenon in a normative sample. Further studies will need to be carried out to further identify the dosage and other intervention parameters. Numerous limitations of these studies on the asymptomatic participants have already been discussed in chapters 5 & 6.

10.3.1.3 Key messages

In summary, based on the responses from the asymptomatic adults the three key take home messages from the laboratory study are given below.

1) Both high and low doses of CRMRF can induce significant skin and deep physiological responses and potentially provide a longer ‘therapy window’ when compared to PSWT, with the responses being generated at lower estimated SAR levels.

2) Both thermal and non-thermal mechanisms may underpin the temperature and blood flow changes induced by CRMRF in tissues.

3) Similar physiological responses generated in patients might lead to commensurate clinical benefits.

10.3.2 Patients with OA knee

Pathological tissues could respond differently to RF exposure when compared to normal tissues,[105,192] which means a direct extrapolation of the findings from a normative sample to a patient population could be problematic. The literature on the physiological response of patients to RF-based EPAs is less extensive when compared to that of asymptomatic people. As already identified such evidence for RF below the shortwave frequency band is non-existent. Replicating the key elements of the laboratory-based investigation of CRMRF on patients with OA knee alongside investigating the clinical benefits using clinical outcomes were expected to throw light on an otherwise unexplored area that claims to be beneficial in therapy.

10.3.2.1 Main findings

The results from the experiments on patients with OA knee demonstrated that a high dose of CRMRF can provide even greater physiological benefits in patients with OA knee when compared to the effects on a normative sample, while a placebo showed no meaningful effects on either group of participants.

Although the laboratory study on asymptomatic adults involved two additional groups that received a low dose CRMRF and a high dose PSWT, they were not carried forward to the study on patients. As active treatments, the effects of those two interventions were less pronounced when compared to the CRMRF high dose in the laboratory study as explained previously. Clinically, based on an anticipated dose response relationship like those observed in the lab study (Chapters 5 & 6) and those observed in the past shortwave studies on OA knee,[192] as well as asymptomatic adults,[105] a low dose CRMRF intervention was only expected to be clinically less beneficial for a chronic musculoskeletal condition such as OA knee when compared to a high dose CRMRF. Low dose CRMRF may have a significant clinical value when employed as a treatment option in acute conditions where physiological responses without a heating effect are the intended outcome. This would need to be verified through further clinical research. Although PSWT had been researched considerably in the past, its inclusion was outwith the scope of the clinical trial in this project.

The whole body estimated SARs were calculated for the patient study as well, like the laboratory study. The mean (SD) SAR of the active group that received the high dose CRMRF was 0.54 (0.08). Dose-response correlations between groups could not be analysed for the patient study as there was only one RF group. Nonetheless, within the active group like the laboratory study there were no meaningful or significant correlations between the treatment dose or SAR and any of the physiological outcomes.

10.3.2.2 Comparison of the patient data with the normative sample data

As stated, the patient study only examined those physiological parameters that responded to a high dose CRMRF in the asymptomatic sample. The changes to the experimental protocol when the study was conducted on patients have already been detailed in Chapter 9. Several of the comparative details between the two studies have also been discussed in the same chapter. This section aims to draw on the key points and issues that were identified.

In summary, the physiological effects of CRMRF on patients were significantly more pronounced in patients than in the asymptomatic sample. The patients received a 10% higher overall treatment dose on average when the two were compared. However, their SARs did not differ significantly, and the patient SAR was in fact marginally lower as reported. There may be several reasons why the patients can receive a higher overall dose of CRMRF energy than the asymptomatic participants in the laboratory study. The patients who participated in the active group had a significantly higher BMI (and body weight) and body fat percentage compared to the asymptomatic participants (data reported in chapters 6 & 8). The higher body weight also meant that the patients potentially had a higher volume of tissues receiving the treatment compared to the healthy participants and were thus able to absorb a higher quantity of CRMRF energy yet maintaining a lower rate of absorption (SAR).

The above argument is vindicated by the fact that there was a strong positive correlation between the active group CRMRF dose and the BMI of the group participants. This point is further supported by the comparative estimated whole-body SARs in both groups of participants. That is, although the patients received a higher average dose, their estimated whole-body SAR was lower than that of the asymptomatic participants. Effectively, considering the points discussed above the patients could generate a substantially higher physiological response despite receiving a lower amount of energy per unit body mass. Despite the greater physiological responses among the patients, a direct comparison of the results of the two studies may not be valid owing to not only the differences in dosage/SAR, but also the other reasons given below.

The CRMRF being a continuous mode RF is expected to cause heat build-up in tissues; it is challenging to deliver a pre-set dose to all participants unless substantially lower doses are delivered where there will be no significant heat build -up. Hence, the dosing in both studies was regulated according to the recipients' reported thermal perception that might have been different among the two samples. Even if both studies had employed similar average doses of CRMRF, comparison of the physiological responses between the two would still have been problematic. Firstly, for the skin physiological measures both the devices and the site of measurement were changed for the clinical study. No validity studies were undertaken prior to the clinical trial to establish the agreement between the Biopac and the FlexComp Infiniti units owing to time constraints. All comparisons between the two sets of data are

done based on face validity between the two devices. The skin response and rate of change of response may both have varied due to either/both reasons. For the deep blood flow, the site of measurement and the ultrasound probe remained the same across studies; however, the ultrasound scanner device was changed to a portable version for the clinical study. Therefore, owing to the above reasons, the statistical comparison (reported in chapter 9) was restricted to between the percentage changes in scores from the baseline where the baseline was taken as zero in all groups (data normalization).

The demographic and anthropometric factors differed significantly between the laboratory study and the clinical study. This, alongside the presence of pathology may have contributed to the patients' differences in perception of the RF energy. In addition, because of the urge to receive treatment, the patients may have shown a more positive attitude towards the RF delivery, whereas for the asymptomatic people this could have been a potentially unnecessary experience. The patients' subjective feedback on the 'pleasantness of treatment' justified this viewpoint since the patients suggested that they liked their knee being subjected to heat treatment because they believed it reduced pain and stiffness. No measure on tissue extensibility was used in the clinical study. Since the patients might have had limited tissue extensibility due to the stiffness associated with their OA knee, it is possible that a measure of tissue extensibility might have obtained a different result when compared to the asymptomatic people.

10.4 The clinical outcomes from the OA knee study

During the set-up period for the RCT, several hinderances and long delays were encountered in the administrative procedures between the NHS Trust and the University itself. The Trust and the university were not able to expedite matters in a coordinated and timely manner despite the study gaining the NHS Ethics approval relatively quickly. The researcher understands that a valid existing contract was not in place between the two bodies, which otherwise would have helped to speed up the process. The researcher also spent considerable time in identifying and establishing a study centre. In hindsight, the preparation for the RCT should have been instigated much earlier to allow for all potential delays, such as those identified above.

On the contrary, once the RCT was started the recruitment of 45 patients affected by OA knee into the clinical trial was achieved within seven months from the start of recruitment. The fact that more than half of all suitable patients who were contacted consented to take part helped to speed up recruitment. Although it was anticipated that a greater number of participants would be needed to account for potential drop-outs, a smaller actual drop-out rate meant that 45 was sufficient to meet the necessary statistical power. With the kind co-operation of the departmental staff at the study centre, the communication with participants,

the recruitment process and the running of the trial materialised effectively as anticipated. The intervention design, intervention duration and treatment session times were decided based on what was realistically able to be achieved in a clinical environment and the current best practice. It was well-accepted by all trial participants. On reflection, it appears that the above intervention design and the clinical outcome measures used have been effective given the positive results from the study. However, whether better results could have been obtained with alternate intervention parameters is unknown and warrants further research.

10.4.1 Main findings

The randomised controlled trial on patients with OA knee showed that a high dose of CRMRF can produce statistically and clinically significant gains in pain and function in the short to medium term, which is also significantly more pronounced than the effect produced by a placebo or a control treatment condition involving standard care only. The subjective feedback from the participants indicated that the intervention substantially improved their functional quality of life in the short to medium term. All patients in the active group could reduce their pain medication intake and many who were being considered for invasive procedures by their consultant, were able to postpone the same (either statistic was not documented as an outcome in the study).

The return of symptoms towards the end of three months after the intervention was in part due to the treatment effect wearing off and supposedly also due to the participants' increased physical activity as result of pain relief. The latter observation is based on the patient feedback received, where some have said unaccustomed physical activity led to their symptoms resurfacing. This is further supported by the observation that several participants who continued to restrict their physical activity despite their symptoms reducing after CRMRF intervention have continued to sustain their improvement even at the end of the three-month follow-up.

The study demonstrated that a significant increase in the physiological parameters have also been associated with a significant improvement in the clinical outcomes of pain and function, although they did not necessarily have the same effect sizes. To investigate if these two responses were correlated so that whether a rise in the physiological responses can indicate potential clinical benefits, a correlational analysis was performed between the percentage changes in the physiological parameters of the actively treated group and that in the main clinical outcomes of the group. There were no such correlations or even a trend towards such a correlation noted. This meant that based on the results of this study a change in the physiological responses did not indicate potential clinical benefits. This is also supported by the fact that while the placebo CRMRF intervention produced significant clinical benefits (although the effect was much smaller than the active treatment), it had not produced any

meaningful physiological response. Similarly, the changes in the applied dose of CRMRF or the SAR among the participants within the active group did not correlate with the rate of change in clinical outcomes. In other words, whether the percentage change in the clinical outcomes of one participant was different from that of another participant in the active group was not influenced solely by their treatment dose or SAR.

Since only one group receiving an active RF treatment was employed in the study, a comparison with other forms of RF (such as PSWT) or dose-response relations between multiple doses of CRMRF was not investigated. Overall, the findings of the clinical trial are promising. The literature review suggested that PSWT may be beneficial for the treatment of OA knee. As a separate RF-based EPA, CRMRF may also be an effective treatment option for the management of OA knee. More studies need to be conducted to examine if the results could be replicated in different settings, for more clinical conditions and in other patient groups and locations. Dosimetry studies and comparative studies with other similar EPAs that claim to be effective for the management of OA knee are also necessary. The current findings will provide credible baseline data for such future research, especially since the findings achieved sufficient statistical power.

10.4.2 Key messages

To conclude, the three key take home messages from the hospital-based investigation are given below.

1) The physiological effects of CRMRF obtained from asymptomatic participants were replicated in patients with OA knee and the effects were more pronounced in the patient group.
2) Significant short to medium term gains in pain and function were obtained with a four-week CRMRF intervention over placebo and the current standard care (control) interventions, and the gains were more pronounced in females than in males.
3) The rise in SKT and local blood flow might be indicative of potential clinical effects, but they do not necessarily define the possibility or extent of those clinical benefits.

10.5 Concluding remarks

The research project has successfully completed all its segments. The work attempted to execute a logical progression and this thesis reports the project in its entirety. In hindsight, the work was completed meeting the full expectations of the researcher despite experiencing significant delays owing to Ethics approval and other administrative matters, slow participant recruitment and various hurdles relating to the setting up and running of a clinical trial within the NHS environment. However, apart from the time loss there has not been any adverse impact on the overall execution of the project or the potential patient benefits.

The focus of the project was pre-determined by the external funder for this work. Whilst they were neither directly involved in the design nor implementation of any of the components, their focus was determined *a priori* and was part of the contract between the company and the University. There was no reason to seek an adjustment to this contract clause given the potential value of CMFRF to a patient population, such as those with OA Knee. However, in hindsight, there has not been adequate patient and public involvement in the whole project, and especially in the RCT (where it was more relevant) apart from considering the patient satisfaction post intervention via a subjective 'pleasantness of treatment' feedback. It may be argued that the project was carried out with limited resources to a predetermined focus and hence it would have been challenging to employ such a comprehensive approach. It is proposed that future research in the area should ensure the involvement of patients, potential patients and other members of the health care profession in its development, design and delivery.

Significant new findings that contribute to the existing body of evidence, informing clinical practice and that could guide future research to new extents were obtained. These findings have been reported back to the external stakeholder who remains committed to further research in the future. To the author's knowledge other research projects relating to the biological effects of CRMRF are being carried out at other centres, in collaboration with the manufacturer. Some of these works have already been published.[204,205] The findings from the current project are expected to inform on the future research, some of which are in the planning stage. For example, the manufacturer is likely to conduct studies investigating deep tissue thermal responses to CRMRF application, and how the proposed treatment effects might be altering the tissue characteristics in the presence of a pathology.

Ultimately, the obtained knowledge is expected to benefit the patient community. Some of the results from the earlier stages reported in this thesis has already been published in international peer-reviewed journals (see list of publications) and more papers are expected to be published in the future. The results were also presented at university, national and international level conferences. This dissemination is anticipated to aid the academic, clinical and patient community and enable a better understanding of this electrophysical agent.

Above all, this piece of work over the last five years has been a rigorous training exercise for the researcher on "how to conduct research". A range of research skills, both in theory and practice, were developed and consolidated. It gave an opportunity to cultivate critical thinking, structured planning, and the conduct and evaluation of quantitative research. It is hoped that these skills would help the researcher to continue his engagement with clinical research throughout the future.

10.6 Conflict of interest statement

The University received an industry-linked research funding related to this programme of research from Indiba S. A., Barcelona, Spain. The industry funders had no role in the project design, data collection, data analysis or the preparation of this thesis or any other papers that have been published from this project.

11 References

1 Jauchem JR. Effects of low-level radio-frequency (3kHz to 300GHz) energy on human cardiovascular, reproductive, immune, and other systems: a review of the recent literature. Int J Hyg Environ Health. 2008;211(1-2):1-29.

2 Jauchem JR. A literature review of medical side effects from radio-frequency energy in the human environment: involving cancer, tumors, and problems of the central nervous system. J Microw Power Electromagn Energy. 2003;38(2):103-23.

3 Foster KR. Thermal and nonthermal mechanisms of interaction of radio-frequency energy with biological systems. IEEE Trans Plasma Sci. 2000;28(1):15-23.

4 Foster KR, Glaser R. Thermal mechanisms of interaction of radiofrequency energy with biological systems with relevance to exposure guidelines. Health Phys. 2007;92(6):609-20.

5 Sheppard AR, Swicord ML, Balzano Q. Quantitative evaluations of mechanisms of radiofrequency interactions with biological molecules and processes. Health Phys. 2008;95(4):365-96.

6 Swicord ML, Balzano Q, Sheppard AR. A review of physical mechanisms of radiofrequency interaction with biological systems. 2010 Asia-Pacific International Symposium on Electromagnetic Compatibility; Beijing: IEEE; 2010. p. 21-4.

7 Swicord M, Balzano Q. Has electromagnetic energy in the band 0.1-100 GHz useful medical applications? A review of mechanisms and biological database offers dim prospects. IEEE Trans Plasma Sci. 2008;36(4):1638-49.

8 Kitchen S. Thermal effects. In: Watson T, editor. Electrotherapy: Evidence-Based Practice. 12th ed. Edinburgh: Elsevier Churchill Livingstone; 2008. p. 99-114.

9 Petrofsky J, Goraksh N, Alshammari F, Mohanan M, Soni J, Trivedi M*, et al.* The ability of the skin to absorb heat; the effect of repeated exposure and age. Case Rep Clin Pract Rev. 2011;17(1):CR1-CR8.

10 McLellan K, Petrofsky JS, Bains G, Zimmerman G, Prowse M, Lee S. The effects of skin moisture and subcutaneous fat thickness on the ability of the skin to dissipate heat in young and old subjects, with and without diabetes, at three environmental room temperatures. Med Eng Phys. 2009;31(2):165-72.

11 Petrofsky JS, Laymon M. Heat transfer to deep tissue - effect of body fat and heating modality. J Med Eng Technol 2009. 2008:1-12.

12 Collins CM, Liu W, Wang J, Gruetter R, Vaughan JT, Ugurbil K*, et al.* Temperature and SAR Calculations for a Human Head Within Volume and Surface Coils at 64 and 300 MHz. J Magn Reson Imaging. 2004;19(5):650-6.

13 Kahiel HM, Hussein KFA. SAR distribution in the tissues of human knee subjected to microwave radiation and its dependence on the radiated power. Int J Healthc Tech Manag. 2012;13(1-3):62-70.

14 Markov M. Nonthermal mechanism of interactions between electromagnetic fields and biological systems: A calmodulin example. Environmentalist. 2011;31(2):114-20.

15 Belyaev I. Nonthermal biological effects of microwaves: Current knowledge, further perspective, and urgent needs. Electromagn Biol Med. 2005;24(3):375-403.

16 Rao VS, Titushkin IA, Moros EG, Pickard WF, Thatte HS, Cho MR. Nonthermal effects of radiofrequency-field exposure on calcium dynamics in stem cell-derived neuronal cells: Elucidation of calcium pathways. Radiat Res. 2008;169(3):319-29.

17 Adair ER. Thermal physiology of radiofrequency radiation (RFR) interactions in animals and humans. Radiofrequency Radiation Standards; Biological Effects, Dosimetry, Epidemiology and Public Health Policy. 1995:245-69.

18 Al-Mandeel M, M., Watson T. Pulsed and continuous short wave therapy. In: Watson T, editor. Electrotherapy: Evidence-Based Practice. 12th ed. Edinburgh: Elsevier Churchill Livingstone; 2008. p. 137-60.

19 Silverman DR, Pendleton L. A comparison of the effects of continuous and pulsed short-wave diathermy on peripheral circulation. Arch Phys Med Rehabil. 1968;49(8):429-36.

20 Foster KR, Morrissey JJ. Thermal aspects of exposure to radiofrequency energy: report of a workshop. Int J Hyperthermia. 2011;27(4):307-19.

21 Challis LJ. Mechanisms for interaction between RF fields and biological tissue. Bioelectromagnetics. 2005;Suppl 7:S98-S106.

22 Adair ER, Black DR. Thermoregulatory responses to RF energy absorption. Bioelectromagnetics. 2003;Suppl 6:S17-38.

23 Laurence JA, French PW, Lindner RA, McKenzie DR. Biological effects of electromagnetic fields--mechanisms for the effects of pulsed microwave radiation on protein conformation. J Theor Biol. 2000;206(2):291-8.

24 Chiabrera A, Bianco B, Moggia E, Kaufman JJ. Zeeman-Stark modeling of the RF EMF interaction with ligand binding. Bioelectromagnetics. 2000;21(4):312-24.

25 Adair ER, Kelleher SA, Mack GW, Morocco TS. Thermophysiological responses of human volunteers during controlled whole-body radio frequency exposure at 450 MHz. Bioelectromagnetics. 1998;19(4):232-45.

26 Adair ER, Cobb BL, Mylacraine KS, Kelleher SA. Human exposure at two radio frequencies (450 and 2450 MHz): Similarities and differences in physiological response. Bioelectromagnetics. 1999;20(SUPPL. 4):12-20.

27 Adair ER, Mylacraine KS, Allen SJ. Thermophysiological consequences of whole body resonant RF exposure (100 MHz) in human volunteers. Bioelectromagnetics. 2003;24(7):489-501.

28 Adair ER, Mylacraine KS, Cobb BL. Partial-body exposure of human volunteers to 2450 MHz pulsed or CW fields provokes similar thermoregulatory responses. Bioelectromagnetics. 2001;22(4):246-59.

29 Adair ER, Blick DW, Allen SJ, Mylacraine KS, Ziriax JM, Scholl DM. Thermophysiological responses of human volunteers to whole body RF exposure at 220 MHz. Bioelectromagnetics. 2005;26(6):448-61.

30 Kokolus KM, Capitano ML, Lee CT, Eng JW, Waight JD, Hylander BL*, et al.* Baseline tumor growth and immune control in laboratory mice are significantly influenced by subthermoneutral housing temperature. Proc Natl Acad Sci U S A. 2013;110(50):20176-81.

31 Lodhi IJ, Semenkovich CF. Why we should put clothes on mice. Cell Metab. 2009;9(2):111-2.

32 Gordon CJ. Thermal physiology of laboratory mice: Defining thermoneutrality. J Therm Biol. 2012;37(8):654-85.

33 Silny J. Demodulation in tissue, the relevant parameters and the implications for limiting exposure. Health Phys. 2007;92(6):604-8.

34 Adair ER, Mylacraine KS, Cobb BL. Human exposure to 2450 MHz CW energy at levels outside the IEEE C95.1 standard does not increase core temperature. Bioelectromagnetics. 2001;22(6):429-39.

35 Adair RK. Hypothetical biophysical mechanisms for the action of weak low frequency electromagnetic fields at the cellular level. Radiat Prot Dosimetry. 1997;72(3-4):271-8.

36 Nuccitelli R. Endogenous ionic currents and DC electric fields in multicellular animal tissues. Bioelectromagnetics. 1992;Suppl 1:147-57.

37 Barsoum YH, Pickard WF. Radio-frequency rectification in electrogenic and nonelectrogenic cells of Chara and Nitella. J Membr Biol. 1982;65(1-2):81-7.

38 Pickard WF, Rosenbaum FJ. Biological effects of microwaves at the membrane level: two possible athermal electrophysiological mechanisms and a proposed experimental test. Math Biosci. 1978;39(3-4):235-53.

39 Markov MS. Effects of electromagnetic fields on biological systems. Electromagn Biol Med. 2013;32(2):121-2.

40 Pang XF, Zhang AY. Mechanism and properties of non-thermally biological effect of the millimeter waves. Int J Infrared Millimeter Waves. 2004;25(3):531-52.

41 Postow E, Swicord ML. Modulated fields and "window" effects. Handbook of Biological Effects of Electromagnetic Fields. 1996:535-80.

42 Jauchem JR. Health effects of microwave exposures: a review of the recent (1995-1998) literature. J Microw Power Electromagn Energy. 1998;33(4):263-74.

43 Johansen C. Electromagnetic fields and health effects - Epidemiologic studies of cancer, disease of the central nervous system and arrhythmia-related heart disease. Scand J Work Environ Health. 2004;30(SUPPL. 1):1-80.

44 Repacholi MH. Low-level exposure to radiofrequency electromagnetic fields: health effects and research needs. Bioelectromagnetics. 1998;19(1):1-19.

45 de Seze R. Epidemiology, human experiments and overexposures to assess health risk. Meas Contr. 1998;31(6):176-9.

46 Krewski D, Byus CV, Glickman BW, Lotz WG, Mandeville R, McBride ML*, et al.* Recent advances in research on radiofrequency fields and health. J Toxicol Environ Health B Crit Rev. 2001;4(1):145-59.

47 Litvak E, Foster KR, Repacholi MH. Health and Safety Implications of Exposure to Electromagnetic Fields in the Frequency Range 300 Hz to 10 MHz. Bioelectromagnetics. 2002;23(1):68-82.

48 Repacholi MH. Health risks from the use of mobile phones. Toxicol Lett. 2001;120(1-3):323-31.

49 Krusen FH. Short wave diathermy in industrial rehabilitation. Am J Surg. 1938;42(3):845-50.

50 Harris JF. THe treatment of calcified subdeltoid (subacromial) bursitis by diathermia. J Am Med Assoc. 1923;81(2):98-.

51 Burt JB. Short-wave Diathermy: (Section of Physical Medicine). Proc R Soc Med. 1935;28(3):301-18.

52 Krusen FH. Short wave diathermy. J Am Med Assoc. 1935;104:1237-9.

53 Taylor RB. Some Observations on Short Wave Therapy. Can Med Assoc J. 1936;34(2):183-5.

54 Liebesny P. Athermic shortwave therapy. Arch Phys Ther. 1938;19(Dec):736-40.

55 Valtonen EJ, Alaranta H. Comparative clinical study of the effect of short-wave and long-wave diathermy on osteo-arthritis of the knee and hip. Scand J Rehabil Med. 1971;3(3):109-12.

56 Shah SGS, Farrow A. Trends in the availability and usage of electrophysical agents in physiotherapy practices from 1990 to 2010: a review. Phys Ther Rev. 2012;17(4):207-26.

57 Goats GC. Pulsed electromagnetic (short-wave) energy therapy. Br J Sports Med. 1989;23(4):213-6.

58 Goats GC. Continuous short-wave (radio-frequency) diathermy. Br J Sports Med. 1989;23(2):123-7.

59 Goats GC. Microwave diathermy. Br J Sports Med. 1990;24(4):212-8.

60 Foley-Nolan D. Pulsed low energy high frequency fields: Current status and future trends. Complement Med Res. 1990;4(3):41-5.

61 Kitchen S, Partridge C. Review of shortwave diathermy continuous and pulsed patterns. Physiotherapy. 1992;78(4):243-52.

62 Hayne C. Pulsed frequency energy, its place in physiotherapy. Physiotherapy. 1984;70:259-66.

63 Barnaba S, Papalia R, Ruzzini L, Sgambato A, Maffulli N, Denaro V. Effect of Pulsed Electromagnetic Fields on Human Osteoblast Cultures. Physiother Res Int. 2012.

64 Hill J, Lewis M, Mills P, Kielty C. Pulsed short-wave diathermy effects on human fibroblast proliferation. Arch Phys Med Rehabil. 2002;83(6):832-6.

65 Lehmann JF, McDougall JA, Guy AW, Warren CG, Esselman PC. Heating patterns produced by shortwave diathermy applicators in tissue substitute models. Arch Phys Med Rehabil. 1983;64(12):575-77.

66 Wang JL, Chan RC, Cheng HH, Huang CJ, Lu YC, Chen IS*, et al.* Short waves-induced enhancement of proliferation of human chondrocytes: involvement of extracellular signal-regulated map-kinase (erk). Clin Exp Pharmacol Physiol. 2007;34(7):581-5.

67 Bansal PS, Sobti VK, Roy KS. Histomorphochemical effects of shortwave diathermy on healing of experimental muscular injury in dogs. Indian J Exp Biol. 1990;28(8):766-70.

68 Brown M, Baker RD. Effect of pulsed short wave diathermy on skeletal muscle injury in rabbits. Phys Ther. 1987;67(2):208-14.

69 Constable JD, Scapicchio AP, Opitz B. Studies of the effects of diapulse treatment of various aspects of wound healing in experimental animals. J Surg Res. 1971;11(5):254-7.

70 Fenn JE. Effect of pulsed electromagnetic energy (Diapulse) on experimental hematomas. Can Med Assoc J. 1969;100(5):251-4.

71 Jayanand, Behari J, Lochan R. Effects of low level pulsed radio frequency fields on induced osteoporosis in rat bone. Indian J Exp Biol. 2003;41(6):581-6.

72 Li Q, Kao H, Matros E, Peng C, Murphy GF, Guo L. Pulsed radiofrequency energy accelerates wound healing in diabetic mice. Plast Reconstr Surg. 2011;127(6):2255-62.

73 Nadasdi M. Inhibition of experimental arthritis by athermic pulsating short waves in rats. Orthopedics. 1960;2:105-7.

74 Vanharanta H. Effect of short-wave diathermy on mobility and radiological stage of the knee in the development of experimental osteoarthritis. Am J Phys Med. 1982;61(2):59-65.

75 Warren CG, Lehmann JF, Koblanski JN. Elongation of rat tail tendon: effect of load and temperature. Arch Phys Med Rehabil. 1971;52(10):465-74.

76 Behari J, Jayanand J. Low level pulsed radio frequency field and its remedial effect on osteoporosis and bone fracture. Progress in Electromagnetics Research Symposium, PIERS 2005; Hangzhou2005. p. 736-9.

77 Abramson DI, Bell Y, Rejal H, Tuck S, Jr., Burnett C, Fleischer CJ. Changes in blood flow, oxygen uptake and tissue temperatures produced by therapeutic physical agents. II. Effect of short-wave diathermy. Am J Phys Med. 1960;39:87-95.

78 Abramson DI, Chu LS, Tuck S, Jr., Lee SW, Richardson G, Levin M. Effect of tissue temperatures and blood flow on motor nerve conduction velocity. J Am Med Assoc. 1966;198(10):1082-8.

79 Abramson DI, Harris AJ, Beaconsfield P. Changes in peripheral blood flow produced by short-wave diathermy. Arch Phys Med Rehabil. 1957;38(6):369-76.

80 Al-Mandeel MM, Watson T. The thermal and nonthermal effects of high and low doses of pulsed short wave therapy (PSWT). Physiother Res Int. 2010;15(4):199-211.

81 Bennett RL, Hines Jr EA, Krusen FH. Effect of short-wave diathermy on the cutaneous temperatures of the feet. Am Heart J. 1941;21(4):490-503.

82 Brucker JB, Knight KL, Rubley MD, Draper DO. An 18-day stretching regimen, with or without pulsed, shortwave diathermy, and ankle dorsiflexion after 3 weeks. J Athl Train. 2005;40(4):276–80.

83 Draper DO, Knight K, Fujiwara T, Castel JC. Temperature change in human muscle during and after pulsed short-wave diathermy. J Orthop Sports Phys Ther. 1999;29(1):13-22.

84 Draper DO, Miner L, Knight KL, Ricard MD. The Carry-Over Effects of Diathermy and Stretching in Developing Hamstring Flexibility. J Athl Train. 2002;37(1):37-42.

85 Flax HJ, Miller RN, Horvath SM. Alterations in peripheral circulation and tissue temperature following local application of short wave diathermy. Arch Phys Med Rehabil. 1949;30(10):630-7.

86 Grynbaum BB, Megibow RS, Bierman W. The effect of short wave diathermy upon digital circulation as determined by microplethysmography. Arch Phys Med Rehabil. 1950;31(10):629-31.

87 Karasuno H, Morozumi K, Fujiwara T, Goh AC, Yamamoto I, Senga F. Changes in intramuscular blood volume induced by continuous shortwave diathermy. J Phys Ther Sci. 2005;17(2):71-9.

88 Kottke FJ, Koza DW, et al. Studies of deep circulatory response to short wave diathermy and microwave diathermy in man. Arch Phys Med Rehabil. 1949;30(7):431-7.

89 Lehmann JF, McMillan JA, Brunner GD, Blumberg JB. Comparative study of the efficiency of short-wave, microwave and ultrasonic diathermy in heating the hip joint. Arch Phys Med Rehabil. 1959;40:510-2.

90 Morrissey L. Effects of shortwave diathermy upon volume blood flow through the calf of the leg. J Am Phys Ther Assoc. 1966;46(9):946-52.

91 Peres SE, Draper DO, Knight KL, Ricard MD. Pulsed Shortwave Diathermy and Prolonged Long-Duration Stretching Increase Dorsiflexion Range of Motion More Than Identical Stretching Without Diathermy. J Athl Train. 2002;37(1):43-50.

92 Siems LL, Kosman AJ, Osborne SL. A comparative study of short wave and microwave diathermy on blood flow; the role of the somatic and sympathetic nerves in

the vascular response to deep tissue heating. Arch Phys Med Rehabil. 1948;29(12):759-64.

93 Silverman DR. A Comparison of the Effects of Continuous and Pulsed Short Wave Diathermy: Resistance to Bacterial Infection in Mice. Arch Phys Med Rehabil. 1964;45:491-9.

94 Tuttle WW, Fitts L. The effect of heat produced by short wave diathermy on the activity of muscle. J Lab Clin Med. 1944;29(6):609-13.

95 Valtonen EJ, Lilius HG, Svinhufvud U. Effects of three modes of application of short wave diathermy on the cutaneous temperature of the legs. Eura Medicophys. 1973;9(2):49-52.

96 Verrier M, Falconer K, Crawford JS. A comparison of tissue temperature following two shortwave diathermy techniques. Physiother Can. 1977;29(1):21-5.

97 Vesselinova L. Electromagnetic fields in clinical practice of physical and rehabilitation medicine: A health hazard assessment of personnel. Environmentalist. 2012;32(2):249-55.

98 Hernandez-Bule ML, Roldan E, Matilla J, Trillo MA, Ubeda A. Radiofrequency currents exert cytotoxic effects in NB69 human neuroblastoma cells but not in peripheral blood mononuclear cells. Int J Oncol. 2012;41(4):1251-9.

99 Kato S, Asada R, Kageyama K, Saitoh Y, Miwa N. Anticancer effects of 6-o-palmitoyl-ascorbate combined with a capacitive-resistive electric transfer hyperthermic apparatus as compared with ascorbate in relation to ascorbyl radical generation. Cytotechnology. 2011;63(4):425-35.

100 Hernandez-Bule ML, Cid MA, Trillo MA, Leal J, Ubeda A. Cytostatic response of HepG2 to 0.57 MHz electric currents mediated by changes in cell cycle control proteins. Int J Oncol. 2010;37(6):1399-405.

101 Mitchell SM, Trowbridge CA, Fincher AL, Cramer JT. Effect of diathermy on muscle temperature, electromyography, and mechanomyography. Muscle Nerve. 2008;38(2):992-1004.

102 Hernandez-Bule ML, Trillo MA, Cid MA, Leal J, Ubeda A. In vitro exposure to 0.57-MHz electric currents exerts cytostatic effects in HepG2 human hepatocarcinoma cells. Int J Oncol. 2007;30(3):583-92.

103 Hutchison WJ, Burdeaux BD, Jr. The effects of short-wave diathermy on bone repair. J Bone Joint Surg Am. 1951;33(A:1):155-65.

104 Wessman HC, Kottke FJ. The effect of indirect heating on peripheral blood flow, pulse rate, blood pressure, and temperature. Arch Phys Med Rehabil. 1967;48(11):567-76.

105 Bricknell R, Watson T. The thermal effects of pulsed shortwave therapy. BJTR. 1995;2:430-4.

106 Martínez-Rodríguez A, Bello O, Yañez-Brage I. Effect of a single pulsed shortwave diathermy treatment on extensibility of the hamstrings. Int J Athl Ther Train. 2014;19(1):6-10.

107 Garcia LM, Soares AB, Simieli C, Boratino AV, Guirro RR. On the effect of thermal agents in the response of the brachial biceps at different contraction levels. J Electromyogr Kinesiol. 2014;24(6):881-7.

108 Reilingh ML, van Bergen CJ, Gerards RM, van Eekeren IC, de Haan RJ, Sierevelt IN*, et al.* Effects of Pulsed Electromagnetic Fields on Return to Sports After Arthroscopic Debridement and Microfracture of Osteochondral Talar Defects: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Am J Sports Med. 2016;44(5):1292-300.

109 Galace de Freitas D, Marcondes FB, Monteiro RL, Rosa SG, Maria de Moraes Barros Fucs P, Fukuda TY. Pulsed electromagnetic field and exercises in patients with shoulder impingement syndrome: a randomized, double-blind, placebo-controlled clinical trial. Arch Phys Med Rehabil. 2014;95(2):345-52.

110 Sadoghi P, Leithner A, Dorotka R, Vavken P. Effect of pulsed electromagnetic fields on the bioactivity of human osteoarthritic chondrocytes. Orthopedics. 2013;36(3):e360-e5.

111 Liu HF, Yang L, He HC, Zhou J, Liu Y, Wang CY*, et al.* Pulsed electromagnetic fields on postmenopausal osteoporosis in Southwest China: a randomized, active-controlled clinical trial. Bioelectromagnetics. 2013;34(4):323-32.

112 Giusti A, Giovale M, Ponte M, Fratoni F, Tortorolo U, De Vincentiis A*, et al.* Short-term effect of low-intensity, pulsed, electromagnetic fields on gait characteristics in older adults with low bone mineral density: a pilot randomized-controlled trial. Geriatr Gerontol Int. 2013;13(2):393-7.

113 Galace de Freitas D, Lima Monteiro R, Beretta Marcondes F, Fenzl K, Vantin K, Yukio Fukuda T*, et al.* Pulsed electromagnetic field in patients with shoulder impingement syndrome. Journal of Applied Research. 2013;13(1):28-33.

114 Kim SB, Kim JY, Park SW, Lee NR, Lee SW, Kim YH*, et al.* Comparison of 2 methods of Non-invasive treatment between transcutaneous electrical stimulation and pulsed electromagnetic field stimulation as replacement of invasive manual acupuncture. Acupunct Electrother Res. 2012;37(4):247-61.

115 Sutbeyaz ST, Sezer N, Koseoglu F, Kibar S. Low-frequency pulsed electromagnetic field therapy in fibromyalgia: A randomized, double-blind, sham-controlled clinical study. Clin J Pain. 2009;25(8):722-8.

116 Gupta A, Taly AB, Srivastava A, Kumar S, Thyloth M. Efficacy of pulsed electromagnetic field therapy in healing of pressure ulcers: A randomized control trial. Neurol India. 2009;57(5):622-6.

117 Thamsborg G, Florescu A, Oturai P, Fallentin E, Tritsaris K, Dissing S. Treatment of knee osteoarthritis with pulsed electromagnetic fields: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage. 2005;13(7):575-81.

118 Ganguly KS, Sarkar AK, Datta AK, Rakshit A. A Study of the Effects of Pulsed Electromagnetic Field Therapy with Respect to Serological Grouping in Rheumatoid Arthritis. J Indian Med Assoc. 1998;96(9):272-5.

119 Ieran M, Zaffuto S, Bagnacani M, Annovi M, Moratti A, Cadossi R. Effect of low frequency pulsing electromagnetic fields on skin ulcers of venous origin in humans: A double-blind study. J Orthop Res. 1990;8(2):276-82.

120 Bassett CAL, Pilla AA, Pawluk RJ. A non operative salvage of surgically resistant pseudarthroses and non unions by pulsing electromagnetic fields. A preliminary report. Clin Orthop Relat Res. 1977;No.124:128-43.

121 Wilson DH, Jagadeesh P. experimental regeneration in peripheral nerves and the spinal cord in laboratory animals exposed to a pulsed electromagnetic field. Paraplegia. 1976;14(1):12-20.

122 Rasouli J, Lekhraj R, White NM, Flamm ES, Pilla AA, Strauch B*, et al.* Attenuation of interleukin-1beta by pulsed electromagnetic fields after traumatic brain injury. Neurosci Lett. 2012;519(1):4-8.

123 Seaborne D, Quirion-Degirardi C, Rousseau M, Rivest M, Lambert J. The treatment of pressure sores using pulsed electromagnetic energy (PEME). Physiother Can. 1996;48(2):131-7.

124 Hutchinson D, Witt S, Fairpo CG. Pulsed electromagnetic energy therapy in third molar surgery. Oral Surg Oral Med Oral Pathol. 1978;46(6):748-54.

125 Wilson DH. Comparison of short wave diathermy and pulsed electromagnetic energy in treatment of soft tissue injuries. Physiotherapy. 1974;60(10):309-10.

126 Rohde C, Chiang A, Adipoju O, Casper D, Pilla AA. Effects of pulsed electromagnetic fields on interleukin-1β and postoperative pain: A double-blind, placebo-controlled, pilot study in breast reduction patients. Plast Reconstr Surg. 2010;125(6):1620-9.

127 Reed MW, Bickerstaff DR, Hayne CR, Wyman A, Davies J. Pain relief after inguinal herniorrhaphy. Ineffectiveness of pulsed electromagnetic energy. Br J Clin Pract. 1987;41(6):782-4.

128 Rawe IM, Vlahovic TC. The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: A case report. Int Wound J. 2012;9(3):253-8.

129 Muirhead RJ, Place D, Buswell WA, Heselting J. Pulse electromagnetic energy and pre-tibial lacerations: a randomized clinical trial. Arch Emerg Med. 1991;8(2):152-4.

130 Heden P, Pilla AA. Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients. Aesthetic Plast Surg. 2008;32(4):660-6.

131 Grant A, Sleep J, McIntosh J, Ashurst H. Ultrasound and pulsed electromagnetic energy treatment for perineal trauma. A randomized placebo-controlled trial. Br J Obstet Gynaecol. 1989;96(4):434-9.

132 Foley-Nolan D, Barry C, Coughlan RJ, O'Connor P, Roden D. Pulsed high frequency (27 MHz) electromagnetic therapy for persistent neck pain. A double blind, placebo-controlled study of 20 patients. Orthopedics. 1990;13(4):445-51.

133 Brook J, Dauphinee DM, Korpinen J, Rawe IM. Pulsed Radiofrequency Electromagnetic Field Therapy: A Potential Novel Treatment of Plantar Fasciitis. J Foot Ankle Surg. 2012;51(3):312-6.

134 Shah SGS, Farrow A, Esnouf A. Availability and use of electrotherapy devices: A survey. Int J Ther Rehabil. 2007;14(6):260-4.

135 Shields N, Gormley J, O'Hare N. Short-wave diathermy: A review of existing clinical trials. Phys Ther Rev. 2001;6(2):101-18.

136 Pope GD, Mockett SP, Wright JP. A Survey of Electrotherapeutic Modalities: Ownership and Use in the NHS in England. Physiotherapy. 1995;81(2):82-91.

137 Laufer Y, Dar G. Effectiveness of thermal and athermal short-wave diathermy for the management of knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis cartilage. 2012;20(9):957-66.

138 Guo L, Kubat NJ, Nelson TR, Isenberg RA. Meta-analysis of clinical efficacy of pulsed radio frequency energy treatment. Ann Surg. 2012;255(3):457-67.

139 Marks R, Ghassemi M, Duarte R, Van Nguyen JP. A review of the literature on shortwave diathermy as applied to osteo-arthritis of the knee. Physiotherapy. 1999;85(6):304-16.

140 Rogers LM, Madhavan S, Roth H, Stinear JW. Transforming neurorehabilitation of walking following stroke: the promise of non-invasive brain stimulation--a review. Restor Neurol Neurosci. 2011;29(6):507-16.

141 Machado AF, Santana EF, Tacani PM, Liebano RE. The effects of transcutaneous electrical nerve stimulation on tissue repair: A literature review. Can J Plast Surg. 2012;20(4):237-40.

142 Poltawski L, Watson T. Bioelectricity and microcurrent therapy for tissue healing–a narrative review. Phys Ther Rev. 2009;14(2):104-14.

143 Belivani M, Dimitroula C, Katsiki N, Apostolopoulou M, Cummings M, Hatzitolios AI. Acupuncture in the treatment of obesity: a narrative review of the literature. Acupunct Med. 2013;31(1):88-97.

144 Andersson GB. Epidemiological features of chronic low-back pain. Lancet. 1999;354(9178):581-5.

145 Sammarco VJ, Sammarco GJ, Henning C, Chaim S. Surgical repair of acute and chronic tibialis anterior tendon ruptures. J Bone Joint Surg Am. 2009;91(2):325-32.

146 Flint JH, Wade AM, Giuliani J, Rue JP. Defining the terms acute and chronic in orthopaedic sports injuries: a systematic review. Am J Sports Med. 2014;42(1):235-41.

147 Higgins J, Altman DG. Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. 2008:187-241.

148 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84.

149 Saunders LD, Soomro GM, Buckingham J, Jamtvedt G, Raina P. Assessing the methodological quality of nonrandomized intervention studies. West J Nurs Res. 2003;25(2):223-37.

150 Eng JJ, Teasell R, Miller WC, Wolfe DL, Townson AF, Aubut JA*, et al.* Spinal Cord Injury Rehabilitation Evidence: Methods of the SCIRE Systematic Review. Top Spinal Cord Inj Rehabil. 2007;13(1):1-10.

151 Kaminskyj A, Frazier M, Johnstone K, Gleberzon BJ. Chiropractic care for patients with asthma: A systematic review of the literature. J Can Chiropr Assoc. 2010;54(1):24-32.

152 Shakoor MA, Islam MQ, Zaman MM, Mian MAH, Khan S. Effects of cervical traction and shortwave diathermy on the patients with neck pain. JDMC. 2001;10:91-5.

153 Tung S, Khaski A, Milano E. The application of diapulse in the treatment of decubitus ulcers: Case reports. Contemp Surg. 1995;47:27-33.

154 Bentall RHC, Eckstein HB. A trial involving the use of pulsed electro magnetic therapy on children undergoing orchidopexy. Z Kinderchir. 1975;17(4):380-9.

155 Arghiropol M, Jieanu V, Paslaru L, Vasilco R, Baciu M, Popa N*, et al.* The stimulation of fibronectin synthesis by high peak power electromagnetic energy (Diapulse). Rev Roum Physiol (1990). 1992;29(3-4):77-81.

156 Shakoor MA, Rahman MS, Moyeenuzzaman M. Effects of deep heat therapy on the patients with chronic low back pain. Mymensingh Med J. 2008;17(2 Suppl):S32-8.

157 Comorosan S, Pana I, Pop L, Crăciun C, Cirlea AM, Paslaru L. The influence of pulsed high peak power electromagnetic energy (Diapulse) treatment on posttraumatic algoneurodystrophies. Rev Roum Physiol (1990). 1991;28(3-4):77-81.

158 Incebiyik S, Boyaci A, Tutoglu A. Short-term effectiveness of short-wave diathermy treatment on pain, clinical symptoms, and hand function in patients with mild or moderate idiopathic carpal tunnel syndrome. J Back Musculoskelet Rehabil. 2015;28(2):221-8.

159 Lehmann JF, DeLateur BJ, Stonebridge JB. Selective muscle heating by shortwave diathermy with a helical coil. Arch Phys Med Rehabil. 1969;50(3):117-23.

160 Weber I, Zák K, Malec I, Hontela S. Influence of short wave diathermy on intrauterine temperature. Zentralbl Gynakol. 1969;91(13):416-21.

161 Kovach RI. Temperature distribution in a 2-layer model of a biological object under microwave heating. Med Tekh. 1973;1:18-21.

162 Ilja W, Neninger E, Maria W. Influence of short wave diathermy on intrauterine temperature changes. Zentralbl Gynakol. 1974;13(1):99-105.

163 Davies CTM. The effects of different levels of heat production induced by diathermy and eccentric work on thermoregulation during exercise at a given skin temperature. Eur J Appl Physiol Occup Physiol. 1979;40(3):171-80.

164 Yang WJ, Wang JH. Shortwave and microwave diathermy for deep-tissue heating. Med Biol Eng Comput. 1979;17(4):518-24.

165 Auda SP, Steinert HR, Elias EG, Viravathana T. Selective tumor heating by shortwave radiofrequency (RF). Cancer. 1980;46(9):1962-8.

166 Griffiths H, Kerby IJ, Moore JL, Ahmed A, Smith CW, Mort D*, et al.* A physiological effect on tissue temperature during RF hyperthermia. Br J Cancer. 1984;49(6):801-3.

167 James RD, Williams P, Jones A, Nelis P, Farrow N, Lukka H*, et al.* Determination of human skin pain threshold using 27 MHz radiofrequency heating. Br J Radiol. 1988;61(724):344-6.

168 Jan MH, Lin YF. Clinical heat effect of shortwave diathermy on knee joint. FJPT. 1990;15:7-13.

169 Garrett CL, Draper DO, Knight KL. Heat distribution in the lower leg from pulsed short-wave diathermy and ultrasound treatments. J Athl Train. 2000;35(1):50-5.

170 Murray CC, Kitchen S. Effect of pulse repetition rate on the perception of thermal sensation with pulsed shortwave diathermy. Physiother Res Int. 2000;5(2):73-84.

171 Draper DO, Hawkes AR, Johnson AW, Diede MT, Rigby JH. Muscle heating with Megapulse II shortwave diathermy and ReBound diathermy. J Athl Train. 2013;48(4):477-82.

172 Hawkes AR, Draper DO, Johnson AW, Diede MT, Rigby JH. Heating capacity of ReBound shortwave diathermy and moist hot packs at superficial depths. J Athl Train. 2013;48(4):471-6.

173 Richardson AW. Effect of microwave-induced heating on the blood flow through peripheral skeletal muscles. Am J Phys Med. 1954;33(2):103-7.

174 Schlink F, Rost WE. The effect of ultra-short-wave diathermy on blood. Br J Phys Med. 1954;17(2):39-42.

175 Erdman 2nd WJ. Peripheral blood flow measurements during application of pulsed high frequency currents. Am J Orthop. 1960;2(Aug):196-7.

176 Erdman WJ. Peripheral blood flow measurements during application of pulsed high frequency currents. Am J Orthop. 1960;2:196-7.

177 Millard JB. Effect of high-frequency currents and infra-red rays on the circulation of the lower limb in man. Ann Phys Med. 1961;6:45-66.

178 Downey JA, Frewin DB, Whelan RF. Vascular responses in the forearm to heating by shortwave diathermy. Arch Phys Med Rehabil. 1970;51(6):354-7.

179 Wessman HC. Effect of shortwave diathermy to the abdomen on peripheral circulation during pregnancy. Phys Ther. 1971;51(1):43-7.

180 Hovind H, Nielsen SL. Changes in subcutaneous and muscle blood flow after short-wave diathermy. Bibl Anat. 1973;11:417-22.

181 Hovind H, Nielsen SL. Local blood flow after short-wave diathermy: preliminary report. Arch Phys Med Rehabil. 1974;55(5):217-21.

182 Hovind H, Nielsen SL. The effect of short wave and microwave diathermy on blood flow in subcutaneous and muscle tissue in man. Seventh international congress, June, Montreal. 1974:147-51.

183 Wyper DJ, McNiven DR. Effects of some physiotherapeutic agents on skeletal muscle blood flow. Physiotherapy. 1976;62(3):83-5.

184 Gordon CJ, Ferguson JH. Scaling the physiological effects of exposure to radiofrequency electromagnetic radiation: consequences of body size. Int J Radiat Biol Relat Stud Phys Chem Med. 1984;46(4):387-97.

185 Gersten JW, Wakim KG, et al. The effect of microwave diathermy on the peripheral circulation and on tissue temperature in man. Arch Phys Med Rehabil. 1949;30(1):7-25.

186 Stoner EK. The effect of microwave radiation on the peripheral pulse volume, digital skin temperature and digital blood flow in man. Arch Phys Med Rehabil. 1951;32(6):408-16.

187 Jan MH, Yip PK, Lin KH. Change of arterial blood flow and skin temperature after direct and indirect shortwave heating on knee. FJPT. 1993;18:64-71.

188 Lehmann JF, Masock AJ, Warren CG, Koblanski JN. Effect of therapeutic temperatures on tendon extensibility. Arch Phys Med Rehabil. 1970;51(8):481-7.

189 Giombini A, Giovannini V, Di Cesare A, Pacetti P, Ichinoseki-Sekine N, Shiraishi M*, et al.* Hyperthermia induced by microwave diathermy in the management of muscle and tendon injuries. Br Med Bull. 2007;83(1):379-96.

190 Touchberry C, Le T, Richmond S, Prewitt M, Beck D, Carr D*, et al.* Diathermy treatment increases heat shock protein expression in female, but not male skeletal muscle. Eur J Appl Physiol. 2008;102(3):319-23.

191 Currier DP, Nelson RM. Changes in motor conduction velocity induced by exercise and diathermy. Phys Ther. 1969;49(2):146-52.

192 Al-Mandeel M, M. Pulsed Shortwave Therapy: Its clinical use and physiological effects in healthy and osteoarthritic patients. [PhD thesis]. Hertfordshire, UK: University of Hertfordshire; 2004.

193 Radon K, Parera D, Rose DM, Jung D, Vollrath L. No effects of pulsed radio frequency electromagnetic fields on melatonin, cortisol, and selected markers of the immune system in man. Bioelectromagnetics. 2001;22(4):280-7.

194 Takahashi K, Kurosaki H, Hashimoto S, Takenouchi K, Kamada T, Nakamura H. The effects of radiofrequency hyperthermia on pain and function in patients with knee osteoarthritis: a preliminary report. J Orthop Sci. 2011;16(4):376-81.

195 Robertson VJ, Ward AR, Jung P. The effect of heat on tissue extensibility: A comparison of deep and superficial heating. Arch Phys Med Rehabil. 2005;86(4):819-25.

196 Draper DO. Pulsed shortwave diathermy and joint mobilizations for achieving normal elbow range of motion after injury or surgery with implanted metal: a case series. J Athl Train. 2014;49(6):851-5.

197 Seiger C, Draper DO. Use of pulsed shortwave diathermy and joint mobilization to increase ankle range of motion in the presence of surgical implanted metal: A case series. J Orthop Sports Phys Ther. 2006;36(9):669-77.

198 Guirro EC, Guirro RR, Dibai-Filho AV, Pascote SC, Rodrigues-Bigaton D. Immediate effects of electrical stimulation, diathermy, and physical exercise on lower limb arterial blood flow in diabetic women with peripheral arterial disease: a randomized crossover trial. J Manipulative Physiol Ther. 2015;38(3):195-202.

199 Hamann W, Abou-Sherif S, Thompson S, Hall S. Pulsed radiofrequency applied to dorsal root ganglia causes a selective increase in ATF3 in small neurons. Eur J Pain. 2006;10(2):171-6.

200 Erdine S, Bilir A, Cosman ER, Cosman ER. Ultrastructural changes in axons following exposure to pulsed radiofrequency fields. Pain Pract. 2009;9(6):407-17.

201 Sakai H, Horiguchi N, Endoh D, Nakayama K, Hayashi M. Radiofrequency radiation at 40 kHz induces hepatic injury in Long-Evans Cinnamon (LEC) rats, an animal model for human Wilson disease. J Vet Med Sci. 2011;73(3):299-304.

202 Sakurai T, Narita E, Shinohara N, Miyakoshi J. Intermediate frequency magnetic field at 23 kHz does not modify gene expression in human fetus-derived astroglia cells. Bioelectromagnetics. 2012.

203 Kato S, Saitoh Y, Miwa N. Repressive effects of a capacitive-resistive electric transfer (CRet) hyperthermic apparatus combined with provitamin C on intracellular lipid-droplets formation in adipocytes. Int J Hyperthermia. 2013;29(1):30-7.

204 Hernandez-Bule ML, Martinez-Botas J, Trillo MA, Paino CL, Ubeda A. Antiadipogenic effects of subthermal electric stimulation at 448 kHz on differentiating human mesenchymal stem cells. Mol Med Rep. 2016;13(5):3895-903.

205 Hernandez-Bule ML, Paino CL, Trillo MA, Ubeda A. Electric stimulation at 448 kHz promotes proliferation of human mesenchymal stem cells. Cell Physiol Biochem. 2014;34(5):1741-55.

206 Wise CS, Castleman B, Watkins SL. Effect of diathermy (short wave and microwave) on bone growth in the albino rat. J Bone Joint Surg Am. 1949;31A(3):487-500.

207 Handerson ED, Bennett WA, Herrick JF. Microwave diathermy and the healing of experimentally produced fractures in rabbits. J Bone Joint Surg Am. 1954;36-A(1):64-8.

208 Xu H, Feng L, Zeng Z, Xu S. Experimental study on ultrashort wave therapy on the healing of fracture. Bulletin of Hunan Medical University. 1999;24(2):125-7.

209 Nath PJ, Barman AK, Sarma S. Short-wave diathermy in arthritis in calves. Indian Vet J. 2009;86(1):94-5.

210 Lideo L, Milan R. Ultrasound monitoring of shortwave diathermic treatment of gastrocnemius strain in a dog. J Ultrasound. 2013;16(4):231-4.

211 Raji ARM, Bowden REM. Effects of high-peak pulsed electromagnetic field on the degeneration and regeneration of the common peroneal nerve in rats. J Bone Joint Surg Br. 1983;65(4):478-92.

212 Raji AM. An experimental study of the effects of pulsed electromagnetic field (diapulse) on nerve repair. J Hand Surg. 1984;9(2):105-12.

213 Valtonen EJ. The effect of regional application of short wave diathermy on the blood pressure and diuresis - An experimental study on rats and rabbits. Virchow's Archives for Pathological Anatomy and Physiology and for Clinical Medicine. 1967;342(4):329-33.

214 Overgaard J. Biological effect of 27.12-MHz short-wave diathermic heating in experimental tumors. IEEE Trans Microw Theory Tech. 1978;26(8):523-9.

215 Valtonen EJ. Immediate effect of short wave diathermy on the 5-hydroxytryptamine content of blood and brain in the rat. Am J Phys Med. 1968;47(4):171-4.

216 Valtonen EJ. Effect of treatment with short wave diathermy on the histamine content of various organs. Am J Phys Med. 1968;47(2):75-83.

217 Valtonen EJ. Studies of the respiratory and cardiovascular responses to treatment with short wave diathermy - An experimental study on rats and rabbits. Res Exp Med (Berl). 1968;146(1):58-66.

218 Dogaru GB, Stănescu I, Bódizs G. Effects of pulsed short waves on carbohydrate and lipid metabolism and on renal function. An experimental study. Ann Rom Soc Cell Biol. 2013;18(1):91-5.

219 Krag C, Taudorf U, Siim E, Bolund S. The effect of pulsed electromagnetic energy (Diapulse®) on the survival of experimental skin flaps. A study on rats. Scand J Plast Reconstr Surg. 1979;13(3):377-80.

220 Kaplan L, Uribe JW. The acute effects of radiofrequency energy in articular cartilage: an in vitro study. Arthroscopy. 2000;16(1):2-5.

221 Holm DA, Schneider LK. The effects of non-thermal radio frequency radiation on human lymphocytes in vitro. Experientia. 1970;26(9):992-4.

222 Valtonen EJ. Effect of short-wave diathermy on the smooth musculature of isolated tracheal and intestinal preparations. Am J Phys Med. 1971;50(4):184-91.

223 Bernhardt J. The direct frequency of electromagnetic fields on nerve and muscle cells of man within the frequency range of 1 Hz to 30 MHz. Radiat Environ Biophys. 1979;16(4):309-23.

224 Cao G, Liu L-M, Cleary SF. Cell cycle alterations induced by isothermal 27 MHz radio-frequency radiation exposure. Bioelectrochem Bioenerg. 1995;37(2):131-40.

225 Moffett J, Fray LM, Kubat NJ. Activation of endogenous opioid gene expression in human keratinocytes and fibroblasts by pulsed radiofrequency energy fields. J Pain Res. 2012;5:347-57.

226 Cameron BM. A Three Phase Evaluation of Pulsed, High Frequency, Radio Short Waves (Diapulse): 646 Patients. Am J Orthop. 1964;6:72-8.

227 Kaplan EG, Weinstock RE. Clinical evaluation of diapulse as adjunctive therapy following foot surgery. J Am Podiatry Assoc. 1968;58(5):218-21.

228 Aronofsky DH. Reduction of dental postsurgical symptoms using nonthermal pulsed high-peak-power electromagnetic energy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1971;32(5):688-96.

229 Wilson DH. Treatment of soft-tissue injuries by pulsed electrical energy. Br Med J. 1972;2(5808):269-70.

230 Wright GG. Treatment of soft tissue and ligamentous injuries in professional footballers. Physiotherapy. 1973;59(12):385-7.

231 Pasila M, Visuri T, Sundholm A. Pulsating shortwave diathermy: value in treatment of recent ankle and foot sprains. Arch Phys Med Rehabil. 1978;59(8):383-6.

232 Nwuga VC. Relative therapeutic efficacy of vertebral manipulation and conventional treatment in back pain management. Am J Phys Med. 1982;61(6):273-8.

233 Barclay V, Collier RJ, Jones A. Treatment of various hand injuries by pulsed electromagnetic energy (diapulse). Physiotherapy. 1983;69(6):186-8.

234 Barker AT, Barlow PS, Porter J. A double-blind clinical trial of low power pulsed shortwave therapy in the treatment of a soft tissue injury. Physiotherapy. 1985;71(12):500-4.

235 Santiesteban AJ, Grant C. Post-surgical effect of pulsed shortwave therapy. J Am Podiatr Med Assoc. 1985;75(6):306-9.

236 McGill SN. The effects of pulsed shortwave therapy on lateral ligament sprain of the ankle. NZ J Physiother. 1988;16:21-4.

237 Foley-Nolan D, Moore K, Codd M, Barry C, O'Connor P, Coughlan RJ. Low energy high frequency pulsed electromagnetic therapy for acute whiplash injuries. A double blind randomized controlled study. Scand J Rehabil Med. 1992;24(1):51-9.

238 Livesley PJ, Mugglestone A, Whitton J. Electrotherapy and the management of minimally displaced fracture of the humerus. Injury. 1992;23(5):323-6.

239 Pennington GM, Danley DL, Sumko MH, Bucknell A, Nelson JH. Pulsed, non-thermal, high-frequency electromagnetic energy (Diapulse) in the treatment of grade I and grade II ankle sprains. Mil Med. 1993;158(2):101-4.

240 Buzzard BM, Pratt RK, Briggs PJ, Siddique MS, Tasker A, Robinson S. Is Pulsed Shortwave Diathermy Better than Ice Therapy for the Reduction of Oedema following Calcaneal Fractures? Physiotherapy. 2003;89(12):734-42.

241 Rawe IM, Lowenstein A, Barcelo CR, Genecov DG. Control of Postoperative Pain with a Wearable Continuously Operating Pulsed Radiofrequency Energy Device: A Preliminary Study. Aesthetic Plast Surg. 2012;36(2):458-63.

242 Czyz CN, Foster JA, Lam VB, Holck DE, Wulc AE, Cahill KV*, et al.* Efficacy of pulsed electromagnetic energy in postoperative recovery from blepharoplasty. Dermatol Surg. 2012;38(3):445-50.

243 Goldin JH, Broadbent NR, Nancarrow JD, Marshall T. The effects of Diapulse on the healing of wounds: a double-blind randomised controlled trial in man. Br J Plast Surg. 1981;34(3):267-70.

244 Rhodes LC. The adjunctive utilization of Diapulse therapy (pulse high peak power electromagnetic energy) in accelerating tissue healing in oral surgery. Quart NDA. 1981;39:166-75.

245 Nicolle FV, Bentall RM. Use of radio-frequency pulsed energy in the control of postoperative reaction in blepharoplasty. Aesthetic Plast Surg. 1982;6(3):169-71.

246 Ma Y, Li J, Liu Y. Short wave diathermy for small spontaneous pneumothorax. Thorax. 1997;52:561-2.

247 Al-Badawi EA, Mehta N, Forgione AG, Lobo SL, Zawawi KH. Efficacy of pulsed radio frequency energy therapy in temporomandibular joint pain and dysfunction. Cranio. 2004;22(1):10-20.

248 Costantino C, Pogliacomi F, Vaienti E. Cryoultrasound therapy and tendonitis in athletes: a comparative evaluation versus laser CO2 and t.e.ca.r. therapy. Acta Biomed. 2005;76(1):37-41.

249 Alcidi L, Beneforti E, Maresca M, Santosuosso U, Zoppi M. Low power radiofrequency electromagnetic radiation for the treatment of pain due to osteoarthritis of the knee. Reumatismo. 2007;59(2):140-5.

250 Taverner MG, Ward TL, Loughnan TE. Transcutaneous pulsed radiofrequency treatment in patients with painful knee awaiting total knee joint replacement. Clin J Pain. 2010;26(5):429-32.

251 Nelson FR, Zvirbulis R, Pilla AA. Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: A randomized double-blind pilot study. Rheumatol Int. 2013;33(8):2169-73.

252 Balogh SE. Transcutaneous application of pulsed radiofrequency: four case reports. Pain Pract. 2004;4(4):310-3.

253 Taverner MG, Loughnan TE, Soon CW. Transcutaneous application of pulsed radiofrequency treatment for shoulder pain. Pain Pract. 2013;13(4):310-5.

254 Watson T. Electrotherapy: Evidence-Based Practice. 12th ed. London: Elsevier Churchill Livingstone; 2008.

255 Sluka KA, Bjordal JM, Marchand S, Rakel BA. What makes transcutaneous electrical nerve stimulation work? Making sense of the mixed results in the clinical literature. Phys Ther. 2013;93(10):1397-402.

256 Hamilton DE, Bywaters EGL, Please NW. A controlled trial of various forms of physiotherapy in arthritis. BMJ. 1959;1(5121):542-4.

257 Harris R. Effect of short wave diathermy on radio-sodium clearance from the knee joint in the normal and in rheumatoid arthritis. Arch Phys Med Rehabil. 1961;42:241-9.

258 Wright V. Treatment of osteo-arthritis of the knees. Ann Rheum Dis. 1964;23:389-91.

259 Clarke GR, Willis LA, Stenner L, Nichols PJR. Evaluation of physiotherapy in the treatment of osteoarthrosis of the knee. Rheumatol Rehabil. 1974;13(4):190-7.

260 Bansil CK, Joshi JB. Effectiveness of shortwave diathermy and ultrasound in the treatment of osteo-arthritis of the knee joint. Med J Zambia. 1975;9(5):138-9.

261 Chamberlain MA, Care G, Harfield B. Physiotherapy in osteoarthrosis of the knees. A controlled trial of hospital versus home exercises. Int Rehabil Med. 1982;4(2):101-6.

262 Quirk AS, Newman RJ, Newman KJ. An evaluation of interferential therapy, shortwave diathermy and exercise in the treatment of osteoarthrosis of the knee. Physiotherapy. 1985;71(2):55-7.

263 Svarcova J, Trnavsky K, Zvarova J. The influence of ultrasound, galvanic currents and shortwave diathermy on pain intensity in patients with osteoarthritis. Scand J Rheumatol. 1988;17(SUPPL. 67):83-5.

264 Jan MH, Lai JS. The effects of physiotherapy on osteoarthritic knees of females. J Formos Med Assoc. 1991;90(10):1008-13.

265 Sewell H, Bulstrode S, Clarke AK, Hall J, Ring EFJ. A double-blind study of the effects of pulsed electromagnetic energy (Megapulse) on pain and inflammation in knee joints of patients with rheumatoid arthritis. Physiother Theor Pract. 1991;7(4):255-9.

266 Klaber Moffett JA, Richardson PH, Frost H, Osborn A. A placebo controlled double blind trial to evaluate the effectiveness of pulsed short wave therapy for osteoarthritic hip and knee pain. Pain. 1996;67(1):121-7.

267 Tüzün EH, Otman S, Kirdi N. Comparison of different methods of pulsed shortwave diathermy in knee osteoarthritis. Pain Clin. 2003;15(4):421-7.

268 Callaghan MJ, Whittaker PE, Grimes S, Smith L. An evaluation of pulsed shortwave on knee osteoarthritis using radioleucoscintigraphy: A randomised, double blind, controlled trial. Joint Bone Spine. 2005;72(2):150-5.

269 Laufer Y, Zilberman R, Porat R, Nahir AM. Effect of pulsed short-wave diathermy on pain and function of subjects with osteoarthritis of the knee: a placebo-controlled double-blind clinical trial. Clin Rehabil. 2005;19(3):255-63.

270 Jan MH, Chai HM, Wang CL, Lin YF, Tsai LY. Effects of repetitive shortwave diathermy for reducing synovitis in patients with knee osteoarthritis: an ultrasonographic study. Phys Ther. 2006;86(2):236-44.

271 Cantarini L, Leo G, Giannitti C, Cevenini G, Barberini P, Fioravanti A. Therapeutic effect of spa therapy and short wave therapy in knee osteoarthritis: a randomized, single blind, controlled trial. Rheumatol Int. 2007;27(6):523-9.

272 Manhal FS, Mecheser AE, Hussein SA. Effectiveness of short wave diathermy and therapeutic ultrasound on the management of patients with knee osteoarthritis. Sci J Nursing. 2007;20(1-2):11-9.

273 Silva ALP, Imoto DM, Croci AT. Comparison of cryotherapy, exercise and short waves in knee osteoarthritis treatment. Acta Orthop Bras. 2007;15(4):204-9.

274 Cetin N, Aytar A, Atalay A, Akman MN. Comparing hot pack, short-wave diathermy, ultrasound, and TENS on isokinetic strength, pain, and functional status of women with osteoarthritic knees: a single-blind, randomized, controlled trial. Am J Phys Med Rehabil. 2008;87(6):443-51.

275 Fukuda TY, Ovanessian V, Cunha RAD, Filho ZJ, Cazarini C, Rienzo FA*, et al.* Pulsed short wave effect in pain and function in patients with knee osteoarthritis. J Appl Res. 2008;8(3):189-98.

276 Ovanessian V, Cazarini Junior C, Cunha RA, Carvalho NAA, Fukuda TY. Use of different doses of pulsed short waves in the treatment of patients with osteoarthritis of the knee. Rev Ciências Med (PUCCAMP). 2008;17:149-55.

277 Rattanachaiyanont M, Kuptniratsaikul V. No additional benefit of shortwave diathermy over exercise program for knee osteoarthritis in peri-/post-menopausal women: An equivalence trial. Osteoarthritis Cartilage. 2008;16(7):823-8.

278 Akyol Y, Durmus D, Alayli G, Tander B, Bek Y, Canturk F*, et al.* Does short-wave diathermy increase the effectiveness of isokinetic exercise on pain, function, knee muscle strength, quality of life and depression in the patients with knee osteoarthritis? A randomised controlled clinical study. Eur J Phys Rehabil Med. 2010;46(3):325-36.

279 Fukuda TY, Alves da Cunha R, Fukuda VO, Rienzo FA, Cazarini C, Jr., Carvalho Nde A*, et al.* Pulsed shortwave treatment in women with knee osteoarthritis: a multicenter, randomized, placebo-controlled clinical trial. Phys ther. 2011;91(7):1009-17.

280 Atamaz FC, Durmaz B, Baydar M, Demircioglu OY, Iyiyapici A, Kuran B*, et al.* Comparison of the Efficacy of Transcutaneous Electrical Nerve Stimulation, Interferential Currents, and Shortwave Diathermy in Knee Osteoarthritis: A Double-Blind, Randomized, Controlled, Multicenter Study. Arch Phys Med Rehabil. 2012;93(5):748-56.

281 Teslim OA, Adebowale AC, Ojoawo AO, Sunday OA, Bosede A. Comparative effects of pulsed and continuous short wave diathermy on pain and selected physiological parameters among subjects with chronic knee osteoarthritis. Technol Health Care. 2013;21(5):433-40.

282 Boyaci A, Tutoglu A, Boyaci N, Aridici R, Koca I. Comparison of the efficacy of ketoprofen phonophoresis, ultrasound, and short-wave diathermy in knee osteoarthritis. Rheumatol Int. 2013;33(11):2811-8.

283 Ahmed MS, Shakoor MA, Khan AA. Evaluation of the effects of shortwave diathermy in patients with chronic low back pain. Bangladesh Med Res Counc Bull. 2009;35(1):18-20.

284 Davies JE, Gibson T, Tester L. The value of exercises in the treatment of low back pain. Rheumatol Rehabil. 1979;18(4):243-7.

285 Gibson T, Grahame R, Harkness J, Woo P, Blagrave P, Hills R. Controlled comparison of short-wave diathermy treatment with osteopathic treatment in non-specific low back pain. Lancet. 1985;1(8440):1258-61.

286 Kerem M, Yigiter K. Effects of continuous and pulsed short-wave diathermy in low back pain. Pain Clin. 2002;14(1):55-9.

287 Sweetman BJ, Heinrich I, Anderson JAD. A randomized controlled trial of exercises, short wave diathermy, and traction for low back pain, with evidence of diagnosis-related response to treatment. J Orthop Rheumatol. 1993;6(4):159-66.

288 Wagstaff P, Wagstaff S, Downey M. A pilot study to compare the efficacy of continuous and pulsed magnetic energy [short-wave diathermy] on the relief of low back pain. Physiotherapy. 1986;72(11):563-6.

289 Kim MK, Ji SG, Cha HK, Chang JS. Effects of electromagnetic diathermy in conjunction with nerve mobilization in the management of lower back pain. J Phys Ther Sci. 2012;24(12):1337-9.

290 Shakoor MA, Al Hasan S, Moyeenuzzaman M, Deb AK. Treatment with short wave diathermy on chronic low back pain. JCMCTA. 2010;21(1):40-4.

291 Lamina S, Hanif S, Gagarawa YS. Short wave diathermy in the symptomatic management of chronic pelvic inflammatory disease pain: A randomized controlled trial. Physiother Res Int. 2011;16(1):50-6.

292 Balogun JA, Okonofua FE. Management of chronic pelvic inflammatory disease with shortwave diathermy : A case report. Phys Ther. 1988;68(10):1541-5.

293 Burgess TW. The treatment of chronic female pelvic sepsis by short-wave diathermy: a review of fifty cases. Med J Aust. 1950;2(8):285-7.

294 Lamina S, Hanif S. Shortwave diathermy in the management of chronic pelvic inflammatory disease pain: case reports. JNSP. 2008;16(1):31-6.

295 Punnonen R, Gronroos M, Liukko P. The use of pulsed high-frequency therapy (curapuls) in gynecology and obstetrics. Acta Obstetricia et Gynecologica Scandinavica. 1980;59(2):187-8.

296 Waters EG. Short-wave therapy in gynecology and obstetrics. Experiences with one hundred twenty cases. Am J Obstet Gynecol. 1938;35(1):143-9.

297 Dziedzic K, Hill J, Lewis M, Sim J, Daniels J, Hay EM. Effectiveness of manual therapy or pulsed shortwave diathermy in addition to advice and exercise for neck disorders: a pragmatic randomized controlled trial in physical therapy clinics. Arthritis Rheum. 2005;53(2):214-22.

298 Lewis M, James M, Stokes E, Hill J, Sim J, Hay E*, et al.* An economic evaluation of three physiotherapy treatments for non-specific neck disorders alongside a randomized trial. Rheumatology. 2007;46(11):1701-8.

299 Boyaci A, Tutoglu A, Koca I, Kocaturk O, Celen E. Comparison of the Short-Term Effectiveness of Short-Wave Diathermy Treatment in Patients With Carpal Tunnel Syndrome: A Randomized Controlled Trial. Arch Rheumatol. 2014;29(4):298-303.

300 Michel R. Use of pulsed radio frequency energy in the effective treatment of recalcitrant plantar fasciitis: Six case histories. Foot. 2012;22(1):48-52.

301 Guler-Uysal F, Kozanoglu E. Comparison of the early response to two methods of rehabilitation in adhesive capsulitis. Swiss Med Wkly. 2004;134(23-24):353-8.

302 Ginsberg AJ. Pulsed short wave in the treatment of bursitis with calcification. Int Rec Med. 1961;174:71-5.

303 Gray RJ, Quayle AA, Hall CA, Schofield MA. Physiotherapy in the treatment of temporomandibular joint disorders: a comparative study of four treatment methods. Br Dent J. 1994;176(7):257-61.

304 McCray RE, Patton NJ. Pain relief at trigger points: A comparison of moist heat and shortwave diathermy. J Orthop Sports Phys Ther. 1984;5(4):175-8.

305 Talaat AM, el-Dibany MM, el-Garf A. Physical therapy in the management of myofacial pain dysfunction syndrome. Ann Otol Rhinol Laryngol. 1986;95(3 Pt 1):225-8.

306 Allberry J, Manning FR, Smith EE. Treatment of herpes zoster with short-wave diathermy to the spinal cord. Practitioner. 1972;208(247):687-8.

307 Shandles ID, Pruchniewski J, Reynolds KL. Heel neuroma: The enigma of recalcitrant heel pain and an innovative approach highlighting sixty surgical cases and a review of two hundred and fifty-seven symptomatic but non-surgical cases. Foot. 2002;12(1):10-20.

308 Oke KI, Kubeyinje SO, Dada O. Shortwave diathermy therapy in the management of pain and functional limitation in femoral head avascular necrosis: A report of 4 cases in a tertiary hospital in Nigeria. Res J Med Sci. 2011;5(6):324-9.

309 Cao LY, Jiang MJ, Yang SP, Zhao L, Wang JM. Pulsed electromagnetic field therapy for the treatment of knee osteoarthritis: a systematic review. Zhongguo Gu Shang. 2012;25(5):384-8.

310 Nguyen JV, Marks R. Pulsed electromagnetic fields for treating osteo-arthritis. Physiotherapy. 2002;88(8):458-70.

311 Itoh M, Montemayor Jr JS, Matsumoto E, Eason A, Lee MH, Folk FS. Accelerated wound healing of pressure ulcers by pulsed high peak power electromagnetic energy (Diapulse). Decubitus. 1991;4(1):24-5, 9.

312 Comorosan S, Vasilco R, Arghiropol M, Paslaru L, Jieanu V, Stelea S. The effect of diapulse therapy on the healing of decubitus ulcer. Rom J Physiol. 1993;30(1-2):41-5.

313 Salzberg CA, Cooper-Vastola SA, Perez F, Viehbeck MG, Byrne DW. The effects of non-thermal pulsed electromagnetic energy (diapulse) on wound healing of pressure ulcers in spinal cord-injured patients: a randomized, double-blind study. Ostomy Wound Manage. 1995;41(3):42-4, 6, 8 passim.

314 Kloth LC, Berman JE, Sutton CH. Effect of pulsed radio frequency stimulation on wound healing: A double-blind pilot clinical study. In: Bersani F, editor. Electricity and Magnetism in Biology and Medicine. New York: Plenum; 1999. p. 875-8.

315 Larsen JA, Overstreet J. Pulsed radio frequency energy in the treatment of complex diabetic foot wounds: two cases. J Wound Ostomy Continence Nurs. 2008;35(5):523-7.

316 Porreca EG, Giordano-Jablon GM. Treatment of severe (Stage III and IV) chronic pressure ulcers using pulsed radio frequency energy in a quadriplegic patient. Eplasty. 2008;8:451-5.

317 Frykberg R, Tierney E, Tallis A, Klotzbach T. Cell proliferation induction: Healing chronic wounds through low-energy pulsed radiofrequency. Int J Low Extrem Wounds. 2009;8(1):45-51.

318 Fletcher S. Successful treatment of venous stasis ulcers with combination compression therapy and pulsed radio frequency energy in a patient scheduled for amputation. J Wound Ostomy Continence Nurs. 2011;38(1):91-4.

319 Frykberg R, Martin E, Tallis A, Tierney E. A case history of multimodal therapy in healing a complicated diabetic foot wound: Negative pressure, dermal replacement and pulsed radio frequency energy therapies. Int Wound J. 2011;8(2):132-9.

320 Frykberg RG, Driver VR, Lavery LA, Armstrong DG, Isenberg RA. The use of pulsed radio frequency energy therapy in treating lower extremity wounds: results of a retrospective study of a wound registry. Ostomy Wound Manage. 2011;57(3):22-9.

321 Maier M. Pulsed Radio Frequency Energy in the Treatment of Painful Chronic Cutaneous Wounds: A Report of Two Cases. Pain Med. 2011;12(5):829-32.

322 Conner-Kerr T, Isenberg RA. Retrospective analysis of pulsed radiofrequency energy therapy use in the treatment of chronic pressure ulcers. Adv Skin Wound Care. 2012;25(6):253-60.

323 Sharp IK, Lightwood R. Stimulation of bone union by externally applied radio-frequency energy. Injury. 1983;14(6):523-30.

324 Draper DO, Castel JC, Castel D. Low-watt pulsed shortwave diathermy and metal-plate fixation of the elbow. Athl Ther Today. 2004;9(5):28-32.

325 Draper DO, van Patten J. Shortwave diathermy and joint mobilizations for postsurgical restoration of knee motion. Athl Ther Today. 2010;15(1):39-41.

326 Johnson W, Draper DO. Increased range of motion and function in an individual with breast cancer and necrotizing fasciitis-manual therapy and pulsed short-wave diathermy treatment. Case Rep Med. 2010;2010:1-4.

327 Hedenius P, Odeblad E, Wahlstrõm L. Some preliminary investigations on the therapeutic effect of pulsed short waves in intermittent claudication. Curr Ther Res Clin Exp. 1966;8(7):317-21.

328 Santoro D, Ostrander L, Lee BY, Cagir B. Inductive 27.12 MHz. Diathermy in arterial peripheral vascular disease. Baltimore, MD, USA: IEEE; 1994. p. 776-7.

329 Hovind H, Nielsen SL. Changes in circulation in subcutaneous tissue and muscle tissue after treatment with diathermy (Danish). Ugeskrift for laeger. 1974;136(41):2294-8.

330 Bennell KL, Hall M, Hinman RS. Osteoarthritis year in review 2015: rehabilitation and outcomes. Osteoarthritis cartilage. 2016;24(1):58-70.

331 Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015;49(24):1554-7.

332 Fitzgerald GK, Hinman RS, Zeni J, Jr., Risberg MA, Snyder-Mackler L, Bennell KL. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials of rehabilitation interventions for osteoarthritis. Osteoarthritis cartilage. 2015;23(5):803-14.

333 Bitton R. The economic burden of osteoarthritis. Am J Manag Care. 2009;15(8 Suppl):S230-5.

334 Buckwalter JA, Martin JA. Osteoarthritis. Adv Drug Deliv Rev. 2006;58(2):150-67.

335 Taylor NAS, Tipton MJ, Kenny GP. Considerations for the measurement of core, skin and mean body temperatures. J Therm Biol. 2014;46:72-101.

336 Aaron JEB, Ian BS, Geoffrey MM, Joseph TC. Does the technique employed for skin temperature assessment alter outcomes? A systematic review. Physiol Meas. 2015;36(9):R27.

337 van Marken Lichtenbelt WD, Daanen HAM, Wouters L, Fronczek R, Raymann RJEM, Severens NMW*, et al.* Evaluation of wireless determination of skin temperature using iButtons. Physiol Behav. 2006;88(4-5):489-97.

338 Ng DK, Chan CH, Lee RS, Leung LC. Non-contact infrared thermometry temperature measurement for screening fever in children. Ann Trop Paediatr. 2005;25(4):267-75.

339 Paes BF, Vermeulen K, Brohet RM, van der Ploeg T, de Winter JP. Accuracy of tympanic and infrared skin thermometers in children. Arch Dis Child. 2010;95(12):974-8.

340 Ring EFJ, McEvoy H, Jung A, Zuber J, Machin G. New standards for devices used for the measurement of human body temperature. J Med Eng Tech. 2010;34(4):249-53.

341 Guyton AC, Hall JE. Textbook of Medical Physiology. 12th ed. Hall JE, editor. Philadelphia: Elsevier Saunders; 2011.

342 Charkoudian N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. Mayo Clin Proc. 2003;78(5):603-12.

343 Tyler CJ. The effect of skin thermistor fixation method on weighted mean skin temperature. Physiol Meas. 2011;32(10):1541-7.

344 Klopfenstein Jr LR. Software linearization techniques for thermocouples, thermistors, and RTDs. ISA Trans. 1994;33(3):293-305.

345 Yadav B, Srivastava R, Singh S, Kumar A, Yadav A. Temperature Sensors Based on Semiconducting Oxides: An Overview (arXiv: 1205.2712). 2012.

346 Harper Smith AD, Crabtree DR, Bilzon JL, Walsh NP. The validity of wireless iButtons and thermistors for human skin temperature measurement. Physiol Meas. 2010;31(1):95-114.

347 Haidar SG, Charity RM, Bassi RS, Nicolai P, Singh BK. Knee skin temperature following uncomplicated total knee replacement. Knee. 2006;13(6):422-6.

348 Packham TL, Fok D, Frederiksen K, Thabane L, Buckley N. Reliability of infrared thermometric measurements of skin temperature in the hand. J Hand Ther. 2012;25(4):358-61; quiz 62.

349 Kelechi TJ, Good A, Mueller M. Agreement and repeatability of an infrared thermometer. J Nurs Meas. 2011;19(1):55-64.

350 Burnham RS, McKinley RS, Vincent DD. Three types of skin-surface thermometers: a comparison of reliability, validity, and responsiveness. Am J Phys Med Rehabil. 2006;85(7):553-8.

351 Oerlemans HM, Graff MJ, Dijkstra-Hekkink JB, de Boo T, Goris RJ, Oostendorp RA. Reliability and normal values for measuring the skin temperature of the hand with an infrared tympanic thermometer: a pilot study. J Hand Ther. 1999;12(4):284-90.

352 Kelechi TJ, Michel Y, Wiseman J. Are infrared and thermistor thermometers interchangeable for measuring localized skin temperature? J Nurs Meas. 2006;14(1):19-30.

353 Ring EFJ, Ammer K. Infrared thermal imaging in medicine. Physiol Meas. 2012;33(3):R33.

354 Lahiri BB, Bagavathiappan S, Jayakumar T, Philip J. Medical applications of infrared thermography: A review. Infrared Phys Tech. 2012;55(4):221-35.

355 Szentkuti A, Kavanagh HS, Grazio S. Infrared thermography and image analysis for biomedical use. Periodicum Biologorum. 2011;113(4):385-92.

356 Frize M, Adéa C, Payeur P, Di Primio G, Karsh J, Ogungbemile A, editors. Detection of rheumatoid arthritis using infrared imaging. 2011; Lake Buena Vista, FL.

357 Hildebrandt C, Raschner C, Ammer K. An overview of recent application of medical infrared thermography in sports medicine in Austria. Sensors. 2010;10(5):4700-15.

358 Jiang LJ, Ng EYK, Yeo ACB, Wu S, Pan F, Yau WY*, et al.* A perspective on medical infrared imaging. J Med Eng Tech. 2005;29(6):257-67.

359 Ring EFJ, Ammer K. The technique of infra red imaging in medicine. Thermol Int. 2000;10(1):7-14.

360 Thomas R. Handbook of Non-Invasive Methods and the Skin. 2006:753-68.

361 Krause BF. Accuracy and response time comparisons of four skin temperature-monitoring devices. Nurse Anesth. 1993;4(2):55-61.

362 Shenep JL, Adair JR, Hughes WT, Roberson PK, Flynn PM, Brodkey TO*, et al.* Infrared, thermistor, and glass-mercury thermometry for measurement of body temperature in children with cancer. Clin Pediatr. 1991;30(4 Suppl):36-41; discussion 9.

363 Jeong IC, Yoon H, Kang H, Yeom H. Effects of skin surface temperature on photoplethysmograph. J Healthc Eng. 2014;5(4):429-38.

364 Mawhinney C, Jones H, Joo CH, Low DA, Green DJ, Gregson W. Influence of cold-water immersion on limb and cutaneous blood flow after exercise. Med Sci Sports Exerc. 2013;45(12):2277-85.

365 Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm. J Appl Physiol. 1948;1(2):93-122.

366 Petrofsky JS. Resting blood flow in the skin: does it exist, and what is the influence of temperature, aging, and diabetes? J Diabetes Sci Technol. 2012;6(3):674-85.

367 Petrofsky JS, Berk L, Alshammari F, Lee H, Hamdan A, Yim JE*, et al.* The interrelationship between air temperature and humidity as applied locally to the skin: The resultant response on skin temperature and blood flow with age differences. Med Sci Monit. 2012;18(4):CR201-CR8.

368 Petrofsky JS, Al-Malty AM, Prowse M. Relationship between multiple stimuli and skin blood flow. Med Sci Monit. 2008;14(8):CR399-CR405.

369 Allen J. Photoplethysmography and its application in clinical physiological measurement. Physiol Meas. 2007;28(3):R1-R39.

370 Clark S, Campbell F, Moore T, Jayson MIV, King TA, Herrick AL. Laser Doppler imaging - A new technique for quantifying microcirculatory flow in patients with primary Raynaud's phenomenon and systemic sclerosis. Microvasc Res. 1999;57(3):284-91.

371 Bornmyr S, Svensson H, Lilja B, Sundkvist G. Skin temperature changes and changes in skin blood flow monitored with laser Doppler flowmetry and imaging: A methodological study in normal humans. Clin Physiol. 1997;17(1):71-81.

372 Machens HG, Pallua N, Mailaender P, Pasel J, Frank KH, Reimer R*, et al.* Measurements of tissue blood flow by the Hydrogen clearance technique (HCT): A comparative study including Laser Doppler flowmetry (LDF) and the Erlangen micro-lightguide spectrophotometer (EMPHO). Microsurgery. 1995;16(12):808-17.

373 Agache PG, Dupond AS. Recent advances in non-invasive assessment of human skin blood flow. Acta Derm Venereol Suppl. 1994(185):47-51.

374 Oberg PA. Laser-Doppler flowmetry. Crit Rev Biomed Eng. 1990;18(2):125-61.

375 Kvernebo K, Megerman J, Hamilton G, Abbott WM. Response of skin photoplethysmography, laser Doppler flowmetry and transcutaneous oxygen tensiometry to stenosis-induced reductions in limb blood flow. Eur J Vasc Surg. 1989;3(2):113-20.

376 Hales JRS, Stephens FRN, Fawcett AA, Daniel K, Sheahan J, Westerman RA*, et al.* Observations on a new non-invasive monitor of skin blood flow. Clin Exp Pharmacol Physiol. 1989;16(5):403-15.

377 Cochrane T, Sheriff SB, Boulton AJM, Ward JD, Atkins RM. Laser Doppler flowmetry: In the assessment of peripheral vascular disorders? A preliminary evaluation. Clin Phys Physiol Meas. 1986;7(1):31-42.

378 Blažek V, Wu T, Hölscher D. Near-infrared CCD imaging - Possibilities for noninvasive and contactless 2D mapping of dermal venous hemodynamics. Proc SPIE. 2000;3923:2-9.

379 Partsch H. Photoplethysmography: A simple method with wide clinical application. Folia Angiologica. 1981;29(9-10):174-8.

380 Nilsson GE, Tenland T, Ake Oberg P. A new instrument for continuous measurement of tissue blood flow by light beating spectroscopy. IEEE Trans Biomed Eng. 1980;27(1):12-9.

381 Nilsson GE, Tenland T, Oberg PA. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. IEEE Trans Biomed Eng. 1980;27(10):597-604.

382 Challoner AVJ. Photoelectric plethysmography for estimating cutaneous blood flow. In: Rolfe P, editor. Non-invasive Physiological Measurements. London: Academic Press; 1979. p. 125-51.

383 Holloway Jr GA, Watkins DW. Laser Doppler measurement of cutaneous blood flow. J Investig Dermatol. 1977;69(3):306-9.

384 Henderson HP, Hackett MEJ. The value of thermography in peripheral vascular disease. Angiology. 1978;29(1):65-75.

385 Kostuik JP, Wood D, Hornby R, Feingold S, Mathews V. The measurement of skin blood flow in peripheral vascular disease by epicutaneous application of Xenon133. J Bone Joint Surg Am. 1976;58(6):833-7.

386 Hertzman AB. Photoelectric plethysmography of the fingers and toes in man. Proc Soc Exp Biol Med. 1937;37(3):529-34.

387 Hertzman AB. The blood supply of various skin areas as estimated by the photoelectric plethysmograph. Am J Physiol. 1938;124(2):328-40.

388 Greenfield ADM, Whitney RJ, Mowbray JF. Methods for the investigation of peripheral blood flow. Br Med Bull. 1963;19(2):101-9.

389 Weinman J. Photoplethysmography. Manual of Psycho-Physiological Methods. 1967.

390 Fine S, Weinman J. The use of photoconductive cells in photoplethysmography. Medbioengineering. 1973;11(4):455-63.

391 Aoyagi T, Kishi M, Yamaguchi K, Watanabe S. Improvement of the earpiece oximeter. Abstracts of the Japanese Society of Medical Electronics and Biological Engineering. 1974:90-1.

392 Stern RM. Ear lobe photoplethysmography. Psychophysiology. 1974;11(1):73-5.

393 Kartchner MM, McRae LP, Crain V, Whitaker B. Oculoplethysmography: An adjunct to arteriography in the diagnosis of extracranial carotid occlusive disease. Am J Surg. 1976;132(6):728-32.

394 Schultz-Ehrenburg U, Blazek V. Innovations in venous photoplethysmography. Dermatology, Progress and Perspectives: Proceedings of the 18th World Congress of Dermatology. 1993:849-51.

395 Blazek V, Schultz-Ehrenburg U, Fronek A, Pflug JJ, Bawol MP. Quantitative audiophotoplethysmography. Phlebologie. 1996;25(5):159-64.

396 Severinghaus JW, Kelleher JF. Recent developments in pulse oximetry. Anesthesiology. 1992;76(6):1018-38.

397 Giltvedt J, Sira A, Helme P. Pulsed multifrequency photoplethysmograph. Med Biol Eng Comput. 1984;22(3):212-5.

398 Essex TJH, Byrne PO. A laser Doppler scanner for imaging blood flow in skin. J Biomed Eng. 1991;13(3):189-94.

399 Schultz-Ehrenburg U, Blazek V. New possibilities for photoplethysmography. Phlebology Digest. 1993;4:5-11.

400 Wardell K, Jakobsson A, Nilsson GE. Laser Doppler perfusion imaging by dynamic light scattering. IEEE Trans Biomed Eng. 1993;40(4):309-16.

401 Bergstrand S, Lindberg LG, Ek AC, Lindén M, Lindgren M. Blood flow measurements at different depths using photoplethysmography and laser Doppler techniques. Skin Res Tech. 2009;15(2):139-47.

402 Hagblad J, Lindberg LG, Andersson AK, Bergstrand S, Lindgren M, Ek AC*, et al.* A technique based on laser Doppler flowmetry and photoplethysmography for simultaneously monitoring blood flow at different tissue depths. Med Biol Eng Comput. 2010;48(5):415-22.

403 Hagblad J, Folke M, Lindberg LG, Linden M. Technical issues related to the long-term monitoring of blood flow at different depths using LDF and PPG. Physiol Meas. 2012;33(6):985-96.

404 Alian AA, Shelley KH. Photoplethysmography. Best Pract Res Clin Anaesthesiol. 2014;28(4):395-406.

405 Sandberg M, Zhang Q, Styf J, Gerdle B, Lindberg LG. Non-invasive monitoring of muscle blood perfusion by photoplethysmography: Evaluation of a new application. Acta Physiol Scand. 2005;183(4):335-43.

406 Rauh R, Posfay A, Mück-Weymann M. Quantification of inspiratory-induced vasoconstrictive episodes: A comparison of laser Doppler fluxmetry and photoplethysmography. Clin Physiol Funct Imag. 2003;23(6):344-8.

407 Grohmann G, Krauss M, Lindloh C, Pohlmann G, Eidner G. NIR-photoplethysmography-a noninvasive method for the early diagnosis and control of circulation parameters in peripheral vascular diseases. 2. Bedside measurements. Perfusion. 1996;9:300-10.

408 Cejnar M, Kobler H, Hunyor SN. Quantitative photoplethysmography: Lambert-Beer law or inverse function incorporating light scatter. J Biomed Eng. 1993;15(2):151-4.

409 Lindberg LG, Tamura T, Oberg PA. Photoplethysmography. Part 1. Comparison with laser Doppler flowmetry. Med Biol Eng Comput. 1991;29(1):40-7.

410 Lindberg LG, Oberg PA. Photoplethysmography. Part 2. Influence of light source wavelength. Med Biol Eng Comput. 1991;29(1):48-54.

411 Kamal AA, Harness JB, Irving G, Mearns AJ. Skin photoplethysmography--a review. Comput Methods Programs Biomed. 1989;28(4):257-69.

412 Cooke ED, Bowcock SA, Smith AT. Photoplethysmography of the distal pulp in the assessment of the vasospastic hand. Angiology. 1985;36(1):33-40.

413 de Trefford J, Lafferty K. What does photoplethysmography measure? Med Biol Eng Comput. 1984;22(5):479-80.

414 Fredriksson I, Larsson M, Strömberg T. Measurement depth and volume in laser Doppler flowmetry. Microvasc Res. 2009;78(1):4-13.

415 Merla A, Di Romualdo S, Di Donato L, Proietti M, Salsano F, Romani GL. Combined thermal and laser Doppler imaging in the assessment of cutaneous tissue perfusion. Conf Proc IEEE Eng Med Biol Soc. 2007;2007:2630-3.

416 Nilsson GE, Salerud EG, Strömberg T, Wårdell K. Laser Doppler perfusion monitoring and imaging. Biomedical Photonics Handbook. 2003:1-24.

417 Kubli S, Waeber B, Dalle-Ave A, Feihl F. Reproducibility of laser Doppler imaging of skin blood flow as a tool to assess endothelial function. J Cardiovasc Pharmacol. 2000;36(5):640-8.

418 Bircher A, De Boer EM, Agner T, Wahlberg JE, Serup J. Guidelines for measurement of cutaneous blood flow by laser Doppler flowmetry: A report from the standardization group of the European Society of Contact Dermatitis. Contact dermatitis. 1994;30(2):65-72.

419 Abay TY, Kyriacou PA. Comparison of NIRS, laser Doppler flowmetry, photoplethysmography, and pulse oximetry during vascular occlusion challenges. Physiol Meas. 2016;37(4):503-14.

420 Ubbink DT. Toe blood pressure measurements in patients suspected of leg ischaemia: A new laser Doppler device compared with photoplethysmography. Eur J Vasc Endovasc Surg. 2004;27(6):629-34.

421 Malvezzi L, Castronuovo Jr JJ, Swayne LC, Cone D, Trivino JZ. The correlation between three methods of skin perfusion pressure measurement: Radionuclide washout, laser Doppler flow, and photoplethysmography. J Vasc Surg. 1992;15(5):823-30.

422 Carpentier PH. Laser-doppler: Principles and indications. J Physique. 1987;48:271-4.

423 Hertzman AB. Photoelectric plethysmography of the nasal septum in man. Proc Soc Exp Biol Med. 1937;37:290-2.

424 Hertzman AB, Spealman CR. Observations on the finger volume pulse recorded photoelectrically. Am J Physiol. 1937;119:334-5.

425 Lew HL, Date ES, Pan SS, Wu P, Ware PF, Kingery WS. Sensitivity, specificity, and variability of nerve conduction velocity measurements in carpal tunnel syndrome. Arch Phys Med Rehabil. 2005;86(1):12-6.

426 Valls-Sole J, Leote J, Pereira P. Antidromic vs orthodromic sensory median nerve conduction studies. Clin Neurophysiol Pract. 2016;1:18-25.

427 Cohn TG, Wertsch JJ, Pasupuleti DV, Loftsgaarden JD, Schenk VA. Nerve conduction studies: orthodromic vs antidromic latencies. Arch Phys Med Rehabil. 1990;71(8):579-82.

428 Dawson GD, Scott JW. The recording of nerve action potentials through skin in man. J Neurol Neurosurg Psychiatry. 1949;12(4):259-67.

429 Dawson GD. The relative excitability and conduction velocity of sensory and motor nerve fibres in man. J Physiol. 1956;131(2):436-51.

430 Gilliatt RW, Sears TA. Sensory nerve action potentials in patients with peripheral nerve lesions. J Neurol Neurosurg Psychiatry. 1958;21(2):109-18.

431 Olson WH, BeMent SL. Compound action potential reconstructions and predicted fiber diameter distributions. Prog Clin Biol Res. 1981;52:57-83.

432 Woodbury PB, Ulinski PS. Conduction velocity, size and distribution of optic nerve axons in the turtle, Pseudemys scripta elegans. Anat Embryol. 1986;174(2):253-63.

433 van Veen BK, Schellens RL, Stegeman DF, Schoonhoven R, Gabreels-Festen AA. Conduction velocity distributions compared to fiber size distributions in normal human sural nerve. Muscle Nerve. 1995;18(10):1121-7.

434 Cragg BG, Thomas PK. Changes in conduction velocity and fibre size proximal to peripheral nerve lesions. J Physiol. 1961;157:315-27.

435 Calosevic S, Dinjar K, Calosevic S, Kurbel S, Steiner R. Hidden information in three-axial ECG data of normal subjects: Fractal dimensions of corresponding points from successive QRS loops as a potential sport and age dependent marker. Gen Physiol Biophys. 2016.

436 Chakraborty S, Pal S, editors. Photoplethysmogram signal based biometric recognition using linear discriminant classifier. 2016 2nd International Conference on Control, Instrumentation, Energy and Communication, CIEC 2016; 2016.

437 Constantinescu V, Matei D, Cuciureanu D, Corciova C, Ignat B, Popescu CD. Cortical modulation of cardiac autonomic activity in ischemic stroke patients. Acta Neurol Belg. 2016.

438 Maheshkumar K, Dilara K, Maruthy KN, Sundareswaren L. Validation of PC-based Sound Card with Biopac for Digitalization of ECG Recording in Short-term HRV Analysis. N Am J Med Sci. 2016;8(7):307-11.

439 Maity P, De S, Pal A, Dhara PC. An experimental study to evaluate musculoskeletal disorders and postural stress of female craftworkers adopting different sitting postures. Int J Occup Saf Ergon. 2016;22(2):257-66.

440 Pino EJ, Chavez JA, Aqueveque P. Noninvasive ambulatory measurement system of cardiac activity. Conf Proc IEEE Eng Med Biol Soc. 2015;2015:7622-5.

441 Singh K, Bhargav H, Srinivasan TM. Effect of uninostril yoga breathing on brain hemodynamics: A functional near-infrared spectroscopy study. Int J Yoga. 2016;9(1):12-9.

442 Zegarra-Parodi R, Pazdernik VK, Roustit M, Park PY, Degenhardt BF. Effects of pressure applied during standardized spinal mobilizations on peripheral skin blood flow: A randomised cross-over study. Man Ther. 2016;21:220-6.

443 Noe F, Amarantini D, Paillard T. How experienced alpine-skiers cope with restrictions of ankle degrees-of-freedom when wearing ski-boots in postural exercises. J Electromyogr Kinesiol. 2009;19(2):341-6.

444 Mandryk RL, Atkins MS. A fuzzy physiological approach for continuously modeling emotion during interaction with play technologies. Int J Hum Comput Stud. 2007;65(4):329-47.

445 Mandryk RL, Inkpen KM, Calvert TW. Using psychophysiological techniques to measure user experience with entertainment technologies. Behav Inform Tech. 2006;25(2):141-58.

446 Eriksson R, Persson HW, Dymling SO, Lindstrom K. Evaluation of Doppler ultrasound for blood perfusion measurements. Ultrasound Med Biol. 1991;17(5):445-52.

447 Adler RS, Rubin JM, Fowlkes JB, Carson PL, Pallister JE. Ultrasonic estimation of tissue perfusion: A stochastic approach. Ultrasound Med Biol. 1995;21(4):493-500.

448 Pedersen M, Fredberg U, Langberg H. Sonoelastography as a Diagnostic Tool in the Assessment of Musculoskeletal Alterations: A Systematic Review. Eur J Ultrasound. 2012;33(05):441-6.

449 Pickerell DM. Elastography: Imaging of tomorrow? J Diagn Med Sonogr. 2010;26(3):109-13.

450 Docker M, Bazin S, Dyson M, Kirk D, Kitchen S, Low J*, et al.* Guidelines for the safe use of pulsed shortwave therapy equipment. Physiotherapy. 1994;80(4):233-5.

451 Martin CJ, McCallum HM, Strelley S, Heaton B. Electromagnetic fields from therapeutic diathermy equipment: A review of hazards and precautions. Physiotherapy. 1991;77(1):3-7.

452 Scott S. Diathermy. In: Kitchen S, editor. Electrotherapy: Evidence-Based Practice. Edinburgh: Churchill Livingstone; 2002. p. 145-65.

453 Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420-8.

454 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

455 Drust B, Atkinson G, Gregson W, French D, Binningsley D. The effects of massage on intra muscular temperature in the vastus lateralis in humans. Int J Sports Med. 2003;24(6):395-9.

456 Jackson AS, Pollock ML. Generalized equations for predicting body density of men. Br J Nutr. 1978;40(3):497-504.

457 Lehmann J, DeLateur B. Therapeutic heat. In: Lehmann J, editor. Therapeutic Heat and Cold. 4th ed. Baltimore: Williams & Wilkins; 1990. p. 470-4.

458 Cleary SF. In vitro studies of the effects of nonthermal radiofrequency and microwave radiation. In: Bernhardt JH, Mattes R, Repacholi MH, editors. Non-Thermal Effects of RF Electromagnetic Fields Proceedings of the International Seminar on Biological Effects of Non-Thermal Pulsed and Amplitude Modulated RF Electromagnetic Fields and Related Health Risks, Munich, Germany, November 20-21, 1996; November 20-21, 1996; Munich, Germany: International Commission on Non-Ionizing Radiation Protection (ICNIRP); 1997; 1997. p. 119-30.

459 Draper DO, Castro JL, Feland B, Schulthies S, Eggett D. Shortwave Diathermy and Prolonged Stretching Increase Hamstring Flexibility More Than Prolonged Stretching Alone. J Orthop Sports Phys Ther. 2004;34(1):13-20.

460 Petrofsky JS, Laymon M, Lee H. Effect of heat and cold on tendon flexibility and force to flex the human knee. Med Sci Monit. 2013;19:661-7.

461 Lehmann J, DeLateur B. Therapeutic Heat and Cold. Therapeutic heat. 1990:471-581.

462 Prentice W, Draper D. Shortwave and microwave diathermy. In: Prentice W, editor. Therapeutic Modalities in Rehabilitation. 4th ed. New York: McGraw-Hill; 2011. p. 433-62.

463 Kvarstein G, Mawe L, Indahl A, Hol PK, Tennoe B, Digernes R*, et al.* A randomized double-blind controlled trial of intra-annular radiofrequency thermal disc therapy--a 12-month follow-up. Pain. 2009;145(3):279-86.

464 de Louw AJ, van Kleef M, Vles JS. Percutaneous radiofrequency lesion adjacent to the dorsal root ganglion in the treatment of spasticity and pain in children with cerebral palsy. Pain Pract. 2002;2(3):265-8.

465 Sluijter M, Racz G. Technical aspects of radiofrequency. Pain Pract. 2002;2(3):195-200.

466 Curley SA, Palalon F, Sanders KE, Koshkina NV. The Effects of Non-Invasive Radiofrequency Treatment and Hyperthermia on Malignant and Nonmalignant Cells. Int J Environ Res Publ Health. 2014;11(9):9142-53.

467 Juang T, Stauffer PR, Craciunescu OA, Maccarini PF, Yuan Y, Das SK*, et al.* Thermal dosimetry characteristics of deep regional heating of non-muscle invasive bladder cancer. Int J Hyperthermia. 2014;30(3):176-83.

468 Cihoric N, Tsikkinis A, van Rhoon G, Crezee H, Aebersold DM, Bodis S*, et al.* Hyperthermia-related clinical trials on cancer treatment within the ClinicalTrials.gov registry. Int J Hyperthermia. 2015:1-6.

469 Knight CA, Rutledge CR, Cox ME, Acosta M, Hall SJ. Effect of superficial heat, deep heat, and active exercise warm-up on the extensibility of the plantar flexors. Phys Ther. 2001;81(6):1206-14.

470 Field SB, Morris CC. The relationship between heating time and temperature: its relevance to clinical hyperthermia. Radiother Oncol. 1983;1(2):179-86.

471 Hall EJ, Roizin-Towle L. Biological effects of heat. Cancer Res. 1984;44(10 Suppl):4708s-13s.

472 Dewey WC. Arrhenius relationships from the molecule and cell to the clinic. Int J Hyperthermia. 2009;25(1):3-20.

473 Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. Int J Hyperthermia. 2003;19(3):267-94.

474 van Rhoon GC, Samaras T, Yarmolenko PS, Dewhirst MW, Neufeld E, Kuster N. CEM43 degrees C thermal dose thresholds: a potential guide for magnetic resonance radiofrequency exposure levels? Eur Radiol. 2013;23(8):2215-27.

475 Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. Int J Radiat Oncol Biol Phys. 1984;10(6):787-800.

476 Low J, Reed A. Electromagnetic fields: shortwave diathermy, pulsed electromagnetic energy and magnetic therapies. In: Low J, Reed A, editors. Electrotherapy explained: Principles and practice. 1st ed. London: Butterworth Heinemann; 1990. p. 221-60.

477 Weerapong P, Hume PA, Kolt GS. The mechanisms of massage and effects on performance, muscle recovery and injury prevention. Sports medicine (Auckland, NZ). 2005;35(3):235-56.

478 Kingston L, Claydon L, Tumilty S. The effects of spinal mobilizations on the sympathetic nervous system: A systematic review. Man Ther. 2014;19(4):281-7.

479 Zegarra-Parodi R, Park PY, Heath DM, Makin IR, Degenhardt BF, Roustit M. Assessment of skin blood flow following spinal manual therapy: a systematic review. Man Ther. 2015;20(2):228-49.

480 Goats GC. Massage--the scientific basis of an ancient art: Part 2. Physiological and therapeutic effects. Br J Sports Med. 1994;28(3):153-6.

481 King HH, Jänig W, Patterson MM. The Science and Clinical Application of Manual Therapy. 1st ed: Elsevier Health Sciences; 2010.

482 Lowe WW. Orthopedic Massage: Theory and Technique. 2nd ed: Elsevier Health Sciences; 2009.

483 Zullino DF, Krenz S, Fresard E, Cancela E, Khazaal Y. Local back massage with an automated massage chair: general muscle and psychophysiologic relaxing properties. J Altern Complement Med. 2005;11(6):1103-6.

484 Olson B. Effects of massage for prevention of pressure ulcers. Decubitus. 1989;2(4):32-7.

485 Sefton JM, Yarar C, Berry JW, Pascoe DD. Therapeutic massage of the neck and shoulders produces changes in peripheral blood flow when assessed with dynamic infrared thermography. J Altern Complement Med. 2010;16(7):723-32.

486 Portillo-Soto A, Eberman LE, Demchak TJ, Peebles C. Comparison of blood flow changes with soft tissue mobilization and massage therapy. J Altern Complement Med. 2014;20(12):932-6.

487 Franklin NC, Ali MM, Robinson AT, Norkeviciute E, Phillips SA. Massage therapy restores peripheral vascular function after exertion. Arch Phys Med Rehabil. 2014;95(6):1127-34.

488 Taspinar F, Aslan UB, Sabir N, Cavlak U. Implementation of matrix rhythm therapy and conventional massage in young females and comparison of their acute effects on circulation. J Altern Complement Med. 2013;19(10):826-32.

489 Namkoong S, Shim J, Kim S, Shim J. Effects of different sitting positions on skin temperature of the lower extremity. J Phys Ther Sci. 2015;27(8):2637-40.

490 Arthur RM, Straube WL, Trobaugh JW, Moros EG. Non-invasive estimation of hyperthermia temperatures with ultrasound. Int J Hyperthermia. 2005;21(6):589-600.

491 Wust P, Cho CH, Hildebrandt B, Gellermann J. Thermal monitoring: invasive, minimal-invasive and non-invasive approaches. Int J Hyperthermia. 2006;22(3):255-62.

492 van Nguyen JV, Marks R. Pulsed electromagnetic fields for treating osteo-arthritis. Physiotherapy. 2002;88(8):458-70.

493 Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N*, et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage. 2007;15(9):981-1000.

494 Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: A review of community burden and current use of primary health care. Ann Rheum Dis. 2001;60(2):91-7.

495 Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum. 1987;30(8):914-8.

496 Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis. Prevalence in the population and relationship between symptoms and x-ray changes. Ann Rheum Dis. 1966;25(1):1-24.

497 McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: The importance of the patellofemoral joint. Ann Rheum Dis. 1992;51(7):844-9.

498 Van Saase JLCM, Van Romunde LKJ, Cats A, VanDenBroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis. 1989;48(4):271-80.

499 Felson DT. Epidemiology of hip and knee osteoartrritis. Epidemiol Rev. 1988;10(1):1-28.

500 Ingvarsson T, Hägglund G, Lohmander LS. Prevalence of hip osteoarthritis in Iceland. Ann Rheum Dis. 1999;58(4):201-7.

501 Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH*, et al.* Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 1998;41(5):778-99.

502 Tepper S, Hochberg MC. Factors associated with hip osteoarthritis: Data from the first national health and nutrition examination survey (NHANES-1). Am J Epidemiol. 1993;137(10):1081-8.

503 Dawson J, Linsell L, Zondervan K, Rose P, Randall T, Carr A*, et al.* Epidemiology of hip and knee pain and its impact on overall health status in older adults. Rheumatology. 2004;43(4):497-504.

504 Mannoni A, Briganti MP, Di Bari M, Ferrucci L, Costanzo S, Serni U*, et al.* Epidemiological profile of symptomatic osteoarthritis in older adults: A population based study in Dicomano, Italy. Ann Rheum Dis. 2003;62(6):576-8.

505 Buckwalter JA, Lappin DR. The disproportionate impact of chronic arthralgia and arthritis among women. Clin Orthop Relat Res. 2000(372):159-68.

506 Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P*, et al.* The incidence and natural history of knee osteoarthritis in the elderly: The Framingham osteoarthritis study. Arthritis Rheum. 1995;38(10):1500-5.

507 Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum. 1995;38(8):1134-41.

508 Buckwalter JA, Heckman JD, Petrie DP. Aging of the north American population: New challenges for orthopaedics. J Bone Joint Surg Am. 2003;85(4):748-58.

509 Chen A, Gupte C, Akhtar K, Smith P, Cobb J. The Global Economic Cost of Osteoarthritis: How the UK Compares. Arthritis. 2012;2012:698709.

510 Rosen J, Sancheti P, Fierlinger A, Niazi F, Johal H, Bedi A. Potential Impact of Biologically Derived Hyaluronic Acid on Quality of Life in Patients with Knee Osteoarthritis in the United States. Adv Ther. 2016;33(12):2200-10.

511 Buckwalter JA, Martin J. Degenerative joint disease. Clin Symp. 1995;47(2):1-32.

512 Buckwalter JA, Mankin HJ. Articular cartilage. Part II: Degeneration and osteoarthrosis, repair, regeneration, and transplantation. J Bone Joint Surg Am. 1997;79(4):612-32.

513 Cooper C, Dennison E. The Natural History and Prognosis of Osteoarthritis. In: Brandt KD, Doherty M, Lohmander LS, editors. Osteoarthritis. Oxford: Oxford University Press; 1998. p. 237– 49.

514 Dennison E, Cooper C. Osteoarthritis: epidemiology and classification. In: Hochberg MC, Silman AJ, Smolen JS, editors. Rheumatology. London: Mosby; 2003. p. 1781–91.

515 Dieppe P. The classification and diagnosis of osteoarthritis. In: Kuettner KE, Goldberg VM, editors. Osteoarthritic disorders. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1995. p. 5–12.

516 Buckwalter JA, Martin J, Mankin HJ. Synovial joint degeneration and the syndrome of osteoarthritis. Instr Course Lect. 2000;49:481-9.

517 Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K*, et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-49.

518 Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum. 1986;29:1039-49.

519 Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR*, et al.* Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. Arthritis Rheum. 1995;38(11):1541-6.

520 McAlindon T, Dieppe P. Osteoarthritis: definitions and criteria. Ann Rheum Dis. 1989;48(7):531-2.

521 Claessens AA, Schouten JS, van den Ouweland FA, Valkenburg HA. Do clinical findings associate with radiographic osteoarthritis of the knee? Ann Rheum Dis. 1990;49(10):771-4.

522 Odding E, Valkenburg HA, Algra D, Vandenouweland FA, Grobbee DE, Hofman A. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam study. Ann Rheum Dis. 1998;57(4):203-8.

523 Davis AM, MacKay C. Osteoarthritis year in review: Outcome of rehabilitation. Osteoarthritis Cartilage. 2013;21(10):1414-24.

524 Rodriguez-Merchan EC. Conservative treatment of acute knee osteoarthritis: A review of the Cochrane Library. J Acute Dis. 2016;5(3):190-3.

525 McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM*, et al.* OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363-88.

526 Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, Conaghan PG*, et al.* EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis. 2013;72(7):1125-35.

527 Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J*, et al.* American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012;64(4):465-74.

528 Nguyen C, Lefevre-Colau MM, Poiraudeau S, Rannou F. Rehabilitation (exercise and strength training) and osteoarthritis: A critical narrative review. Ann Phys Rehabil Med. 2016;59(3):190-5.

529 Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev. 2015;1:CD004376.

530 Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK*, et al.* OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010;18(4):476-99.

531 Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. Semin Arthritis Rheum. 2014;43(6):701-12.

532 Vignon É, Valat J-P, Rossignol M, Avouac B, Rozenberg S, Thoumie P*, et al.* Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). Joint Bone Spine. 2006;73(4):442-55.

533 Brosseau L, Rahman P, Poitras S, Toupin-April K, Paterson G, Smith C*, et al.* A Systematic Critical Appraisal of Non-Pharmacological Management of Rheumatoid Arthritis with Appraisal of Guidelines for Research and Evaluation II. PLoS One. 2014;9(5):e95369.

534 Regnaux JP, Lefevre-Colau MM, Trinquart L, Nguyen C, Boutron I, Brosseau L*, et al.* High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. Cochrane Database Syst Rev. 2015(10):CD010203.

535 Rannou F, Poiraudeau S. Non-pharmacological approaches for the treatment of osteoarthritis. Best Pract Res Clin Rheumatol. 2010;24(1):93-106.

536 Pisters MF, Veenhof C, van Meeteren NL, Ostelo RW, de Bakker DH, Schellevis FG*, et al.* Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. Arthritis Rheum. 2007;57(7):1245-53.

537 Fitzgerald GK, Fritz JM, Childs JD, Brennan GP, Talisa V, Gil AB*, et al.* Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multi-center, factorial randomized clinical trial. Osteoarthritis Cartilage. 2016;24(8):1340-9.

538 Jamtvedt G, Dahm KT, Christie A, Moe RH, Haavardsholm E, Holm I*, et al.* Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. Phys Ther. 2008;88(1):123-36.

539 Fransen M, McConnell S, Bell M. Exercise for osteoarthritis of the hip or knee. Cochrane Database Syst Rev. 2003(3):CD004286.

540 French HP, Brennan A, White B, Cusack T. Manual therapy for osteoarthritis of the hip or knee – A systematic review. Man Ther. 2011;16(2):109-17.

541 Deyle GD, Allison SC, Matekel RL, Ryder MG, Stang JM, Gohdes DD*, et al.* Physical therapy treatment effectiveness for osteoarthritis of the knee: A randomized comparison of supervised clinical exercise and manual therapy procedures versus a home exercise program. Phys Ther. 2005;85(12):1301-17.

542 Abbott JH, Robertson MC, Chapple C, Pinto D, Wright AA, Leon de la Barra S*, et al.* Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. Osteoarthritis Cartilage. 2013;21(4):525-34.

543 Perlman AI, Sabina A, Williams AL, Njike VY, Katz DL. Massage therapy for osteoarthritis of the knee: a randomized controlled trial. Arch Intern Med. 2006;166(22):2533-8.

544 Pollard H, Ward G, Hoskins W, Hardy K. The effect of a manual therapy knee protocol on osteoarthritic knee pain: a randomised controlled trial. J Can Chiropract Assoc. 2008;52(4):229-42.

545 Osteoarthritis: Care and Management in Adults. London: National Clinical Guideline Centre, 2014.; 2014 Feb.

546 Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P*, et al.* EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145-55.

547 Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. BMC Musculoskelet Disord. 2007;8:51.

548 Osiri M, Welch V, Brosseau L, Shea B, McGowan J, Tugwell P*, et al.* Transcutaneous electrical nerve stimulation for knee osteoarthritis. Cochrane Database Syst Rev. 2000(4):CD002823.

549 Roberts J, Dicenso A. Identifying the best research design to fit the question. Part 1: quantitative designs. Evid Base Nurs. 1999;2(1):4-6.

550 Kendall JM. Designing a research project: randomised controlled trials and their principles. Emerg Med J. 2003;20(2):164-8.

551 Brown WA. Expectation, the placebo effect and the response to treatment. R I Med J (2013). 2015;98(5):19-21.

552 Holmes RD, Tiwari AK, Kennedy JL. Mechanisms of the placebo effect in pain and psychiatric disorders. Pharmacogenomics J. 2016;16(6):491-500.

553 Bialosky JE, Bishop MD, George SZ, Robinson ME. Placebo response to manual therapy: something out of nothing? J Man Manip Ther. 2011;19(1):11-9.

554 Crossley KM, Bennell KL, Cowan SM, Green S. Analysis of outcome measures for persons with patellofemoral pain: which are reliable and valid? Arch Phys Med Rehabil. 2004;85(5):815-22.

555 Bennell K, Bartam S, Crossley K, Green S. Outcome measures in patellofemoral pain syndrome: test retest reliability and inter-relationships. Phys Ther Sport. 2000;1(2):32-41.

556 Lara-Muñoz C, de Leon SP, Feinstein AR, Puente A, Wells CK. Comparison of Three Rating Scales for Measuring Subjective Phenomena in Clinical Research: I. Use of Experimentally Controlled Auditory Stimuli. Arch Med Res. 2004;35(1):43-8.

557 Chesworth BM, Culham E, Tata GE, Peat M. Validation of outcome measures in patients with patellofemoral syndrome. J Orthop Sports Phys Ther. 1989;10(8):302-8.

558 Harrison E, Quinney H, Magee D, Sheppard MS, McQuarrie A. Analysis of outcome measures used in the study of patellofemoral pain syndrome. Physiother Can. 1995;47(4):264-72.

559 Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain. 2011;152(10):2399-404.

560 Price DD, Patel R, Robinson ME, Staud R. Characteristics of electronic visual analogue and numerical scales for ratings of experimental pain in healthy subjects and fibromyalgia patients. Pain. 2008;140(1):158-66.

561 Dijkers M. Comparing quantification of pain severity by verbal rating and numeric rating scales. J Spinal Cord Med. 2010;33(3):232-42.

562 Myles PS, Urquhart N. The linearity of the visual analogue scale in patients with severe acute pain. Anaesth Intensive Care. 2005;33(1):54-8.

563 Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain. 1983;17(1):45-56.

564 Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH*, et al.* Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41(6):1073-93.

565 Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. J Shoulder Elbow Surg. 2009;18(6):927-32.

566 Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med. 1996;27(4):485-9.

567 Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001;38(6):633-8.

568 Bellamy N. Pain assessment in osteoarthritis: Experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum. 1989;18(4 SUPPL. 2):14-7.

569 Bellamy N. WOMAC Osteoarthritis Index: A users guide. WOMAC Osteoarthritis Index: A User's Guide. 1995.

570 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt L. Validation study of WOMAC: A health status instrument for measuring clinically-important patient-relevant outcomes following total hip or knee arthroplasty in osteoarthritis. J Orthop Rheumatol. 1988;1:95-108.

571 McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. Arthritis Care Res. 2001;45(5):453-61.

572 Hmamouchi I, Allali F, Tahiri L, Khazzani H, Mansouri LE, Ali Ou Alla S*, et al.* Clinically important improvement in the WOMAC and predictor factors for response to non-specific non-steroidal anti-inflammatory drugs in osteoarthritic patients: a prospective study. BMC Res Notes. 2012;5:58-.

573 Angst F, Aeschlimann A, Steiner W, Stucki G. Responsiveness of the WOMAC osteoarthritis index as compared with the SF-36 in patients with osteoarthritis of the legs undergoing a comprehensive rehabilitation intervention. Ann Rheum Dis. 2001;60(9):834-40.

574 Davies GM, Watson DJ, Bellamy N. Comparison of the responsiveness and relative effect size of the Western Ontario and McMaster Universities Osteoarthritis Index and

the short-form medical outcomes study survey in a randomized, clinical trial of osteoarthritis patients. Arthritis Care Res. 1999;12(3):172-9.

575 Pua YH, Cowan SM, Wrigley TV, Bennell KL. Discriminant validity of the Western Ontario and McMaster Universities Osteoarthritis index physical functioning subscale in community samples with hip osteoarthritis. Arch Phys Med Rehabil. 2009;90(10):1772-7.

576 Ryser L, Wright BD, Aeschlimann A, Mariacher-Gehler S, Stucki G. A new look at the Western Ontario and McMaster Universities Osteoarthritis Index using Rasch analysis. Arthritis Care Res. 1999;12(5):331-5.

577 Angst F, Ewert T, Lehmann S, Aeschlimann A, Stucki G. The factor subdimensions of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) help to specify hip and knee osteoarthritis. a prospective evaluation and validation study. J Rheumatol. 2005;32(7):1324-30.

578 Stratford PW, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. Osteoarthritis Cartilage. 2007;15(3):266-72.

579 Thumboo J, Chew LH, Soh CH. Validation of the Western Ontario and McMaster University Osteoarthritis Index in Asians with osteoarthritis in Singapore. Osteoarthritis Cartilage. 2001;9(5):440-6.

580 Kennedy D, Stratford PW, Pagura SM, Wessel J, Gollish JD, Woodhouse LJ. Exploring the factorial validity and clinical interpretability of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Physiother Can. 2003;55(3):160-8.

581 Bellamy N. WOMAC: a 20-year experiential review of a patient-centered self-reported health status questionnaire. J Rheumatol. 2002;29(12):2473-6.

582 Bellamy N, Campbell J, Hill J, Band P. A comparative study of telephone versus onsite completion of the WOMAC 3.0 osteoarthritis index. J Rheumatol. 2002;29(4):783-6.

583 Bellamy N, Campbell J, Stevens J, Pilch L, Stewart C, Mahmood Z. Validation study of a computerized version of the Western Ontario and McMaster Universities VA3.0 Osteoarthritis Index. J Rheumatol. 1997;24(12):2413-5.

584 Theiler R, Spielberger J, Bischoff HA, Bellamy N, Huber J, Kroesen S. Clinical evaluation of the WOMAC 3.0 OA Index in numeric rating scale format using a computerized touch screen version. Osteoarthritis Cartilage. 2002;10(6):479-81.

585 Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-8.

586 Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. Arthritis Care Res. 2011;63 Suppl 11:S350-70.

587 Arnadottir SA, Mercer VS. Effects of footwear on measurements of balance and gait in women between the ages of 65 and 93 years. Phys Ther. 2000;80(1):17-27.

588 Schwartz AV, Villa ML, Prill M, Kelsey JA, Galinus JA, Delay RR*, et al.* Falls in older Mexican-American women. J Am Geriatr Soc. 1999;47(11):1371-8.

589 Steffen TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. Phys Ther. 2002;82(2):128-37.

590 Barry E, Galvin R, Keogh C, Horgan F, Fahey T. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. BMC Geriatr. 2014;14:14.

591 Sprint G, Cook DJ, Weeks DL. Toward Automating Clinical Assessments: A Survey of the Timed Up and Go. IEEE Rev Biomed Eng. 2015;8:64-77.

592 Bisca GW, Morita AA, Hernandes NA, Probst VS, Pitta F. Simple Lower Limb Functional Tests in Patients With Chronic Obstructive Pulmonary Disease: A Systematic Review. Arch Phys Med Rehabil. 2015;96(12):2221-30.

593 Hafsteinsdottir TB, Rensink M, Schuurmans M. Clinimetric properties of the Timed Up and Go Test for patients with stroke: a systematic review. Top Stroke Rehabil. 2014;21(3):197-210.

594 Alexandre TS, Meira DM, Rico NC, Mizuta SK. Accuracy of Timed Up and Go Test for screening risk of falls among community-dwelling elderly. Rev Bras Fisioter. 2012;16(5):381-8.

595 Di Fabio RP, Seay R. Use of the "fast evaluation of mobility, balance, and fear" in elderly community dwellers: validity and reliability. Phys Ther. 1997;77(9):904-17.

596 Noren AM, Bogren U, Bolin J, Stenstrom C. Balance assessment in patients with peripheral arthritis: applicability and reliability of some clinical assessments. Physiother Res Int. 2001;6(4):193-204.

597 Rockwood K, Awalt E, Carver D, MacKnight C. Feasibility and measurement properties of the functional reach and the timed up and go tests in the Canadian study of health and aging. J Gerontol A Biol Sci Med Sci. 2000;55(2):M70-3.

598 Bennie S, Bruner K, Dizon A, Fritz H, Goodman B, Peterson S. Measurements of Balance: Comparison of the Timed "Up and Go" Test and Functional Reach Test with the Berg Balance Scale. J Phys Ther Sci. 2003;15(2):93-7.

599 van Hedel HJ, Wirz M, Dietz V. Assessing walking ability in subjects with spinal cord injury: validity and reliability of 3 walking tests. Arch Phys Med Rehabil. 2005;86(2):190-6.

600 Freter SH, Fruchter N. Relationship between timed 'up and go' and gait time in an elderly orthopaedic rehabilitation population. Clin Rehabil. 2000;14(1):96-101.

601 Schoene D, Wu SM, Mikolaizak AS, Menant JC, Smith ST, Delbaere K*, et al.* Discriminative ability and predictive validity of the timed up and go test in identifying older people who fall: systematic review and meta-analysis. J Am Geriatr Soc. 2013;61(2):202-8.

602 Gautschi OP, Stienen MN, Corniola MV, Joswig H, Schaller K, Hildebrandt G*, et al.* Assessment of the Minimum Clinically Important Difference in the Timed Up and Go Test After Surgery for Lumbar Degenerative Disc Disease. Neurosurgery. 2016.

603 Saito I, Okada K, Nishi T, Wakasa M, Saito A, Sugawara K*, et al.* Foot pressure pattern and its correlation with knee range of motion limitations for individuals with medial knee osteoarthritis. Arch Phys Med Rehabil. 2013;94(12):2502-8.

604 Gogia PP, Braatz JH, Rose SJ, Norton BJ. Reliability and validity of goniometric measurements at the knee. Phys Ther. 1987;67(2):192-5.

605 Pisters MF, Veenhof C, van Dijk GM, Heymans MW, Twisk JW, Dekker J. The course of limitations in activities over 5 years in patients with knee and hip osteoarthritis with moderate functional limitations: risk factors for future functional decline. Osteoarthritis Cartilage. 2012;20(6):503-10.

606 van Dijk GM, Veenhof C, Lankhorst GJ, Dekker J. Limitations in activities in patients with osteoarthritis of the hip or knee: the relationship with body functions, comorbidity and cognitive functioning. Disabil Rehabil. 2009;31(20):1685-91.

607 van Dijk GM, Veenhof C, Spreeuwenberg P, Coene N, Burger BJ, van Schaardenburg D*, et al.* Prognosis of limitations in activities in osteoarthritis of the hip or knee: a 3-year cohort study. Arch Phys Med Rehabil. 2010;91(1):58-66.

608 Holla JF, Steultjens MP, Roorda LD, Heymans MW, Ten Wolde S, Dekker J. Prognostic factors for the two-year course of activity limitations in early osteoarthritis of the hip and/or knee. Arthritis Care Res. 2010;62(10):1415-25.

609 Messier SP, Loeser RF, Hoover JL, Semble EL, Wise CM. Osteoarthritis of the knee: effects on gait, strength, and flexibility. Arch Phys Med Rehabil. 1992;73(1):29-36.

610 Hoogeboom TJ, van Meeteren NL, Kim RH, Stevens-Lapsley JE. Linear and curvilinear relationship between knee range of motion and physical functioning in people with knee osteoarthritis: a cross-sectional study. PLoS One. 2013;8(9):e76173.

611 Gajdosik RL, Bohannon RW. Clinical measurement of range of motion. Review of goniometry emphasizing reliability and validity. Phys Ther. 1987;67(12):1867-72.

612 Moore ML. The measurement of joint motion; the technic of goniometry. Phys Ther Rev. 1949;29(6):256-64.

613 Boone DC, Azen SP, Lin CM, Spence C, Baron C, Lee L. Reliability of goniometric measurements. Phys Ther. 1978;58(11):1355-60.

614 Pandya S, Florence JM, King WM, Robison JD, Oxman M, Province MA. Reliability of goniometric measurements in patients with Duchenne muscular dystrophy. Phys Ther. 1985;65(9):1339-42.

615 Rome K, Cowieson F. A reliability study of the universal goniometer, fluid goniometer, and electrogoniometer for the measurement of ankle dorsiflexion. Foot Ankle Int. 1996;17(1):28-32.

616 Bezalel T, Carmeli E, Katz-Leurer M. The effect of a group education programme on pain and function through knowledge acquisition and home-based exercise among patients with knee osteoarthritis: A parallel randomised single-blind clinical trial. Physiotherapy. 2010;96(2):137-43.

617 Barr S, Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF*, et al.* A comparative study of signal versus aggregate methods of outcome measurement based on the WOMAC Osteoarthritis Index. Western Ontario and McMaster Universities Osteoarthritis Index. J Rheumatol. 1994;21(11):2106-12.

618 Sim J, Waterfield J. Validity, reliability and responsiveness in the assessment of pain. Physiother Theory Pract. 1997;13(1):23-37.

619 Giske L, Sandvik L, Roe C. Comparison of daily and weekly retrospectively reported pain intensity in patients with localized and generalized musculoskeletal pain. Eur J Pain. 2010;14(9):959-65.

620 Jensen MP, Mardekian J, Lakshminarayanan M, Boye ME. Validity of 24-h recall ratings of pain severity: biasing effects of "Peak" and "End" pain. Pain. 2008;137(2):422-7.

621 Bolton JE, Humphreys BK, van Hedel HJ. Validity of weekly recall ratings of average pain intensity in neck pain patients. J Manipulative Physiol Therapeut. 2010;33(8):612-7.

622 Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med. 2001;38(6):639-43.

623 Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. J Orthop Surg Res. 2015;10:24.

624 Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Care Res. 2001;45(4):384-91.

625 Kim H, Suzuki T, Saito K, Kim M, Kojima N, Ishizaki T, et al. Effectiveness of exercise with or without thermal therapy for community-dwelling elderly Japanese women with non-specific knee pain: a randomized controlled trial. Arch Gerontol Geriatr. 2013;57(3):352-9.

626 Weng MC, Lee CL, Chen CH, Hsu JJ, Lee WD, Huang MH, et al. Effects of Different Stretching Techniques on the Outcomes of Isokinetic Exercise in Patients with Knee Osteoarthritis. Kaohsiung J Med Sci. 2009;25(6):306-15.

627 Thorstensson CA, Roos EM, Petersson IF, Ekdahl C. Six-week high-intensity exercise program for middle-aged patients with knee osteoarthritis: a randomized controlled trial. BMC Musculoskelet Disord. 2005;6:27.

628 Sibbald B, Roland M. Understanding controlled trials: Why are randomised controlled trials important? BMJ. 1998;316(7126):201.

629 Spieth PM, Kubasch AS, Penzlin AI, Illigens BM-W, Barlinn K, Siepmann T. Randomized controlled trials – a matter of design. Neuropsychiatr Dis Treat. 2016;12:1341-9.

12 Appendices

12.1 Appendix 2.1: Key words and filter terms used in the literature searching

Main search terms ('OR' key words)

Electromagnetic field

Electromagnet*

EMF

EME

Radiofrequency

Radio frequency

Radio-frequency

RF

Radio wave

Microwave

Millimetre wave

Shortwave

Short wave

Short-wave

Diathermy

SWD

SWT

SW

Electric field therapy

EFT

Tecar

CRET

High frequency current

High frequency therapy

High frequency energy

High frequency

High-frequency

HFT

HFC

HFE

HF

Primary filter ('AND' key words)

Biological effects

Physiological effects

Clinical effects

Therapeutic effects

Thermal effects

Biolog*

Physiolog*

Clinic*

Therap*

Therm*

Effects

Skin

Muscle

Tissue

Blood

Elast*

Exten*

Elongation

Cell*

Nerv*

Metabol*

Biochem*

Pathol*

Disease

Treatment

Medic*

Secondary filter ('NOT' key words)

Invasive

Percutaneous

Ablation

Ablat*

Surgery

Surgical

Radiotherapy

Radiotherap*

Mobile phone

Telephon*

Radar

MRI

PET

Tomograph*

RFID

Television

TV

Polymer

Spectroscop*

Aviation

Telemetry

FM

Robot*

Plant

Seed

Germinat*

Ocean*

Fish*

Communicat*

12.2 Appendix 2.2: Cochrane risk of bias assessment tool

The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Possible approach for *summary assessments* outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

Criteria for judging risk of bias in the 'Risk of bias' assessment tool

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: ▪ Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: ▪ Sequence generated by odd or even date of birth; ▪ Sequence generated by some rule based on date (or day) of admission; ▪ Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: ▪ Allocation by judgement of the clinician; ▪ Allocation by preference of the participant; ▪ Allocation based on the results of a laboratory test or a series of tests; ▪ Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: ▪ Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); ▪ Sequentially numbered drug containers of identical appearance; ▪ Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: ▪ Using an open random allocation schedule (e.g. a list of random numbers); ▪ Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); ▪ Alternation or rotation; ▪ Date of birth; ▪ Case record number; ▪ Any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); ▪ The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any of the following: ▪ The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; ▪ The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Not all of the study's pre-specified primary outcomes have been reported; ▪ One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; ▪ One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); ▪ One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; ▪ The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: ▪ Had a potential source of bias related to the specific study design used; or ▪ Stopped early due to some data-dependent process (including a formal-stopping rule); or ▪ Had extreme baseline imbalance; or ▪ Has been claimed to have been fraudulent; or ▪ Had some other problem.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: ▪ Insufficient information to assess whether an important risk of bias exists; or ▪ Insufficient rationale or evidence that an identified problem will introduce bias.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; ▪ Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; ▪ Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient information to permit judgement of 'Yes' or 'No'; ▪ The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No missing outcome data; ▪ Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); ▪ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; ▪ Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ▪ 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; ▪ Potentially inappropriate application of simple imputation.

12.3 Appendix 2.3: Downs and Black checklist for randomised and non-randomised studies

ALL CRITERIA	DESCRIPTION OF CRITERIA (with additional explanation as required, determined by consensus of raters)	POSSIBLE ANSWERS
1	**Is the hypothesis/aim/objective of the study clearly described?** Must be explicit	Yes/No
2	**Are the main outcomes to be measured clearly described in the Introduction or Methods section?** If the main outcomes are first mentioned in the Results section, the question should be answered no. **ALL** primary outcomes should be described for YES	Yes/No
3	**Are the characteristics of the patients included in the study clearly described?** In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. Single case studies must state source of patient	Yes/No
4	**Are the interventions of interest clearly described?** Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes/No
5	**Are the distributions of principal confounders in each group of subjects to be compared clearly described?** A list of principal confounders is provided. YES = age, severity	Yes/No
6	**Are the main findings of the study clearly described?** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.	Yes/No
7	**Does the study provide estimates of the random variability in the data for the main outcomes?** In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported	Yes/No
8	**Have all important adverse events that may be a consequence of the intervention been reported?** This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events (COMPLICATIONS BUT NOT AN INCREASE IN PAIN).	Yes/No
9	**Have the characteristics of patients lost to follow-up been described?** If not explicit = NO. RETROSPECTIVE – if not described = UTD; if not explicit re: numbers agreeing to participate = NO. Needs to be >85%	Yes/No
10	**Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?**	Yes/No
11	**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?** The study must identify the source population for patients and describe how the patients were selected.	Yes/No/UTD
12	**Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** The proportion of those asked who agreed should be stated.	Yes/No/UTD
13	**Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?** For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. Must state type of hospital and country for YES.	Yes/No/UTD
14	**Was an attempt made to blind study subjects to the intervention they have received?** For studies where the patients would have no way of knowing which intervention they received, this should be answered yes. Retrospective, single group = NO; UTD if > 1 group and blinding not explicitly stated	Yes/No/UTD
15	**Was an attempt made to blind those measuring the main outcomes of the intervention?** Must be explicit	Yes/No/UTD
16	**If any of the results of the study were based on "data dredging", was this made clear?** Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective = YES	Yes/No/UTD
17	**In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?** Where follow-up was the same for all study patients the answer should yes. Studies where differences in follow-up are ignored should be answered no. Acceptable range 1 yr follow up = 1 month each way; 2 years follow up = 2 months; 3 years follow up = 3months.....10years follow up = 10 months	Yes/No/UTD
18	**Were the statistical tests used to assess the main outcomes appropriate?** The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do = NO	Yes/No/UTD
19	**Was compliance with the intervention/s reliable?** Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. Surgical studies will be YES unless procedure not completed.	Yes/No/UTD
20	**Were the main outcome measures used accurate (valid and reliable)?** Where outcome measures are clearly	Yes/No/UTD

	described, which refer to other work or that demonstrates the outcome measures are accurate = YES. ALL primary outcomes valid and reliable for YES	
21	**Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?** Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients	Yes/No/UTD
22	**Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?** For a study which does not specify the time period over which patients were recruited, the question should be answered as UTD. Surgical studies must be <10 years for YES, if >10 years then NO	Yes/No/UTD
23	**Were study subjects randomised to intervention groups?** Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation.	Yes/No/UTD
24	**Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?** All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	Yes/No/UTD
25	**Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?** In nonrandomised studies if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as no. If no significant difference between groups shown then YES	Yes/No/UTD
26	**Were losses of patients to follow-up taken into account?** If the numbers of patients lost to follow-up are not reported = unable to determine.	Yes/No/UTD
27	**Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%** Sample sizes have been calculated to detect a difference of x% and y%.	1-5

12.4 Appendix 4.1: Biopac system specifications

BIOPAC Systems, Inc.

HARDWARE GUIDE

info@biopac.com
support@biopac.com
www.biopac.com

MP SYSTEM SPECIFICATIONS – FOR MP150 AND MP100

Analog Inputs

Number of Channels:	16
Absolute Maximum Input:	±15 V
Operational Input Voltage:	±10 V
A/D Resolution:	16 Bits
Accuracy (% of FSR):	±0.003
Input impedance:	1.0 MΩ

Application Programming Interfaces options:

- Hardware Interface BHAPI
- Software Interface ACKAPI

Analog Outputs

Number of Channels:	2
Max output with acquisition:	MP150: 2 channels, MP100: 1 channel
Output Voltage Range:	±10 V
D/A Resolution:	MP150: 16 bits, MP100: 12 Bits
Accuracy (% of FSR):	MP150: ±0.003, MP100: ±0.02
Output Drive Current:	±5 mA (max)
Output Impedance:	100 Ω

Digital I/O

Number of Channels:	16
Voltage Levels:	TTL, CMOS
Output Drive Current:	±20 mA (max)
External Trigger Input:	TTL, CMOS compatible - See also: External Trigger Inputs

Time Base

Min Sample Rate:	2 samples/hour
Trigger Options:	Internal, External or Signal Level

Power

Amplifier Module Isolation:	Provided by the MP unit, isolated clean power
CE Marking:	EC Low Voltage and EMC Directives
Leakage current:	<8 µA (Normal), <400 µA (Single Fault)
Fuse:	2 A (fast blow)

Device specific specs	*MP150*	*MP100*
Max Sample Rate MP Internal Memory:	200 K samples/sec (400K aggregate)	70 K samples/sec (70 K aggregate)
PC Memory/Disk:	200 K samples/sec (400K aggregate)	11 K samples/sec (16K aggregate)
Internal Buffer:	6 M samples	16 K samples
Waveform Output Buffer:	500 K samples	4 K samples
Serial Interface Type/Rate:	Ethernet: UDP (10M bits/sec)	Serial: RS422 (800 Kbits/sec)
Transmission Type:	Ethernet	USB only (Windows via USB1W or Mac via USB1M)
Maximum cable length:	100 meters (Ethernet cable)	7 meters (USB + SERIAL cable)
Power Requirements:	12VDC @ 2 amp (uses AC150A)	12 VDC @ 1amp (uses AC100A)
Dimensions:	10cm x 11cm x 19cm	7cm x 29cm x 25cm
Weight:	1.0 kg	1.8 kg
OS Compatibility		
Ethernet Interface		
Windows	Windows XP, Vista, 7	Not supported
Mac	OS X	Not supported
USB Interface		
Windows	Not supported	Windows XP, Vista, 7
Mac	Not supported	OS X

ISOLATION

Designed to satisfy the following Medical Safety Test Standards affiliated with IEC601-1:

- Creepage and Air Clearance
- Dielectric Strength
- Patient Leakage Current

Contact BIOPAC for additional details.

SIGNAL CONDITIONING MODULE COMPATIBILITY

$CO_2$100C	EGG100C	HLT100C	PPG100C
DA100C	EMG100C	LDF100C	RSP100C
EBI100C	EOG100C	MCE100C	SKT100C
ECG100C	ERS100C	$O_2$100C	STM100C
EEG100C	GSR100C	OXY100C/E	TEL100C

CLEANING PROCEDURES

Be sure to unplug the power supply from the MP150/100 before cleaning. To clean the MP150/100, use a damp, soft cloth. Abrasive cleaners are not recommended as they might damage the housing. Do not immerse the MP150/100 or any of its components, as this can damage the system. Let the unit air-dry until it is safe to reconnect the power supply.

AC150/100A POWER SUPPLIES

The 12-volt in-line switching transformer connects the MP unit to the AC mains wall outlet. One transformer is included with each MP System; replacements can be ordered separately. These transformers are specified to satisfy IEC60601-1 requirements and will accommodate 120-240 VAC (50/60 Hz) mains input.

12.5 Appendix 4.2: MATLAB algorithm for colour Doppler image analysis in the laboratory study

```
clear;

NbFrame = 12;

counter = zeros(1,NbFrame,'uint32');
colourIndex = zeros(1,NbFrame,'uint32');
imageROI = zeros(165,226,3,'uint8');
ROI_height = 1;
ROI_width = 1;

%Flag to search the ROI (go=true > search ROI & go=false > stop searching
%ROI)
go = true;

%Size of the ROI window
height = 165;
width = 226;

for framecounter = 1:NbFrame
    ROI_height = 1;
    ROI_width = 1;
    go = true;

    strframecounter = int2str(framecounter);
    imagename = strcat('S3N1S2_T_PRE_20140711122826_
(',strframecounter,').bmp');


    %Search for the ROI
    rawImage = imread(imagename);
    size_raw_img = size(rawImage);
    heightRaw = size_raw_img(1);
    widthRaw = size_raw_img(2);
    for scanHeight = 1:heightRaw
       for scanWidth = 1:widthRaw
        if (go == true && (rawImage(scanHeight,scanWidth,1) == 0 &&
rawImage(scanHeight,scanWidth,2) == 236 && rawImage(scanHeight,scanWidth,3)
== 0))
            go = false;
            for scanROI_H = (scanHeight + 1) : (scanHeight + 165)
                ROI_width = 1;
                for scanROI_W = (scanWidth+1) : (scanWidth + 226)
                    imageROI(ROI_height,ROI_width,:) =
rawImage(scanROI_H,scanROI_W,:);
                    ROI_width = ROI_width + 1;
                end
                ROI_height = ROI_height + 1;
            end
        end
       end
    end


%     imageScale = imread('scale.bmp');
%     size_img_ref = size(imageScale);
%     heightref = size_img_ref(1);
```

```
% Calculate the colour doppler index
        for m = 1:height
            for n = 1:width
                %Test whether or not the pixel is grey or not
                  if ((imageROI(m,n,1) == imageROI(m,n,2)) &&
(imageROI(m,n,2) == imageROI(m,n,3)))
                       im(m,n) = 0;
                  else
                      counter(framecounter) = counter(framecounter) + 1;
                      im(m,n) = imageROI(m,n,2);
                      %Add up the green component for the calculation of
                      %the index
                      colourIndex(framecounter) = colourIndex(framecounter)
+ uint32(imageROI(m,n,2));
                  end
            end
        end

end

% U8 = im2uint8(im);
% imshow(U8);
```

12.6 Appendix 4.3: MATLAB algorithm for power Doppler image analysis in the laboratory study

```
clear;

NbFrame = 20;

counter = zeros(1,NbFrame,'uint32');
powerIndex = zeros(1,NbFrame,'uint32');
imageROI = zeros(165,226,3,'uint8');
ROI_height = 1;
ROI_width = 1;

%Flag to search the ROI (go=true > search ROI & go=false > stop searching
%ROI)
go = true;

%Size of the ROI window
height = 165;
width = 226;

for framecounter = 1:NbFrame
    ROI_height = 1;
    ROI_width = 1;
    go = true;

    strframecounter = int2str(framecounter);
    imagename = strcat('S3N1S2_T_PRE_20140711122826_
(',strframecounter,').bmp');

    %Search for the ROI
    rawImage = imread(imagename);
    size_raw_img = size(rawImage);
    heightRaw = size_raw_img(1);
    widthRaw = size_raw_img(2);
    for scanHeight = 1:heightRaw
       for scanWidth = 1:widthRaw
        if (go == true && (rawImage(scanHeight,scanWidth,1) == 0 &&
rawImage(scanHeight,scanWidth,2) == 236 && rawImage(scanHeight,scanWidth,3)
== 0))
            go = false;
            for scanROI_H = (scanHeight + 1) : (scanHeight + 165)
                ROI_width = 1;
                for scanROI_W = (scanWidth+1) : (scanWidth + 226)
                    imageROI(ROI_height,ROI_width,:) =
rawImage(scanROI_H,scanROI_W,:);
                    ROI_width = ROI_width + 1;
                end
                ROI_height = ROI_height + 1;
            end
        end
       end
    end



% Calculate the power doppler index
        for m = 1:height
            for n = 1:width
```

```
                %Test whether or not the pixel is grey or not
                  if ((imageROI(m,n,1) == imageROI(m,n,2)) &&
(imageROI(m,n,2) == imageROI(m,n,3)))
                       im(m,n) = 0;
                  else
                      counter(framecounter) = counter(framecounter) + 1;
                      im(m,n) = imageROI(m,n,2);
                      powerIndex(framecounter) = powerIndex(framecounter) +
uint32(imageROI(m,n,2));
                  end
            end
        end

end

% U8 = im2uint8(im);
% imshow(U8);

% figure
% ax(1) = subplot(211);
% rgbtest = imread('TestingBestFrame_image001.bmp');
% image(rgbtest); title('Original')
% ax(2) = subplot(212);
% image(im); title('Processed')
% colormap(hot(256))
% linkaxes(ax,'xy')
% axis(ax,'image')
%movie2avi(M, 'D:\Binoy\flow_L1.avi', 'compression', 'None');
```

12.7 Appendix 4.4: MATLAB algorithm for Elastography image analysis in the laboratory study

```
%Scan for the ROI from the left

clear;
%
NbFrame = 10;
%

ROI_height_size = 350;
ROI_width_size = 125;

counter = zeros(1,NbFrame,'uint32');
imageROI = zeros(ROI_height_size,ROI_width_size,3,'uint8');

Index_soft = zeros(1,NbFrame,'uint32');
Index_intermediate = zeros(1,NbFrame,'uint32');
Index_hard = zeros(1,NbFrame,'uint32');

go = true;

pointer = 1;
imageScale = imread('scaleElasticity2.bmp');
size_imageScale = size(imageScale);
heightscale = size_imageScale(1);

scoreTable = csvread('scoringScale.csv');

%Search for the ROI
for framecounter = 1:NbFrame
    ROI_height = 1;
    ROI_width = 1;
    goROI = true;

    strframecounter = int2str(framecounter);
    imagename = strcat('S3N1S1_T_PRE_20140710144418
(',strframecounter,').bmp');
    rawImage = imread(imagename);
    size_raw_img = size(rawImage);
    heightRaw = size_raw_img(1);
    widthRaw = size_raw_img(2);

    %Search for the ROI
    for scanHeight = 1:heightRaw
        for scanWidth = 1:widthRaw
            if (goROI == true && (rawImage(scanHeight,scanWidth,1) == 0 &&
rawImage(scanHeight,scanWidth,2) == 236 && rawImage(scanHeight,scanWidth,3)
== 0))
                goROI = false;
                for scanROI_H = (scanHeight + 1) : (scanHeight +
ROI_height_size)
                    ROI_width = 1;
                    for scanROI_W = (scanWidth + 2) : (scanWidth +
ROI_width_size)
                        imageROI(ROI_height,ROI_width,:) =
rawImage(scanROI_H,scanROI_W,:);
                        ROI_width = ROI_width + 1;
                    end
```

```
                    ROI_height = ROI_height + 1;
                end
            end
        end
    end

    goIndex = true;
    % Calculate the elesticity indexes
    for m = 1:ROI_height_size
        for n = 1:ROI_width_size
            %Find a colour match of the pixel with the scale
            for p = 1:heightscale
                if ((goIndex == true) && (imageROI(m,n,1) ==
imageScale(p,1,1)) && (imageROI(m,n,2) == imageScale(p,1,2)) &&
(imageROI(m,n,3) == imageScale(p,1,3)))
                  goIndex = false;
                  Index_soft(framecounter) = Index_soft(framecounter) +
scoreTable(p,2);
                  Index_intermediate(framecounter) =
Index_intermediate(framecounter) + scoreTable(p,3);
                  Index_hard(framecounter) = Index_hard(framecounter) +
scoreTable(p,1);
                end
            end
            goIndex = true;
        end
    end
end


 figure;plot(Index_intermediate,'DisplayName','Index_intermediate');hold
all;plot(Index_soft,'DisplayName','Index_soft');plot(Index_hard,'DisplayNam
e','Index_hard');hold off;
```

12.8 Appendix 4.5: MATLAB algorithm for colour Doppler image analysis in the clinical study

```
clear;

NbFrame = 37;

counter = zeros(1,NbFrame,'uint32');
colourIndex = zeros(1,NbFrame,'uint32');

% ROI
x_origin = 255;
y_origin = 125;
ROI_width = 441;
ROI_height = 461;

im = zeros(ROI_height,ROI_width,3,'uint8');

for framecounter = 1:NbFrame

    strframecounter = int2str(framecounter);
    imagename = strcat('P3N48_INITIAL_POST_20160729140439_CD
(',strframecounter,').bmp');

    rawImage = imread(imagename);
    size_raw_img = size(rawImage);
    heightRaw = size_raw_img(1);
    widthRaw = size_raw_img(2);

    coordinate_x = 1;
    coordinate_y = 1;


    for scanHeight = y_origin:y_origin + ROI_height
       for scanWidth = x_origin:x_origin + ROI_width
              if (rawImage(scanHeight,scanWidth,1) ==
rawImage(scanHeight,scanWidth,2)) && (rawImage(scanHeight,scanWidth,2) ==
rawImage(scanHeight,scanWidth,3))
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,1) = 0;
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,2) = 0;
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,3) = 0;
              else
                  counter(framecounter) = counter(framecounter) + 1;
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,1) =
rawImage(scanHeight,scanWidth ,2);
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,2) =
rawImage(scanHeight,scanWidth ,2);
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,3) =
rawImage(scanHeight,scanWidth ,2);
                  colourIndex(framecounter) = colourIndex(framecounter) +
uint32(rawImage(scanHeight,scanWidth,2));
              end

       end

    end
end
```

12.9 Appendix 4.6: MATLAB algorithm for power Doppler image analysis in the clinical study

```
clear;

NbFrame = 40;

counter = zeros(1,NbFrame,'uint32');
powerIndex = zeros(1,NbFrame,'uint32');

% ROI
x_origin = 255;
y_origin = 125;
ROI_width = 441;
ROI_height = 461;

im = zeros(ROI_height,ROI_width,3,'uint8');

for framecounter = 1:NbFrame

    strframecounter = int2str(framecounter);
    imagename = strcat('P3N48_INITIAL_POST_20160729140439_PD
(',strframecounter,').bmp');

    rawImage = imread(imagename);
    size_raw_img = size(rawImage);
    heightRaw = size_raw_img(1);
    widthRaw = size_raw_img(2);

    coordinate_x = 1;
    coordinate_y = 1;


    for scanHeight = y_origin:y_origin + ROI_height
       for scanWidth = x_origin:x_origin + ROI_width

              if (rawImage(scanHeight,scanWidth,1) ==
rawImage(scanHeight,scanWidth,2)) && (rawImage(scanHeight,scanWidth,2) ==
rawImage(scanHeight,scanWidth,3))
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,1) = 0;
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,2) = 0;
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,3) = 0;
              else
                  counter(framecounter) = counter(framecounter) + 1;
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,1) =
rawImage(scanHeight,scanWidth ,2);
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,2) =
rawImage(scanHeight,scanWidth ,2);
                  im(scanHeight-y_origin+1,scanWidth-x_origin+1,3) =
rawImage(scanHeight,scanWidth ,2);
                  powerIndex(framecounter) = powerIndex(framecounter) +
uint32(rawImage(scanHeight,scanWidth,2));
              end
       end

    end
end
```

12.10 Appendix 4.7: Biopac equipment calibration

BIOPAC Systems, Inc.

HARDWARE GUIDE

info@biopac.com
support@biopac.com
www.biopac.com

CBLCAL/C CABLE CALIBRATORS FOR BIOPOTENTIAL AMPLIFIERS

CBLCALC Calibration Cable for 100C-series Biopotential Amplifiers

CBLCAL Calibration Cable 100-B series Biopotential Amplifiers

Use CBLCAL/C to verify the calibration of the any of the Biopotential amplifiers. The cable (1.8m) connects between the amplifier input and the UIM100C D/A output 0 or 1. To verify the amplifier's frequency response and gain settings, create a stimulus signal using Acq*Knowledge* and monitor the output of the amplifier connected to the Calibration Cable. The Calibration Cable incorporates a precision 1/1000 signal attenuator.

Amplifier specification tests are performed at the factory before shipping, but a Calibration Cable can ensure users peace of mind by permitting precise frequency response and gain calibrations for exact measurements.

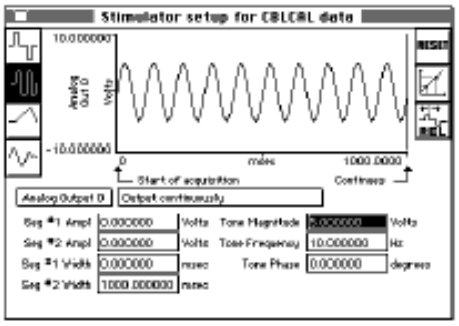
CBLCAL/C CALIBRATION

Hardware Setup

1. Connect the MP150/100, UIM100C and biopotential amplifiers as normal.
2. Connect the CBLCAL/C between the selected amplifier and the UIM100C, inserting the single 3.5mm plug into the Analog Output "0" port on the UIM100C.
3. Connect the end containing several 2mm pins into the corresponding holes on the face of the biopotential amplifier.
4. Select a Gain setting of 1,000 for DA, ECG, EGG, EMG, and EOG, or 5,000 for EEG and ERS.
5. Turn all filters to the desired position.
6. Select an appropriate channel on the top of the amplifier being tested (usually channel one, as this is the default setup in the software).

Software Setup

1. Under **Channel Setup**, insure that the default is set to analog channel one (A1).
2. Under **Acquisition Setup**
   a) Choose a sampling rate of 2000 Hz (or higher).
   b) Choose an acquisition period of at least 5 seconds.
   c) Choose Record Last mode.
3. Under **Stimulator Setup** (see figure below)



a) Select the sine wave for the shape of the output signal.

b) Set the "Seg. #1 Width' to zero. This means that the signal will be transmitted continuously starting at time-point zero.

c) Set "Seg. #2 Width" to 1,000 msec (one second). This is the length of the output signal.

d) Select "Analog Output: 0."

e) Select "Output continuously."

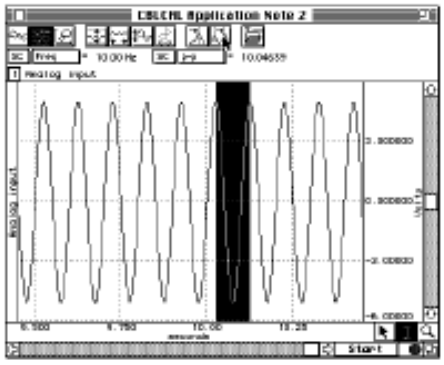
f) The most important settings are the signal magnitude and frequency. Set the magnitude to 5 Volts (i.e., 10 V p-p) if the module gain setting is 1,000. If the lowest module gain setting available is 5,000, choose 1 Volt.

g) Set the frequency to 10 Hz to check the gain calibration (on a sinusoidal signal, this setting is appropriate for all biopotential amplifiers).

CALIBRATION PROCEDURE

Acq*Knowledge* is now set-up to check for the proper calibration of biopotential amplifiers.

1. Start the acquisition. Theoretically, since **record last** mode is enabled signal output is continuous, Acq*Knowledge* could acquire data forever.
2. Stop the acquisition when the waveform has stabilized.
3. Use the "I-beam" cursor to select the latter part of the record.
4. Perform all the calibration measurements on the latter part of the collected record.
   a) Scale the waveform into some semblance of the one in the following figure.



   b) Select the Pk-Pk (peak to peak) measurement to determine amplitude. The measured voltage depends on the voltage input and the gain setting on the amplifier. Use the following formula to determine this number.

Measured Voltage =
(Stimulator Input Voltage) * (1/1,000) * (Biopotential Amplifier Gain Setting)

If the amplifier gain setting is 1,000, it will cancel the CBLCAL/C attenuation (1/1,000). Therefore, the measured voltage will equal the stimulator input voltage. In this example, assuming a gain setting of 1,000 and a stimulator input of 10 V (pk-pk), the expected signal will be very close to 10 V (p-p).

c) It is important to measure the amplitude of the acquired waveform correctly. Highlight several peaks with the "I-beam" cursor.

d) Click the "peak detection" icon at the top of the graph window twice. This will precisely highlight one of the many peak-to-peak amplitudes.

e) Open one of the pop-up measurement, windows and select "p-p" to measure the amplitude of the waveform. This result indicates the vertical distance of the waveform between the two selected peaks (see figure above).

f) To verify the consistency of the difference in peak-to peak values, click the "peak detection" icon again. This will move the cursor to the next available peak below.

g) Repeat this several times to verify the subsequent peak heights. If the measured peak-to-peak height is 10.04 Volts, the acquired signal can be ascertained as ±5.02 Volts. If the stimulator outputs a 5 Volt magnitude signal, then measuring 5.02 Volts (0-pk) is considered accurate for any biopotential amplifier (the analog output stimulator is accurate to within ± .5%). To best determine the accuracy of the amplifier, consider an average of measurements.

12.11 Appendix 4.8: Ethics approval memo (Protocol number: HSK/PG/UH/00015)

UNIVERSITY OF HERTFORDSHIRE
HEALTH AND HUMAN SCIENCES

M E M O R A N D U M

TO **Binoy Kumaran**

CC **Professor Tim Watson**

FROM Dr Richard Southern, Health and Human Sciences ECDA Chairman

DATE **26/04/13**

Protocol number: HSK/PG/UH/00015

Title of study: The physiological effects of Radiofrequency (RF)-based therapy

Your application for ethical approval has been accepted and approved by the ECDA for your school.

This approval is valid:

From: 26/04/13

To: 25/07/13

Please note:

Approval applies specifically to the research study/methodology and timings as detailed in your Form EC1. Should you amend any aspect of your research, or wish to apply for an extension to your study, you will need your supervisor's approval and must complete and submit form EC2. In cases where the amendments to the original study are deemed to be substantial, a new Form EC1 may need to be completed prior to the study being undertaken.

12.12 Appendix 4.9: Raw data from the thermometer validation study

Thermode	Thermofocus	Biopac	Thermode	Thermofocus	Biopac	Thermode	Thermofocus	Biopac	Thermode	Thermofocus	Biopac	Thermode	Thermofocus	Biopac
26	26.1	26.2	29	28.9	29	32	31.5	31.6	35	34.2	34.1	38	36.8	36.7
26	26.1	26.2	29	28.8	29	32	31.4	31.6	35	34	34.1	38	36.8	36.7
26	26.3	26.2	29	28.9	29	32	31.5	31.6	35	34.1	34.1	38	37	36.7
26	26.2	26.2	29	28.9	29	32	31.4	31.6	35	34.1	34.1	38	36.8	36.8
26	26.2	26.2	29	28.8	29	32	31.3	31.6	35	34.1	34.1	38	36.9	36.8
26	26.2	26.2	29	28.9	29	32	31.6	31.5	35	34.1	34.1	38	36.9	36.8
26	26.3	26.2	29	28.8	29	32	31.6	31.5	35	34	34.1	38	37.2	36.7
26	26.3	26.2	29	28.9	29	32	31.5	31.5	35	34	34.1	38	37.1	36.8
26	26.3	26.2	29	28.9	29	32	31.5	31.5	35	34.2	34.1	38	37	36.7
26	26.3	26.2	29	28.9	29	32	31.6	31.5	35	33.9	34.1	38	36.9	36.8
Mean	**26.23**	**26.2**		**28.87**	**29**		**31.49**	**31.55**		**34.07**	**34.1**		**36.94**	**36.75**
SD	**0.08**	**0.00**		**0.05**	**0.00**		**0.10**	**0.05**		**0.09**	**0.00**		**0.13**	**0.05**

12.13 Appendix 4.10: Informed consent for the intrarater reliability study for the ultrasound measurements

HHSECDA Protocol Number: cHSK/PG/UH/00143

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC3

CONSENT FORM FOR STUDIES INVOLVING HUMAN PARTICIPANTS

The material contained in this form may be adapted for use in an alternative consent form, provided the principles of what is contained in the form are retained

I, the undersigned *[please give your name here*, *in BLOCK CAPITALS]*

……

of *[please give contact details here, sufficient to enable the investigator to get in touch with you, such as a postal or email address]*

…..……

hereby freely agree to take part in the study entitled *[insert name of stu*dy *here]*

"Physiological effects of radiofrequency (RF)-based therapy – Stage 2"

1 I confirm that I have been given a Participant Information Sheet (a copy of which is attached to this form) giving particulars of the study, including its aim(s), methods and design, the names and contact details of key people and, as appropriate, the risks and potential benefits, and any plans for follow-up studies that might involve further approaches to participants. I have been given details of my involvement in the study. I have been told that in the event of any significant change to the aim(s) or design of the study I will be informed, and asked to renew my consent to participate in it.

2 I have been assured that I may withdraw from the study at any time without disadvantage or having to give a reason.

3 I have been given information about the risks of my suffering harm or adverse effects. I have been told about the aftercare and support that will be offered to me in the event of this happening, and I have been assured that all such aftercare or support would be provided at no cost to me.

4 I have been told how information relating to me (data obtained in the course of the study, and data provided by me about myself) will be handled: how it will be kept secure, who will have access to it, and how it will or may be used.

5 I have been told what will be done if the study reveals that I have a medical condition which may have existed prior to the study, which I may or may not have been aware of, and which could affect the present or future health of myself or others. If this happens, I will be told about the condition in an appropriate manner and advised on follow-up action I should take. Information about the condition will be passed to my GP, and I may no longer be allowed to take part in the study.

6 I have been told that I may at some time in the future be contacted again in connection with this or another study.

Signature of participant……Date……..

Signature of (principal) investigator……..Date……

Name of (principal) investigator *[in BLOCK CAPITALS please]*

……

12.14 Appendix 4.11: Ethics approval for the intrarater reliability study for the ultrasound measurements (Protocol number: cHSK/PG/UH/00143)

UNIVERSITY OF HERTFORDSHIRE
Health and Human Sciences

M E M O R A N D U M

TO **Binoy Kumaran**

CC **Prof Tim Watson**

FROM Dr Richard Southern,Health and Human Sciences ECDA Chairman

DATE **3rd December 2013**

Protocol number: cHSK/PG/UH/00143

Title of study: Physiological effects of radiofrequency (RF)-based therapy-Stage 2

Your application for ethical approval has been accepted and approved with the following conditions by the ECDA for your school.

Approval Conditions:

- **Permissions will be granted and received prior to recruitment taking place.**
- **HHSECDA protocol number added to PIS and consent form**
- **Remove 'and given a favourable opinion' from the *Who has reviewed this study?* Section of PIS**
- **The PIS must be made more "user friendly"so that participants signing up to the study are fully informed.**

This approval is valid:

From: 3rd December 2013

To: 30th June 2014

Please note:

Your application has been conditionally approved. You must ensure that you comply with the conditions noted above as you undertake your research. Failure to comply with the conditions will be considered a breach of protocol and may result in disciplinary action which could include academic penalties. Additional documentation requested as a condition of this approval protocol may be submitted via your supervisor to the Ethics Clerks as it becomes available. All documentation relating to this study, including the information/documents noted in the conditions above, must

12.15 Appendix 4.12: Raw data from the intrarater reliability study for the ultrasound measurements

Study Number	Baseline CD Velocity	Post CD Velocity	Baseline PD Volume	Post PD Volume	Baseline PD Intensity	Post PD Intensity	Baseline Hardness	Post Hardness	Baseline Hardness Index
USG1	24.69	23.55	1.25	1.16	58.33	51.42	8.95	8.35	11.50
USG2	20.08	21.92	1.33	1.47	42.44	47.16	2.94	2.89	2.97
USG3	28.44	26.55	1.47	1.44	68.75	58.06	10.90	11.15	11.88
USG4	26.48	27.23	2.77	2.66	62.16	61.31	1.21	1.40	1.53
USG5	34.25	33.49	3.02	3.24	67.60	60.77	9.53	9.30	11.04
USG6	19.72	19.77	1.34	1.39	45.53	47.07	5.25	4.70	5.53
USG7	33.50	33.22	2.40	2.29	70.84	67.84	5.48	5.78	6.82
USG8	30.27	27.49	1.42	1.48	42.35	47.00	15.01	14.69	21.28
USG9	30.34	31.34	2.16	2.15	61.53	63.87	6.86	7.24	7.82
USG10	30.90	30.54	1.69	1.71	54.78	62.10	12.58	11.33	15.56
USG11	30.62	29.55	1.85	1.77	47.62	49.54	11.09	12.66	13.14
USG12	21.20	22.24	1.12	1.05	51.92	49.74	7.95	7.85	10.14
Mean	**27.54**	**27.24**	**1.82**	**1.82**	**56.16**	**55.49**	**8.15**	**8.11**	**9.93**
SD	**5.08**	**4.58**	**0.63**	**0.65**	**10.27**	**7.58**	**4.02**	**3.99**	**5.48**

Post Hardness Index	Baseline Intermed.	Post Intermed.	Baseline Intermed. Index	Post Intermed. Index	Baseline Softness	Post Softness	Baseline Softness Index	Post Softness Index
8.66	11.50	12.05	13.80	14.67	5.45	5.50	8.04	7.43
2.96	17.89	17.89	22.84	23.01	5.07	5.11	6.94	7.12
12.24	13.63	13.37	17.38	17.05	1.37	1.38	1.87	1.96
1.51	14.56	14.06	18.09	17.31	10.14	10.44	14.66	14.79
10.73	11.78	12.06	14.27	14.69	4.59	4.54	6.73	6.60
4.86	15.45	16.57	18.94	19.81	5.20	4.63	7.20	6.18
7.06	16.51	16.16	20.05	19.77	3.91	3.96	5.07	5.22
19.47	10.62	10.93	12.81	13.62	0.27	0.28	0.35	0.37
8.48	13.77	13.40	16.94	16.35	5.27	5.27	7.36	7.90
13.12	11.51	12.81	14.11	15.77	1.81	1.76	2.48	2.39
13.82	14.29	12.71	17.55	15.62	0.52	0.53	0.65	0.65
10.01	8.50	8.51	10.61	10.56	9.45	9.54	14.38	14.53
9.41	**13.33**	**13.38**	**16.45**	**16.52**	**4.42**	**4.41**	**6.31**	**6.26**
5.01	**2.66**	**2.57**	**3.43**	**3.25**	**3.16**	**3.21**	**4.71**	**4.74**

12.16 Appendix 5.1: Participant information sheet for the laboratory-based study

Protocol Number: HSK/PG/UH/00015

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET

Title of Research

"The physiological effects of Radiofrequency (RF)-based therapy"

Introduction

You are being invited to take part in a research study. Before you decide whether to do so, it is important that you understand the research that is being done and what your involvement will include. Please take time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?

The proposed is the first of a series of (up to three) laboratory-based studies planned as part of a much wider PhD project, which aims to investigate the physiological response of healthy human adults to regional (local body area) application of Radiofrequency Electromagnetic Field (RF EMF) energy at a frequency of 448 kHz (448,000 Hertz). The purpose of the proposed study (Stage 1) is to investigate the skin thermal responses (how skin surface temperature changes over time) to this energy application. The main aims are:

1. To identify the onset of heating, the point of moderate yet comfortable heating and the point of onset of heat discomfort (decided entirely by you, not the researcher) with the application of above mentioned RF energy.

2. To periodically record the baseline (normal) and peak (after treatment) skin temperature and map out the skin temperature decline over time (thermal decay process) after application of this RF energy.

Do I have to take part?

It is completely up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw if you change your mind at any stage without giving a reason. A decision to withdraw at any time, or a decision not to take part at all, will not disadvantage you in any way.

What will happen to me if I take part?

If you decide to take part in this study, you will be asked to attend the physiotherapy research lab in the Wright Building, College Lane Campus of the University of Hertfordshire for two occasions to receive RF-based treatment to your knee joint area and allow a series of skin temperature measurements to be taken from the treated area. Each session will last about 90 minutes, which includes screening, treatment, and assessments. Kindly note, all these procedures are completely non-invasive.

On arrival to the laboratory the researcher will receive you and an informed consent will be signed by both parties. You will then be changing to appropriate clothing and will sit / lie

down comfortably on a treatment couch with knees extended and resting on a pillow. As a screening process, prior to RF administration your skin over the treatment area will be tested using warm (not warm enough to cause any injury!) and cold water filled test tubes to make sure that you (skin of the area treated) can adequately distinguish between warmth and cold (skin thermal sensitivity). This screening will eliminate any risk of inadvertent injuries due to lack of skin thermal sensation. Hence, if you cannot distinguish between warmth and cold you will not be enrolled into the study. After screening and enrolment, yet before starting the treatment you will go through an acclimatization period. During this period, the researcher will record your 'baseline' (normal) skin temperature of the treatment area using a hand-held skin thermometer and will work you through the experimental procedures and give you written instructions on 'what to do' during the experiment.

The RF energy will be delivered using 'HCR 902 Indiba activ Prorecovery' device manufactured by Indiba S. A., Barcelona, Spain. The device is proven safe for human use (CE marked) and is in use around the world in clinical practice. Round metallic electrodes (active electrode) smeared with a special conducting cream will deliver the energy to the front of your thigh just above the knee joint. An 'inactive' metal plate electrode will be placed under your calf muscles of the same leg to complete the circuit. The intensity of RF energy delivered to your knee will be increased incrementally every 30 seconds starting from the minimum output level. Throughout, you will be asked to report to the investigator, firstly the moment(s) when you begin to feel heat sensation, secondly when the heat builds up moderately (good yet comfortable heating), and finally the moment when you may begin to feel uncomfortable. The treatment will end at this point. There will be clear and simple written instructions on the 'what to do' sheet helping you identify these stages and inform the researcher accordingly. Please note, for the final stage the purpose is not to identify the limit of your heat tolerance, but the starting point where the heat may begin to make you uncomfortable. This point is entirely decided by you and the RF application will be terminated outright when you call out 'STOP'. The researcher will not make any attempt to prolong the RF application beyond this point. Since the treatment will stop at once this point is reached, there should be no risk of any heat injury. The machine itself will only cause a gradual build-up of heat commensurate with the intensity of energy delivered. In addition, it may be noted that similar patient-led scenarios (intensity of treatment adjusted according to patient feedback) already exist and are used safely in clinical practice. Regional (localized) application of RF energy (to your knee joint in this case) is not known to cause any effect elsewhere in the body.

The temperature measurements will be repeated immediately after the treatment is stopped to record the 'peak' skin temperature reached by RF application and subsequently every 30 seconds in order to map the process of skin temperature returning to baseline (thermal decay process). Thus, these post-treatment measurements will continue till the skin temperature returns to the baseline (normal) level.

What are the possible disadvantages, risks or side effects of taking part?

There should be no harmful effects or disadvantages caused by participation in this study. The researcher will be in close proximity for the duration of the treatment and tests to assist if necessary. You can always, at any moment, withdraw from the study. All the assessments we carry out are safe and have been used extensively in other research.

What are the possible benefits of taking part?

We cannot promise the study will help you, but the information we gather from this study will help improve the knowledge base by providing a better understanding of the physiological mechanisms underpinning the mode of action of low frequency RF energy and this particular treatment modality. The information we get from this study will also help us to plan the methodology of the later stages of the research project.

How will my taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence. If you join the study, some parts of your personal details and the data collected

for the study may be looked at by authorized person(s) from the University of Hertfordshire (project supervisory team) to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty. All data and information gathered during the project will be entirely confidential, and nothing that might identify you will be made public. Any information about you that leaves the university will have your personal identification removed so that you cannot be recognized from it. We ask your permission to keep your name, address and phone number at the University of Hertfordshire so that we can contact you to make or change appointments should this be necessary. This information will only be available to the principal researcher involved in the study and will be kept in a locked filing cabinet and/or a password protected university computer. If in the future we decide to use your contact details for another study assessing yet another aspect of your physiological response to this RF therapy, we will have to apply for separate approval from the University of Hertfordshire Research Ethics Committee.

What will happen to the results of the research study?

The results of the study will form part of the final thesis submitted towards the degree of Doctor of Philosophy of the principal investigator. As already mentioned, the methodology of the later stages of this project will depend largely on the results from this study. We also intend to publish the results of this study as well as future studies of this project in a series of relevant international medical conferences and journal publications. However, it can often take up to two years after completion of a study for the results to be published. Hence, the data will need to be stored securely for a period of five years, before it is destroyed. You will not be identified in any report or publication. If you would like a copy of the published results you can contact us.

Who has reviewed this study?

All research that take place in the University of Hertfordshire is looked at by an independent group of people called the Research Ethics Committee (Ethics Committee with Delegated Authority, ECDA), to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the Health and Human Sciences ECDA.

Who can I contact if I have any questions?

If you would like further information or would like to discuss any details personally, please get in touch with myself (Binoy Kumaran) the principal investigator of this project or Prof. Tim Watson, the principal supervisor of this project, either in writing, by phone, or by email.

Name: Binoy Kumaran (Principal investigator)

Phone: 0751 743 0077

Email: b.r.kumaran@herts.ac.uk

Address: Binoy Kumaran, PhD Researcher, Department of Allied Health Professions and Midwifery, School of Health and Social Work, Room 1H159 Yorkon Building, College Lane Campus, University of Hertfordshire.

Name: Prof. Tim Watson (Director of studies)

Phone: 01707 284970

Email: t.watson@herts.ac.uk

Address: Prof. Tim Watson, Department of Allied Health Professions and Midwifery, School of Health and Social Work, College Lane Campus, University of Hertfordshire.

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University Secretary and Registrar.

Thank you very much for reading this information and giving consideration to taking part in this study.

12.17 Appendix 5.2: Informed consent for the laboratory-based study

Protocol Number: HSK/PG/UH/00015

FORM EC3

(Rev. June 11)

University of Hertfordshire

CONSENT FORM FOR STUDIES INVOLVING HUMAN PARTICIPANTS

I, the undersigned *[please give your name here*, *in BLOCK CAPITALS]*

……

of *[please give contact details here, sufficient to enable the investigator to get in touch with you, such as a postal or email address]*

…..……

hereby freely agree to take part in the study entitled:

"The physiological effects of Radiofrequency (RF)-based therapy"

1 I confirm that I have been given a Participant Information Sheet (a copy of which is attached to this form) giving particulars of the study, including its aim(s), methods and design, the names and contact details of key people and, as appropriate, the risks and potential benefits, and any plans for follow-up studies that might involve further approaches to participants. I have been given details of my involvement in the study. I have been told that in the event of any significant change to the aim(s) or design of the study I will be informed and asked to renew my consent to participate in it.

2 I have been assured that I may withdraw from the study at any time without disadvantage or having to give a reason.

3 I have been given information about the risks of my suffering harm or adverse effects. I have been told about the aftercare and support that will be offered to me in the event of this happening, and I have been assured that all such aftercare or support would be provided at no cost to me.

4 I have been told how information relating to me (data obtained in the course of the study, and data provided by me about myself) will be handled: how it will be kept secure, who will have access to it, and how it will or may be used.

5 I have been told what will be done if the study reveals that I have a medical condition which may have existed prior to the study, which I may or may not have been aware of, and which could affect the present or future health of myself or others. If this happens, I will be told about the condition in an appropriate manner and advised on follow-up action I should take. Information about the condition will be passed to my GP, and I may no longer be allowed to take part in the study.

6 I have been told that I may at some time in the future be contacted again in connection with this or another study.

Signature of
participant……Date……..

Signature of (principal)
investigator……...Date……

Name of (principal) investigator *[in BLOCK CAPITALS please]*

……

12.18 Appendix 5.3: Ethics approval for the laboratory-based study (Protocol number: HSK/PG/UH/00015)

UNIVERSITY OF HERTFORDSHIRE
HEALTH AND HUMAN SCIENCES

M E M O R A N D U M

TO **Binoy Kumaran**

CC **Professor Tim Watson**

FROM Dr Richard Southern, Health and Human Sciences ECDA Chairman

DATE **26/04/13**

Protocol number: HSK/PG/UH/00015

Title of study: The physiological effects of Radiofrequency (RF)-based therapy

Your application for ethical approval has been accepted and approved by the ECDA for your school.

This approval is valid:

From: 26/04/13

To: 25/07/13

Please note:

Approval applies specifically to the research study/methodology and timings as detailed in your Form EC1. Should you amend any aspect of your research, or wish to apply for an extension to your study, you will need your supervisor's approval and must complete and submit form EC2. In cases where the amendments to the original study are deemed to be substantial, a new Form EC1 may need to be completed prior to the study being undertaken.

12.19 Appendix 5.4: Randomisation chart for the order of attendance to the laboratory sessions

Study number	Randomisation order		Session 1	Session 2
S1N1	0	1	CAP	RES
S1N2	1	0	RES	CAP
S1N3	0	1	CAP	RES
S1N4	1	0	RES	CAP
S1N5	1	0	RES	CAP
S1N6	0	1	CAP	RES
S1N7	0	1	CAP	RES
S1N8	1	0	RES	CAP
S1N9	0	1	CAP	RES
S1N10	0	1	CAP	RES
S1N11	1	0	RES	CAP
S1N12	1	0	RES	CAP
S1N13	1	0	RES	CAP
S1N14	1	0	RES	CAP
S1N15	0	1	CAP	RES

0 = CAP
1 = RES

12.20 Appendix 5.5: Eligibility questionnaire and subjective information form for the participants

PARTICIPANT SUBJECTIVE INFORMATION FORM

Study number:

Name:

Date of birth: Height (m):

Gender: Weight (kg):

Occupation: Body fat (%):

Contact details: Visceral fat:

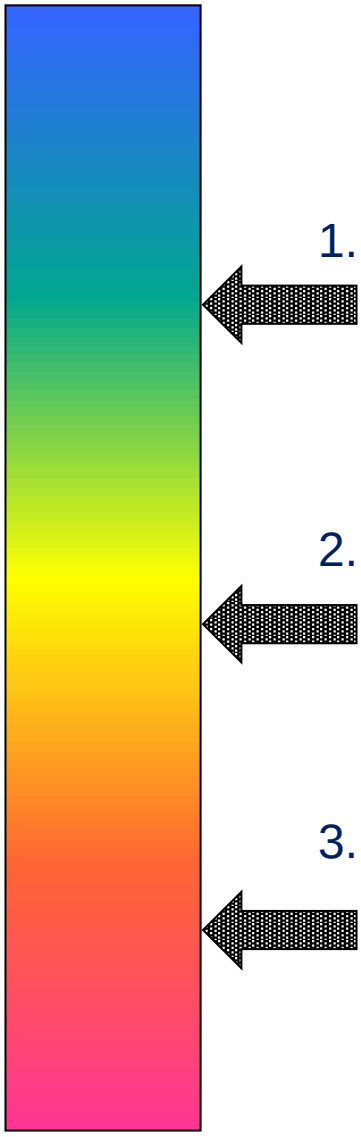
Date and time of assessment: Body Mass Index:

MEDICAL QUESTIONNAIRE: PLEASE TICK THE APPROPRIATE BOXES BELOW

	Yes	No
Did you eat in the last one hour?		
Did you drink coffee or alcoholic beverages in the last one hour?		
Did you do any strenuous exercise in the last one hour?		
Do you smoke?		
Are you pregnant?		
Have you suffered from any infections or high fever in the last week?		
Do you use a hearing aid?		
Do you suffer from hypersensitivity to heat?		
Do you suffer from any skin conditions around your right knee joint?		
Do you suffer from any cardiac or blood pressure related disorders?		
Do you suffer from Diabetes?		
Do you wear a cardiac pacemaker or any other electronic implants?		
Do you have a metal implant in your right lower limb?		
Have you sustained any injury to your right knee joint in the last three months?		
Have you ever suffered from arterial or venous diseases in your legs?		
Have you ever suffered from Tuberculosis?		
Have you ever suffered from Cancer or malignancy?		
Are you allergic to Micropore tape?		

12.21 Appendix 5.6: Image representative of the three heating points to be reported by the participants

THREE TIME POINTS



1. Say **"HEATING"** when you begin to feel any warmth over the treatment area.

2. Say **"DEFINITE HEATING"** when you feel moderate yet comfortable warmth in the treatment area.

3. Say **"STOP"** straight away when the heating starts to become uncomfortable.

12.22 Appendix 5.7: Participant data collection form

Study number:

EXPERIMENTAL DATA COLLECTION FORM

Treatment mode one: CAP / RES

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Side treated: **Right / Left**

Treatment sequence:

Device start time: **30 minutes**

Pre-treatment measurements	Treated side (°C)	Control (°C)
Baseline skin temperature		
Baseline core temperature		

	Time (M: S), Intensity	Mean power (W)
Thermal onset		
Definite thermal		
Thermal discomfort		

Post-treatment measurements	Treated side (°C)	Control (°C)
Peak skin temperature		
Peak core temperature		

Thermal decay process to baseline (°C) every 30 seconds

Follow-up measurements Treated side (°C) Control (°C)

Final skin temperature		
Final core temperature		

Ending room temperature (°C):

Ending room humidity (%):

Treatment mode two: CAP / RES

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Side treated: **Right / Left**

Treatment sequence:

Device start time: **30 minutes**

Pre-treatment measurements Treated side (°C) Control (°C)

Baseline skin temperature		
Baseline core temperature		

	Time (M: S), Intensity	Mean power (W)
Thermal onset		
Definite thermal		
Thermal discomfort		

Post-treatment measurements	Treated side (°C)	Control (°C)
Peak skin temperature		
Peak core temperature		

Thermal decay process to baseline (°C) every 30 seconds

Follow-up measurements	Treated side (°C)	Control (°C)
Final skin temperature		
Final core temperature		

Ending room temperature (°C):

Ending room humidity (%):

12.23 Appendix 6.1: Participant information sheet for the laboratory-based study

HHSECDA Protocol Number: cHSK/PG/UH/00143

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET

Title of Research

"The physiological effects of radiofrequency (RF)-based therapy – Stage 2"

("Stage 2" is a logical progression of the "Stage 1" we have completed recently. In Stage 1 study we investigated some of the more basic aspects of RF-based therapy, the findings of which have informed the design of Stage 2 study)

Introduction

You are being invited to take part in a research study. Before you decide whether to do so, it is important that you understand the research that is being done and what your involvement will include. Please take the time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?

The proposed is the second of a series of laboratory-based studies planned as part of the PhD project, which aims to investigate the physiological responses of healthy human adults to regional (local body area) application of Radiofrequency Electromagnetic Field (RF EMF) energy at a frequency of 448 kHz (Kilo Hertz). The aims of the proposed study (Stage 2) are – firstly, investigate the following physiological responses to the 448 kHz RF energy application, secondly, compare those physiological effects to the effects generated by the application of Pulsed Shortwave Therapy (PSWT, operates at a base RF of 27.12 MHz), and thirdly to investigate whether the addition of manual therapy (massage) to the RF treatment regime changes the physiological responses.

1. Local skin temperature
2. Local skin blood flow
3. Local deep blood flow
4. Local nerve conduction velocity
5. Local pressure pain threshold
6. Core temperature (tympanic)
7. Pulse rate

Do I have to take part?

It is completely up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw at any stage without giving a reason. A decision to withdraw at any time, or a decision not to take part at all, will not affect your education or your relationship with the university (should this be relevant).

How long will my part in the study take?

If you decide to take part in this study, you will be involved in it for the next few weeks attending a minimum of three sessions (or more if you agree), each lasting for about 75 - 90 minutes.

What will happen to me if I take part?

If you decide to take part in this study, you will be asked to attend the physiotherapy research laboratory (LF311) in the Wright Building, College Lane Campus of the University of Hertfordshire to receive RF-based treatment to your knee joint area and allow a series of physiological measurements to be taken from the treated area before and after treatment. Each session will last about 75 - 90 minutes, which includes some paperwork, screening, treatment, and assessments. Kindly note, all these procedures are harmless and completely non-invasive, and in line with procedures routinely employed in current clinical practice.

On arrival to the laboratory the principal investigator will receive you and the first thing to happen is to sign an informed consent by both parties. Some paperwork will follow, where you will be asked screening questions such as “Have you eaten in the last one hour?” or “Did you injure your knee recently?” You will then change to appropriate clothing (shorts) and undergo height, weight and body composition (body mass index, body fat percentage) measurements. Subsequently you will lie down comfortably on a treatment couch with knees extended and resting on a pillow. As a second screening prior to RF administration, your skin over the treatment area will be tested using warm (not warm enough to cause any injury!) and cold water filled test tubes to make sure that you (skin on the area treated) can distinguish adequately between warmth and cold (called ‘skin thermal sensitivity’). This screening will eliminate any risk of inadvertent injuries due to lack of skin thermal sensation. If you cannot distinguish between warmth and cold you will not be enrolled into the study. After screening and enrolment, you will undergo ‘pre-treatment measurements where the researcher will record your 'baseline' (normal) physiological measures (listed in the above section) from the treatment area using a series of non-invasive measurement systems and then talk you through the experimental procedures, what to expect during treatment and what to do if you have a problem. The physiological measurements will be repeated and recorded immediately after the treatment to compare between pre and post treatment values.

The RF energy will be delivered for 15 minutes at a set dosage using either 'HCR 902 Indiba activ Prorecovery' device, or one of the PSWT devices currently used in the Department of Allied Health Professions and Midwifery. Both devices are proven safe for human use (CE marked) and are in use around the world in clinical practice. For the Indiba device round metallic electrodes (active electrode) smeared with a special conducting cream will deliver the energy to the front of your thigh just above the knee joint. An 'inactive' metal plate electrode will be placed under your calf muscles of the same leg to complete the machine circuit. For the PSWT device shortwave energy will be delivered using a large monode drum electrode positioned in air about one centimeter vertically above the treated area (will not touch the skin). The intensity of RF energy delivered to your knee will remain constant for the duration of the treatment in both cases. You may receive either a low intensity (little or no warmth felt) or a moderate intensity (appreciable warmth felt) treatment depending on the number of sessions you choose to attend and the experimental groups you represent. Regional (localized) application of RF energy (around your knee joint in this case) is not known to cause any effect elsewhere in the body. In addition to the RF, you may also receive manual therapy (massage) to the local area performed at the same time. If you feel any discomfort any time during the session, you may ask the investigator to ‘STOP’ the procedures.

What are the possible disadvantages, risks or side effects of taking part?

There should be no harmful effects or disadvantages caused by participation in this study. The researcher will be in close proximity for the duration of the treatment and the tests to

assist if necessary. You can always, at any moment, withdraw from the study. All the assessments we carry out are safe and have been used extensively in other research.

What are the possible benefits of taking part?

We cannot promise the study will help you, but the information we gather from this study will help improve the knowledge base by providing a better understanding of the physiological mechanisms underpinning the mode of action of low frequency RF energy and this particular treatment modality. The information we get from this study will also help us to plan the methodology of the later stages of the research project.

How will my taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence. If you join the study, some parts of your personal details and the data collected for the study may be looked at by authorized person(s) from the University of Hertfordshire (project supervisory team) to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty. All data and information gathered during the project will be entirely confidential, and nothing that might identify you will be made public. Any information about you that leaves the university will have your personal identification removed so that you cannot be recognized from it. We ask your permission to keep your name, address and phone number at the University of Hertfordshire so that we can contact you to make or change appointments should this be necessary. This information will only be available to the principal researcher involved in the study and will be kept in a locked filing cabinet and/or a password protected university computer. If in the future we decide to use your contact details for another study assessing yet another aspect of your physiological response to this RF therapy, we will have to apply for separate approval from the University of Hertfordshire Research Ethics Committee.

What will happen to the results of the research study?

The results of the study will form part of the final thesis submitted towards the degree of Doctor of Philosophy of the principal investigator. As already mentioned, the methodology of the later stages of this project will depend largely on the results from this study. We also intend to publish the results of this study as well as future studies of this project in a series of relevant international medical conferences and journal publications. However, it can often take up to two years after completion of a study for the results to be published. Hence, the data will need to be stored securely for a period of five years, before it is destroyed. You will not be identified in any report or publication. If you would like a copy of the published results you can contact us.

Who has reviewed this study?

All research that take place in the University of Hertfordshire is looked at by an independent group of people called the Research Ethics Committee (Ethics Committee with Delegated Authority, ECDA), to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given approval (protocol number given on the first page) by the Health and Human Sciences ECDA.

Who can I contact if I have any questions?

If you would like further information or would like to discuss any details personally, please get in touch with myself (Binoy Kumaran) the principal investigator of this project or Professor Tim Watson, the principal supervisor of this project, either in writing, by phone, or by email.

Name: Binoy Kumaran (Principal investigator)

Phone: 0751 743 0077

Email: b.r.kumaran@herts.ac.uk

Address: Binoy Kumaran, PhD Researcher, Department of Allied Health Professions and Midwifery, School of Health and Social Work, Room 1H159 Yorkon Building, College Lane Campus, University of Hertfordshire.

Name: Professor Tim Watson (Director of studies)

Phone: 01707 284970

Email: t.watson@herts.ac.uk

Address: Prof. Tim Watson, Department of Allied Health Professions and Midwifery, School of Health and Social Work, College Lane Campus, University of Hertfordshire.

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University Secretary and Registrar.

Thank you very much for reading this information and giving consideration to taking part in this study.

12.24 Appendix 6.2: Ethics approval for the laboratory-based study (Protocol number: cHSK/PG/UH/00143)

UNIVERSITY OF HERTFORDSHIRE
Health and Human Sciences

M E M O R A N D U M

TO **Binoy Kumaran**

CC **Prof Tim Watson**

FROM Dr Richard Southern,Health and Human Sciences ECDA Chairman

DATE **3rd December 2013**

Protocol number: cHSK/PG/UH/00143

Title of study: Physiological effects of radiofrequency (RF)-based therapy-Stage 2

Your application for ethical approval has been accepted and approved with the following conditions by the ECDA for your school.

Approval Conditions:

- **Permissions will be granted and received prior to recruitment taking place.**
- **HHSECDA protocol number added to PIS and consent form**
- **Remove 'and given a favourable opinion' from the *Who has reviewed this study?* Section of PIS**
- **The PIS must be made more "user friendly"so that participants signing up to the study are fully informed.**

This approval is valid:

From: 3rd December 2013

To: 30th June 2014

Please note:

Your application has been conditionally approved. You must ensure that you comply with the conditions noted above as you undertake your research. Failure to comply with the conditions will be considered a breach of protocol and may result in disciplinary action which could include academic penalties. Additional documentation requested as a condition of this approval protocol may be submitted via your supervisor to the Ethics Clerks as it becomes available. All documentation relating to this study, including the information/documents noted in the conditions above, must

12.25 Appendix 6.3: Informed consent for the laboratory-based study

HHSECDA Protocol Number: cHSK/PG/UH/00143

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC3

CONSENT FORM FOR STUDIES INVOLVING HUMAN PARTICIPANTS

The material contained in this form may be adapted for use in an alternative consent form, provided the principles of what is contained in the form are retained

I, the undersigned *[please give your name here*, *in BLOCK CAPITALS]*

……

of *[please give contact details here, sufficient to enable the investigator to get in touch with you, such as a postal or email address]*

…..……

hereby freely agree to take part in the study entitled *[insert name of stu*dy *here]*

"Physiological effects of radiofrequency (RF)-based therapy – Stage 2"

1 I confirm that I have been given a Participant Information Sheet (a copy of which is attached to this form) giving particulars of the study, including its aim(s), methods and design, the names and contact details of key people and, as appropriate, the risks and potential benefits, and any plans for follow-up studies that might involve further approaches to participants. I have been given details of my involvement in the study. I have been told that in the event of any significant change to the aim(s) or design of the study I will be informed and asked to renew my consent to participate in it.

2 I have been assured that I may withdraw from the study at any time without disadvantage or having to give a reason.

3 I have been given information about the risks of my suffering harm or adverse effects. I have been told about the aftercare and support that will be offered to me in the event of this happening, and I have been assured that all such aftercare or support would be provided at no cost to me.

4 I have been told how information relating to me (data obtained in the course of the study, and data provided by me about myself) will be handled: how it will be kept secure, who will have access to it, and how it will or may be used.

5 I have been told what will be done if the study reveals that I have a medical condition which may have existed prior to the study, which I may or may not have been aware of, and which could affect the present or future health of myself or others. If this happens, I will be told about the condition in an appropriate manner and advised on follow-up action I should take. Information about the condition will be passed to my GP, and I may no longer be allowed to take part in the study.

6 I have been told that I may at some time in the future be contacted again in connection with this or another study.

Signature of participant……Date……..

Signature of (principal) investigator……..Date……

Name of (principal) investigator *[in BLOCK CAPITALS please]*

……...

12.26 Appendix 6.4: Randomisation chart for the order of attendance to the laboratory study sessions

Groups	Intervention
RFL	RF Low
RFH	RF High
RFP	RF Placebo
CTR	Control

Randomisation schedule for Stage 2 (Block 4)				
Subjects	Sessions			
	Session 1	Session 2	Session 3	Session 4
S3N1	RFP	RFH	RFL	CTR
S3N2	RFL	CTR	RFH	RFP
S3N3	RFH	RFP	CTR	RFL
S3N4	CTR	RFL	RFP	RFH
S3N5	RFP	RFH	RFL	CTR
S3N6	RFL	CTR	RFH	RFP
S3N7	RFH	RFP	CTR	RFL
S3N8	CTR	RFL	RFP	RFH
S3N9	RFP	RFH	RFL	CTR
S3N10	RFL	CTR	RFH	RFP
S3N11	RFH	RFP	CTR	RFL
S3N12	CTR	RFL	RFP	RFH
S3N13	RFP	RFH	RFL	CTR
S3N14	RFL	CTR	RFH	RFP
S3N15	RFH	RFP	CTR	RFL
S3N16	CTR	RFL	RFP	RFH
S3N17	RFP	RFH	RFL	CTR
S3N18	RFL	CTR	RFH	RFP
S3N19	RFH	RFP	CTR	RFL
S3N20	CTR	RFL	RFP	RFH
S3N21	RFP	RFH	RFL	CTR
S3N22	RFL	CTR	RFH	RFP
S3N23	RFH	RFP	CTR	RFL
S3N24	CTR	RFL	RFP	RFH
S3N25	RFP	RFH	RFL	CTR
S3N26	RFL	CTR	RFH	RFP
S3N27	RFH	RFP	CTR	RFL
S3N28	CTR	RFL	RFP	RFH
S3N29	RFP	RFH	RFL	CTR
S3N30	RFL	CTR	RFH	RFP
S3N31	RFH	RFP	CTR	RFL
S3N32	CTR	RFL	RFP	RFH
S3N33	RFP	RFH	RFL	CTR
S3N34	RFL	CTR	RFH	RFP
S3N35	RFH	RFP	CTR	RFL
S3N36	CTR	RFL	RFP	RFH
S3N37	RFP	RFH	RFL	CTR
S3N38	RFL	CTR	RFH	RFP
S3N39	RFH	RFP	CTR	RFL
S3N40	CTR	RFL	RFP	RFH

12.27 Appendix 6.5: Eligibility questionnaire and subjective information form for the participants

PARTICIPANT SUBJECTIVE INFORMATION FORM

Study number:

Name:

Date of birth: Height (m):

Gender: Weight (kg):

Occupation: Body fat (%):

Contact details: Visceral fat:

Date and time of assessment: Body Mass Index:

MEDICAL QUESTIONNAIRE: PLEASE TICK THE APPROPRIATE BOXES BELOW

	Yes	No
Did you eat in the last one hour?		
Did you drink coffee or alcoholic beverages in the last one hour?		
Did you do any strenuous exercise in the last one hour?		
Do you smoke?		
Are you pregnant?		
Have you suffered from any infections or high fever in the last week?		
Do you use a hearing aid?		
Do you suffer from hypersensitivity to heat?		
Do you suffer from any skin conditions around your right knee joint?		
Do you suffer from any cardiac or blood pressure related disorders?		
Do you suffer from Diabetes?		
Do you wear a cardiac pacemaker or any other electronic implants?		
Do you have a metal implant in your right lower limb?		
Have you sustained any injury to your right knee joint in the last three months?		
Have you ever suffered from arterial or venous diseases in your legs?		
Have you ever suffered from Tuberculosis?		
Have you ever suffered from Cancer or malignancy?		
Are you allergic to Micropore tape?		

12.28 Appendix 6.6: Participant data collection form

Study number:

EXPERIMENTAL DATA COLLECTION FORM

Treatment Session 1:

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Side treated: Right / Left

Pre-treatment measurements and Doses

Baseline skin temperature (treated)	
Baseline core temperature	
Thigh length (cm)	
Leg length (cm)	
Baseline blood pressure	
Baseline pulse rate	

Post-treatment measurements

Peak & Follow-up core temperature	
Peak & Follow-up blood pressure	
Peak & Follow-up pulse rate	

Ending room temperature (°C):

Ending room humidity (%):

Treatment Session 2:

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Side treated: Right / Left

Pre-treatment measurements

Baseline core temperature	
Baseline blood pressure	
Baseline pulse rate	

Post-treatment measurements

Peak & Follow-up core temperature	
Peak & Follow-up blood pressure	
Peak & Follow-up pulse rate	

Ending room temperature (°C):

Ending room humidity (%):

Treatment Session 3:

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Side treated: Right / Left

Pre-treatment measurements

Baseline core temperature	
Baseline blood pressure	
Baseline pulse rate	

Post-treatment measurements

Peak & Follow-up core temperature	
Peak & Follow-up blood pressure	
Peak & Follow-up pulse rate	

Ending room temperature (°C):

Ending room humidity (%):

Treatment Session 4:

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Side treated: Right / Left

Pre-treatment measurements

Baseline core temperature	
Baseline blood pressure	
Baseline pulse rate	

Post-treatment measurements

Peak & Follow-up core temperature	

Peak & Follow-up blood pressure	
Peak & Follow-up pulse rate	

Concealment checker

Session 1	Session 2	Session 3	Session 4

Ending room temperature (°C):

Ending room humidity (%):

12.29 Appendix 6.7: Randomisation chart for the order of attendance to the laboratory sessions in the pilot study determining CRMRF intervention

Study number	Randomisation order		Session 1	Session 2	Session 3 (non-random)
S2N1	0	1	RF	RF & MT	MT
S2N2	0	1	RF	RF & MT	MT
S2N3	0	1	RF	RF & MT	MT
S2N4	1	0	RF & MT	RF	
S2N5	1	0	RF & MT	RF	
S2N6	0	1	RF	RF & MT	
S2N7	1	0	RF & MT	RF	MT
S2N8	1	0	RF & MT	RF	MT
S2N9	0	1	RF	RF & MT	
S2N10	1	0	RF & MT	RF	MT
S2N11	1	0	RF & MT	RF	MT
S2N12	0	1	RF	RF & MT	MT
S2N13	0	1	RF	RF & MT	
S2N14	1	0	RF & MT	RF	
S2N15	0	1	RF	RF & MT	MT

0 = RF	RF - Radiofrequency only
1 = RF & MT	RF & MT - Radiofrequency & Manual therapy
	MT - Manual therapy only

12.30 Appendix 8.1: Visual analogue scale (VAS) for self-reported pain

‘VAS’ Pain Intensity Scale

1. Mark the line at the point which best corresponds to the intensity of **pain** you have experienced in the **last 24 hours** caused by the arthritis in your knee joint.

Least possible pain — **Worst** possible pain

2. Mark the line at the point which best corresponds to the intensity of **pain** you are experiencing **now** caused by the arthritis in your knee joint.

Least possible pain — **Worst** possible pain

12.31 Appendix 8.2: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

‘WOMAC’ OSTEOARTHRITIS INDEX

INSTRUCTIONS TO THE PARTICIPANTS

In Sections A, B, and C questions are asked in the following format. Please mark your answers by putting an “X” in one of the boxes.

EXAMPLES:

1. If you put your “X” in the box on the far left as shown below:

None	Mild	Moderate	Severe	Extreme
X	☐	☐	☐	☐

Then you are indicating that you feel **no** pain.

2. If you put your “X” in the box on the far right as shown below,

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	X

Then you are indicating that you feel **extreme** pain.

3. Please note:
   a) The further to the right you place your “X”, the **more** pain you feel.
   b) The further to the left you place your “X”, the **less** pain you feel.
   c) **Please do not** place your “X” **outside any of the boxes**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Think about your affected knee when answering the questions. Indicate the severity of your pain and stiffness, and the difficulty you have in doing daily activities that (you feel) are caused by the arthritis in your knee.

Section A: PAIN

Think about the pain you felt in your knee due to your arthritis during the last 48 hours.

QUESTION: How much pain have you had..

1. Walking on a flat surface?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

2. When going up or down stairs?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

3. At night while in bed? (that is – pain that disturbs your sleep)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

4. While sitting or lying down?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

5. While standing?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Section B: STIFFNESS

Think about the stiffness (not pain) you felt in your knee due to your arthritis during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

6. How **severe** has your stiffness been **after you first woke up** in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day?**

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Section C: DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your knee during the last 48 hours.

By this we mean **your ability to move around and look after yourself**.

QUESTION: **How much difficulty have you had..**

8. When going down the stairs?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

9. When going up the stairs?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

10. When getting up from a sitting position?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

11. While standing?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

12. When bending to the floor?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

13. When walking on a flat surface?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

14. When getting in or out of a car, or getting on or off a bus?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

15. While going shopping?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

16. When putting on your socks or panty hose or stockings?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

17. When getting out of bed?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

18. When taking off your socks or panty hose or stockings?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

19. While lying in bed?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

20. When getting in or out of the bathtub?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

21. While sitting?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

22. When getting on or off the toilet?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

23. While doing heavy household duties?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

24. While doing light household duties?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

12.32 Appendix 8.3: NHS Health Research Authority (HRA) approval letter (REC reference: 15/NW/0529)

NHS
Health Research Authority
Research Ethics Service

NRES Committee North West - Greater Manchester South
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7704

25 June 2015

Professor Tim Watson
Physiotherapy, Department of Allied Health Professions and Midwifery
School of Health and Social Work
University of Hertfordshire College Lane Campus, Hatfield
AL10 9AB

Dear Professor Watson

Study title:	**Clinical effects of 448 kHz Capacitive Resistive Monopolar Radiofrequency (CRMRF) based therapy on patients suffering from chronic osteoarthritis of the knee joint.**
REC reference:	**15/NW/0529**
Protocol number:	**HSK/PG/NHS/00312**
IRAS project ID:	**173691**

Thank you for your letter of 22 June 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Helen Penistone, nrescommittee.northwest-gmsouth@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

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

Conditions of the favourable opinion

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

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

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

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

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

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

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

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

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

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

Ethical review of research sites

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

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Prof Indem TWIMC Letter 2014-15]		30 July 2014
GP/consultant information sheets or letters [Letter to GP]	1	01 February 2015

Instructions for use of medical device [Indiba Activ 902 Instruction Manual]	1	09 June 2015
Letter from sponsor [In principle approval Clinical trial HSK PG NHS 00312 Prof Tim Watson & Binoy Kumaran]	1	05 June 2015
Letters of invitation to participant [Participant Invitation Letter]	1	01 February 2015
Letters of invitation to participant [Participant Form to Return]	1	01 February 2015
Other [Introduction to GCP Certificate of Completion]	1	05 June 2015
Other [Clin Trials Insurance 2014-15]	1	21 July 2014
Other [Response to reviewer comments]	1	22 June 2015
Participant consent form [Consent Form Version 2]	2	21 June 2015
Participant information sheet (PIS) [Participant Information Sheet Version 2]	2	22 June 2015
REC Application Form [REC_Form_08062015]		08 June 2015
Research protocol or project proposal [Study Protocol]	1	01 February 2015
Summary CV for Chief Investigator (CI) [Short CV Tim Watson]	1	08 June 2015
Summary CV for student [Short CV Binoy Kumaran]	1	08 June 2015
Validated questionnaire [WOMAC Osteoarthritis Index]	1	09 June 2015
Validated questionnaire [VAS Pain Intensity Scale]	1	09 June 2015

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

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

15/NW/0529	Please quote this number on all correspondence

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

Yours sincerely

On behalf of
Professor Sobhan Vinjamuri
Chair

Email: nrescommittee.northwest-gmsouth@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Professor John Senior

Miss Sally Anne Doyle-Caddick,
Hertfordshire Community NHS Trust

12.33 Appendix 8.4: Patient invitation letter to the potential participants in the OA knee trial

NHS REC Reference Number: 15/NW/0529

University HHSECDA Protocol Number: HSK/PG/NHS/00312

Binoy Kumaran

PhD Researcher (Physiotherapy)

School of Health and Social Work

University of Hertfordshire

College Lane

Hatfield, Hertfordshire

AL10 9AB

Date:

Dear

We are currently undertaking a research study to investigate the effects of radiofrequency-based physiotherapy treatment on pain and quality of life of patients who are suffering from osteoarthritis in one or both of their knee joints.

We would like to invite you to take part in the study. Before you decide it is important to understand why the research is being done and what it involves. We have tried to explain the study in the information sheet included with this letter. Please take time to read them carefully. If you would like more information about this project, please don't hesitate to contact me using the phone number or address given at the end of the information sheet. You may also discuss the study with your GP if you wish. In addition, if you would prefer to discuss any aspects of this study with a third person who is an independent advisor to the study, …… is willing to answer any questions you might have. He/she can be contacted on …….

Please take time to decide whether or not you wish to take part. If you would like to help us and join the study, please could you complete the form included with this letter and return it to us in the pre-paid envelope provided. We will then contact you shortly to discuss the project with you and to arrange a suitable day and time for you to come to the outpatient physiotherapy wing of the 'Hemel Hempstead General Hospital' for your first appointment.

Thank you

Yours sincerely

Mr Binoy Kumaran (PhD Researcher)

Professor Tim Watson (Principal / Chief Investigator)

12.34 Appendix 8.5: Participant information sheet in the OA knee trial

NHS REC Reference Number: 15/NW/0529
University HHSECDA Protocol Number: HSK/PG/NHS/00312

PARTICIPANT INFORMATION SHEET

You are being invited to take part in a research study. Before you decide whether to do so, it is important that you understand the research that is being done and what your involvement will include. Please take time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Part I tells you the purpose of this study and what will happen to you if you take part. Part II gives you more detailed information about the conduct of the study. Please do take time to decide whether or not you wish to take part. Thank you for reading.

PART I

Title of Research

"Clinical effects of 448 kHz Capacitive Resistive Monopolar Radiofrequency (CRMRF) based therapy on patients suffering from chronic osteoarthritis of the knee joint."

Why am I being invited?

We understand that you have been diagnosed with osteoarthritis (OA) in one or both of your knee joints, and that you have been referred for physiotherapy treatment. We are planning to undertake a research study in order to test the efficacy of a particular type of physiotherapy treatment, in which you might be eligible to take part. The proposed clinical trial aims to investigate the clinical benefits (if any) of Radiofrequency (RF) Electromagnetic Field based treatment on adult patients like you, who are suffering from OA of the knee joint. The specific name of the treatment used in this study is 'Capacitive Resistive Monopolar Radiofrequency (CRMRF)' and will be delivered using the device 'Indiba Activ 902', manufactured by Indiba S. A., Barcelona, Spain.

What is radiofrequency-based therapy?

Radiofrequency is a part of the electromagnetic fields. They have various applications in the field of medicine. Low energy RF (up to 30 MHz (Megahertz) in frequency) is often used in physiotherapy treatments to relieve pain and inflammation through applying heat at various intensities. Most commonly used RF-based therapy in physiotherapy is called 'shortwave therapy', which operates at a wave frequency of 27.12 MHz. However, the CRMRF therapy used in this study operates at 448 kHz (kilohertz). As of now, CRMRF therapy is not commonly used in the UK although it has been available for clinical use since many years.

How will the aim of the study be achieved?

At the moment we don't know whether the symptoms of OA can be improved with this type of treatment. If it can be improved, is the effect any better than a mere 'placebo effect' or is it genuine? Is it better than the current treatments given to patients with OA? Placebo effect is the phenomenon of someone's symptoms improving when they've only been given a dummy

treatment. To find out, we need to compare the treatments in a so-called 'randomised controlled trial' (RCT). This means that we put people randomly into different treatment groups (three in this study) and compare them at the beginning and end of the study using various outcome measurements. Which treatment you will receive is completely decided by chance. Your allocation to any group will be 'blinded' in order to avoid any potential 'participant bias' due to your knowledge of the group you are in. That means we will not be able to tell you the group you are in until the end of the study.

In this study, the three treatment groups are as follows:

Group I – Will receive CRMRF treatment and current standard NHS treatment.

Group II – Will receive placebo CRMRF treatment and current standard NHS treatment.

Group III – Will receive current standard NHS treatment only.

The current standard NHS treatment for OA knee involves a combination of exercises, advice and supportive therapies (such as hot/cold application, manual therapy and electrical stimulation) as deemed appropriate by your clinician. 'Placebo CRMRF' is a dummy treatment delivered using the same active CRMRF device, but with its output turned off, to investigate the presence of a potential 'placebo effect'.

If you decide against taking part, you will automatically receive the current standard treatment (as in Group III) when your turn comes on the waiting list.

What are the measurements that will be taken?

Two types of measurements will be taken – clinical and physiological.

The clinical measurements taken at various stages during the study are as follows:

1. Pain measurement – A self-reported numerical scale, rating the level of your knee pain from 0 – 10 ('0' means no pain and '10' means maximum pain). You will be asked to mark a point on a 10 cm long line to denote your level of pain.
2. WOMAC – A self-reported easy to score 'quality of life' questionnaire based on your knee joint function. WOMAC stands for Western Ontario and McMaster Universities Osteoarthritis Index.
3. Knee Range of Movement – This will be manually tested by the researcher using a device called 'goniometer' or an 'inclinometer'. It measures how far can you bend or straighten your knee joint.
4. Timed up and go (TUG) test – This is a simple functional test where the time taken by you to complete a functional task is measured. The task is to get up from a chair, walk forward six meters, turn around and walk back to sit on the chair. This will be performed at your 'normal' comfortable pace, which means if you are in pain it may take longer for you to complete the task.

The physiological measurements taken at various stages during the study are as follows:

1. Skin temperature – The local skin temperature on your knee joint will be measured using a non-invasive surface temperature measurement device.
2. Skin blood flow – The amount of blood flow on the skin in your knee joint area will be measured using a non-invasive method called 'photoplethysmography', which involves attaching a small device to your skin surface for the duration of the test.
3. Deep blood flow – Blood flow to the deeper tissues such as the muscles will be measured using Doppler Ultrasound.

Do I have to take part?

It is completely up to you whether or not you take part in this study. If you do decide to take part, you will be asked to sign a consent form. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw at any stage without giving a reason. A decision to withdraw at any time, or a decision not to take part at all, will not affect your care in any way.

How long will I need to be involved?

If you decide to take part in this study, you will be involved in it for the next four months, attending eight treatment sessions during the first four weeks and two follow-up sessions (for measurements only) one month and three months after the treatment is finished. In total you will need to attend 10 sessions in four months.

What will I have to do now?

After reading this document if you consider taking part in this research, please fill in the attached return form and send it to the researcher in the pre-paid envelope. We will contact you to explain any more questions you may have about the study and arrange suitable times for you to come to the outpatient physiotherapy wing of the 'Hemel Hempstead General Hospital' and take part in the study.

What will happen to me if I take part?

If you decide to take part in this study, you will be asked to attend the above stated location to receive CRMRF treatment to your affected knee joint and allow the measurements (as discussed) to be taken. The duration of the sessions you attend will vary. The first and the eighth sessions will be the longest, lasting just over 90 minutes each, which includes some paperwork, screening, treatment, and assessments. Sessions 2–7 and the last two sessions will be substantially shorter. Kindly note that all procedures involved are harmless, completely non-invasive and in line with procedures routinely employed in clinical practice.

On arrival to the clinic the investigator will receive you and will explain the study. You will then be asked to sign a consent form. Subsequently you will be asked to change to appropriate clothing (shorts) to lie down comfortably on a treatment couch with knees extended and resting on a pillow. As a primary screening, your skin over the treatment area will be tested using warm (not warm enough to cause any injury!) and cold water filled test tubes to make sure that you can adequately distinguish between warmth and cold (called 'skin thermal sensitivity'). This screening will eliminate any risk of inadvertent injuries due to lack of skin thermal sensation. **If you cannot distinguish between warmth and cold you will not be enrolled into the study**. After this you will be asked some questions such as "Have you eaten in the last one hour?" or "Did you injure your knee recently?" Your height, weight and body fat levels will also be recorded.

After screening and enrolment, you will undergo the clinical and physiological measurements listed previously. You will then be talked through the experimental procedures, what to expect during the treatment and what to do if you have a problem. The CRMRF energy will be delivered for 15 minutes using the 'Indiba Activ 902' device, which is proven safe for human use (CE marked) and is in use around the world in clinical practice. The schemes of treatment and assessments that will take place at each visit are listed in the section below.

What will happen during the sessions?

Following is what will be done from sessions 1 – 10.

Session 1: Physiological measurements, clinical measurements, CRMRF treatment.

Sessions 2–7: CRMRF treatment, clinical measurements (pain only).

Session 8: Physiological measurements, clinical measurements, CRMRF treatment.

Session 9: First follow-up clinical measurements.

Session 10: Second follow-up clinical measurements.

What are the possible disadvantages, risks or side effects of taking part?

There should be no harmful effects caused by your participation, additional to physically participating in the study and any disadvantages associated with OA itself that may be already explained to you by your consultant/GP. During the assessments you will be asked to perform normal activities of daily life such as walking and bending the knee joint, which may cause some knee discomfort. However, you will be asked to perform those activities in

the same way as you would normally do, minimizing the pain as much as possible. The researcher will also be in close proximity for the duration of the tests to assist if necessary. All the assessments we carry out are safe and have been used extensively in other research.

What if something goes wrong?

Any potential complaint about the way you have been dealt with during the study or any potential harm you might suffer will be addressed. The detailed information on this is given in 'Part II' of this document.

Will my taking part be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part II.

This completes Part I. If the information in Part I has interested you and you are considering participation, please now read the additional information in Part II.

PART II

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the condition. If this happens, we will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, nothing will change in your normal care. Also, on receiving new information we might consider it to be in your best interest to withdraw you from the study. We will explain the reasons for this.

What will happen if I don't want to carry on with the study?

You will be able to withdraw from the study at any time and without having to give a reason. This will not affect your normal care in any way. If you withdraw we will not use the data collected up to your withdrawal.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to make a formal complaint, you can do so through the NHS Complaints Procedure. Details can be obtained from the hospital.

If you are harmed due to someone's negligence, then compensation may be provided. If you are harmed by taking part in this research project by an unforeseen accident (non-negligent harm), then there are no special compensation arrangements in place. However, this is thought to be highly unlikely. Regardless, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

How will my taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence. If you join the study, parts of the data collected from you (except personal data) may be looked at by authorized person(s) from the University of Hertfordshire (sponsors of this study) to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty. All data and information gathered during the project will be entirely confidential, and nothing that might identify you will be made public. Any information about you that leaves the university will have your personal identification removed so that you cannot be recognized from it. We ask your permission to keep your name, address and phone number at the University of Hertfordshire for the duration of your involvement in the study so that we can contact you to

make or change appointments should this be necessary. This information will only be available to the two researchers (named below) involved in the study and will be kept in a locked filing cabinet and/or a password protected university computer.

Will my GP be informed of my involvement in the study?

Your GP will be informed in writing that you are participating in this study, but only if you consent to us to do so.

What will happen to the results of the research study?

The results of the study will form part of the final thesis submitted towards the degree of Doctor of Philosophy of Binoy Kumaran (PhD Researcher). We also intend to disseminate the results of this study in relevant international conferences and journal publications. However, it can often take up to a year or more after the completion of a study for the results to be published. Hence, the data will need to be stored securely for a period of at least one year, before it is destroyed. You will not be identified in any report or publication. You will be given a copy of the final results, but if you would like a copy of the published articles as well, you can contact us.

Who is organising and funding the research?

This research study is organized by the 'University of Hertfordshire' (the sponsor) in collaboration with the 'Hertfordshire Community NHS Trust'. It is funded by the device manufacturer Indiba, S. A., Barcelona, Spain.

Who has reviewed this study?

All research in the NHS is reviewed by an independent group of people called Research Ethics Committee (REC) to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by the NRES Committee Northwest - GM South. In addition, all research that take place in the University of Hertfordshire is reviewed by an independent group of people called the Ethics Committee with Delegated Authority (ECDA) to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given approval by the Health and Human Sciences ECDA (HHSECDA) of the University of Hertfordshire. Both protocol numbers are given on top of the first page.

Who can I contact if I have any questions?

If you would like further information or would like to discuss any details personally, please get in touch with myself (Binoy Kumaran, PhD Researcher) or Professor Tim Watson, the Chief / Principal Investigator of this project, either in writing, by phone, or by email.

Name: Binoy Kumaran (PhD Researcher)

Phone: (44) (0) 751 743 0077

Email: b.r.kumaran@herts.ac.uk

Address: Binoy Kumaran, PhD Researcher, Physiotherapy, Department of Allied Health Professions and Midwifery, School of Health and Social Work, 1H159 Yorkon Building, University of Hertfordshire, College Lane, Hatfield, Hertfordshire, AL10 9AB.

Name: Professor Tim Watson (Chief / Principal Investigator)

Phone: (44) (0) 1707 284970

Email: t.watson@herts.ac.uk

Address: Professor Tim Watson, Physiotherapy, Department of Allied Health Professions and Midwifery, School of Health and Social Work, University of Hertfordshire, College Lane, Hatfield, Hertfordshire, AL10 9AB.

Thank you.

12.35 Appendix 8.6: Participant ‘form to return’ in the OA knee trial

NHS REC Reference Number: 15/NW/0529
University HHSECDA Protocol Number: HSK/PG/NHS/00312

Please fill in the form and return to:

Binoy Kumaran
PhD Researcher (Physiotherapy)
School of Health and Social Work
University of Hertfordshire
College Lane
Hatfield, Hertfordshire
AL10 9AB

From

Your ‘title’ and ‘full name’:
Gender:
Date of Birth:
Contact phone number(s):
Your ‘home’ and ‘email’ (if available) addresses:

Please tick appropriately:

I would like to take part in the study titled **“Clinical effects of 448 kHz Capacitive Resistive Monopolar Radiofrequency (CRMRF) based therapy on patients suffering from chronic osteoarthritis of the knee joint.”**	**Yes**	☐
	No	☐

12.36 Appendix 8.7: Patient randomisation chart for the OA knee clinical trial

Group I	RFH
Group II	RFP
Group III	CTR

1	RFH	10	RFP	19	RFH	28	RFH	37	CTR
2	RFH	11	RFH	20	RFP	29	CTR	38	RFH
3	CTR	12	CTR	21	CTR	30	CTR	39	CTR
4	CTR	13	CTR	22	RFH	31	RFH	40	RFP
5	RFP	14	RFH	23	CTR	32	RFP	41	RFH
6	RFH	15	CTR	24	RFH	33	CTR	42	RFP
7	CTR	16	RFP	25	RFP	34	RFH	43	RFH
8	RFP	17	RFH	26	CTR	35	RFP	44	CTR
9	RFP	18	RFP	27	RFP	36	RFP	45	RFP

46	RFH	55	CTR	64	RFP	73	RFH	82	CTR
47	RFH	56	RFH	65	RFH	74	RFP	83	RFH
48	RFP	57	CTR	66	RFH	75	CTR	84	RFP
49	RFP	58	RFP	67	RFP	76	RFH	85	CTR
50	CTR	59	RFP	68	CTR	77	RFP	86	RFH
51	CTR	60	RFH	69	CTR	78	CTR	87	RFP
52	CTR	61	RFH	70	CTR	79	RFH	88	CTR
53	RFP	62	RFP	71	RFH	80	RFP	89	RFH
54	RFH	63	CTR	72	RFP	81	CTR	90	RFP

12.37 Appendix 8.8: Informed consent for the participants in the OA knee trial

NHS REC Reference Number: 15/NW/0529

University HHSECDA Protocol Number: HSK/PG/NHS/00312

CONSENT FORM

Study ID: …… Site: ……..

Participant ID: …… Initials: …….. DOB: ……

Principal Investigator: Professor Tim Watson PhD Researcher: Mr Binoy Kumaran

Study Title: Clinical effects of 448 kHz Capacitive Resistive Monopolar Radiofrequency (CRMRF) based therapy on patients suffering from chronic osteoarthritis of the knee joint.

Participant to Initial each box

1. I confirm that I have read and understand the Participant Information Sheet, Dated ……. Version …… giving particulars of the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary, and that I can withdraw from the study at any time without having to give a reason, and without my medical care or legal rights being affected. ☐
3. I understand that my medical records may be looked at by responsible members of the research team. I have been assured that strict confidentiality will be maintained. I give permission to these individuals to access my medical records. ☐
4. I agree to my GP being informed on my participation in the study. ☐
5. I agree to take to take part in the above study. ☐

Name of participant	Date	Signature
Name of person taking consent	Date	Signature

Professor Tim Watson

Binoy Kumaran

School of Health and Social Work

University of Hertfordshire

Phone (Binoy Kumaran): (44) (0) 751 743 0077

Email: b.r.kumaran@herts.ac.uk

12.38 Appendix 9.1: Participant data collection form in the OA knee trial

Study number:	NHS REC Reference Number: 15/NW/0529 University HHSECDA Protocol Number: HSK/PG/NHS/00312

EXPERIMENTAL DATA COLLECTION FORM

<u>Pre-intervention Assessment</u> (Session 1)

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Side treated: Right / Left

Pre-treatment measurements and Doses

Baseline skin temperature (treated)	
Baseline core temperature	
Thigh length (cm)	
Leg length (cm)	
Baseline blood pressure	
Baseline pulse rate	
Baseline knee flexion ROM	
Baseline knee extension ROM	
Baseline ‘Timed up and go’ test	

Post-treatment measurements

Peak & Follow-up core temperature	
Peak & Follow-up blood pressure	
Peak & Follow-up pulse rate	

Ending room temperature (°C):

Ending room humidity (%):

Post Intervention Assessment (Session 8)

Date and time of assessment:

Starting room temperature (°C):

Starting room humidity (%):

Pre-treatment measurements

Baseline core temperature	
Baseline blood pressure	
Baseline pulse rate	
Post knee flexion ROM	
Post knee extension ROM	
Post 'Timed up and go' test	

Post-treatment measurements

Peak & Follow-up core temperature	
Peak & Follow-up blood pressure	
Peak & Follow-up pulse rate	

Ending room temperature (°C):

Ending room humidity (%):

Follow-up Assessment One (Session 9)

Date and time of assessment:

First follow-up knee flexion ROM	
First follow-up knee extension ROM	
First follow-up ‘Timed up and go’ test	

Follow-up Assessment Two (Session 10)

Date and time of assessment:

Second follow-up knee flexion ROM	
Second follow-up knee extension ROM	
Second follow-up ‘Timed up and go’ test	

Concealment checker

RF group	**RFP group**	**Control group**