Queen Margaret University

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Manipulation of the foot in the treatment of patients with Morton's neuroma

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Abstract

Introduction
Manipulative therapy's rationale is pragmatically appealing as a non-invasive treatment for Morton's neuroma (MN), involving targeted manipulations of relevant joints. Nevertheless, manipulation's efficacy has received limited scrutiny. This thesis comprised four data-driven chapters offering novel investigations associated with manipulation as a treatment for MN. The latter included a critical appraisal of the clinimetric utility of pressure testing for discomfort thresholds (PTT) as a novel outcome in this context (n = 26; Chapter 5), an exploratory pragmatic controlled trial investigating Manipulation versus Steroid Injection in the treatment of patients with Morton's neuroma focusing on self-reported pain levels (VAS) and PTT (n = 61; Chapter 6) and other PROMs reflecting functionality and health (Chapter 7). A final data chapter (Chapter 8) contributed secondary analyses of data in Chapters 6 and 7 exploring novel factors in enhanced clinical outcomes of non-surgical treatment of Morton's neuroma using descriptive multivariate modelling and discriminant analysis.

Method
The thesis's primary study (Chapters 6 and 7) featured an exploratory, pragmatic randomised controlled trial was designed to investigate the efficacy of an acute, short dosage (6, weekly episodes) of physiologically-principled manipulations, featuring discrete, high-velocity thrusting manoeuvres for treating Morton's Neuroma. Adults electing treatment for Morton's neuroma were randomly allocated to manipulative therapy (n = 29) or corticosteroid injection (n = 32). Baseline and follow-up (at 1·5, 3, 6, 9 and 12 months following treatment cessation) outcome measures of self-reported pain levels (VAS), pressure testing for discomfort thresholds (PTT) and functionality (walking and standing [MOxFQws], pain [MOxFQp)] and social interaction [MOxFQsi]; activities of daily living [FAAMdl], sports participation [FAAMspt] and general health [SF-36 PCS & MCS]) were measured ipsilaterally and by inventory.

Results
Chapters 6 and 7 showed that manipulation elicited substantive gains immediately after intervention (VAS [Cohen's *d*, 3·3; 84·4%]; PTT [*d*, 2·3; 147·0%]; MOxFQws [*d*, 1·4; 52·8%]; MOxFQp [*d*, 1·3; 45·5%]; MOxFQsi [*d*, 0·9; 39·2%]) or accumulated during follow-up (FAAMdl [*d*, 2·2; 40·8%]; FAAMspt [*d*, 1·5; 66·1%]). Concomitant gains interactively for control participants were modest (*d*, 0·4 to 1·0; 16·6% to 45·9%) ($p < 0·05$ to $p < 0·0005$). Retention of improvements following manipulation cessation was substantial for all metrics, significantly better than baseline scores (VAS, PTT, MOxFQws, MOxFQp, MOxFQsi, FAAMdl, FAAMspt, SF-36 PCS and SF-36 MCS [*d*, 1·1 to 3·4; 40·8% to 152·3%]) and consistently exceeded that for corticosteroid injection ($p < 0·01$ to $p < 0·001$). Group mean intra-session and inter-day variability (V%) of PTT (Chapter 5) ranged between 6.8% and 13.6% for experienced and inexperienced test administrators, respectively, and suggested compromised precision amongst serial measurements of PTT over extended periods of time. Within Chapter 8, predictive multivariate modelling showed that in internal classification analyses, 88.9% of patients could be assigned correctly to high- and low-responders to treatment.

Conclusion
(i) Manipulation elicited significant and clinically relevant improvements and retention in self-reported levels of pain, discomfort and functionality for patients electing treatment for Morton's neuroma; (ii) Exploratory multivariate modelling provided a significant prediction model for successful non-surgical treatment outcomes; (iii) Single measurements showed compromised precision amongst serial assessments of PTT.

Keywords
Plantar digital neuralgia; Morton's neuroma; foot manipulation; corticosteroid injection; pain; activity of daily living

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Dedication

This thesis is dedicated to all of my nieces and nephews because I know I am your favourite uncle, even although it's a low bar.

Also, to my children Lisa, Daniel and Adam who have endured/enjoyed my absence since I embarked on this journey of madness. My only wish for you is, above all, that you be happy. To my grandchildren Hollie, Kai and Jack and the others who may or may not choose to put in a late appearance. Since grandads are supposed to offer sagely advice, I offer you mine - never do a PhD. If like most people, you ignore my advice, then I hope you find it as challenging, fruitful, intimidating and as rewarding as I did. I hope it makes you grow as it did me and I hope you get your life back at the end of it. To my children and grandchildren, please remember that wherever life takes you, riches are only to be found in the smiles you make on other people's faces. I love you immeasurably.

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ABBREVIATIONS

ADL - Activities of Daily Living

AMN - Alpha motor neurons

ANOVA - analysis of variance

AOFAS - The American Orthopedic Foot and Ankle Society

ATP - Adenosine Triphosphate

CGR - corticosteroid-glucocorticoid receptor

CNS - central nervous system

CSI - corticosteroid injection

DTML - deep transverse metatarsal ligament

FAAM - Foot and ankle ability measure

FAAMdl - Foot and ankle ability measure daily living subscale

FAAMspt - Foot and ankle ability measure sport subscale

FADI - the foot and ankle disability index

FFI - foot function index

FRS - faces rating scale

GMN - Gamma motor neurons

High-R - high response

HVLAT - high velocity low amplitude thrust manipulation

IMB - intermetatarsal bursa

IRAS - Integrated Research Application System

Low-R - low response

MAN - manipulation

MANOVA - multivariate analysis of variance

MIC - minimally important change

MCID - minimal clinically important difference

MFPDS - Manchester Foot Pain and Disability Schedule

MN - Morton's neuroma

MOxFQ - Manchester-Oxford foot questionnaire

MOxFQsw - Manchester-Oxford foot questionnaire standing/walking subscale

MOxFQp - Manchester-Oxford foot questionnaire pain subscale

MOxFQsi - Manchester-Oxford foot questionnaire social interaction subscale

MRI - magnetic resonance imaging

MSK - musculoskeletal

MTP - metatarsophalangeal joint

NHS - National Health Service

NRS - numerical rating scale

PA - pressure algometry

PASS - patient acceptable symptom state

PDNS - plantar digital nerve stretch test

PIN - participant identification number

PNS - peripheral nervous system

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROMs - patient reported outcome measures

PTM - pressure threshold meter

PTT - pressure threshold testing

QMU - Queen Margaret University

RCT - randomised controlled trial

SEM - standard error of measurement

SF-36 - Short form 36 health survey

SF-36 MCS - Short form 36 health survey mental component

SF-36 PCS - Short form 36 health survey physical component

SQU - squeeze test

USS - ultrasound scan

VAS - Visual analogue scale for pain

VRS - verbal rating scale

WST - webspace tenderness test

CHAPTER ONE

Introduction

1.1. **Introduction**

Morton's neuroma (MN) is a common affliction of the human forefoot which can eventually lead to constant, unrelenting foot pain. The evidence for effective conservative care is scant and ultimately the solution is often a surgical one (Thomson et al 2004). Unfortunately, salvage surgeries are not an uncommon occurrence (Amis et at 1992). Such is the frequency of the condition within health care clinics that any endeavour to establish a more satisfactory conservative intervention than currently exists would be widely welcomed.

Classically, MN presents as a sharp, lancing, burning pain which is difficult to localise precisely but resides in the area of the third inter-digital cleft of the foot (Read, Noakes et al. 1999). There are reports of cases in the second inter-digital cleft but rarely in the first and fourth clefts. Initially intermittent, with time the pain often becomes unrelenting. Pain is usually worse when weight-bearing and with the foot shod (Thomson et al. 2004). It is not uncommon for the patient to report the need to remove shoe gear and massage the area when a painful bout erupts. Despite the often intense nature of the painful episodes, there are rarely any visual clues relating to the pathology. In the most severe cases, a slight dorsal forefoot swelling may be evident, but the foot usually presents as entirely normal to the naked eye.

All sources agree that the condition is more prevalent in females but the ratio varies greatly from paper to paper, with estimates ranging from 3:1 up to 10:1 being reported in the literature (Thomson et al. 2013). There are no reports to the contrary. The prevalence and incidence of MN is currently unknown (Thomson et al. 2004), meaning that the risk and burden of this condition on the wider community is also currently unknown. One historic estimate by Latinovic et al suggests that MN is the most common compressive neuropathy after carpal tunnel syndrome, affecting 87 in every 100,000 females and 50 in every 100,000 males in the UK (Latinovic et al. 2006). Legacy qualms about the limited evidential basis for treatment efficacy prevail (Thomson et al. 2004). Simple case series and few controlled trials demonstrate value in surgical intervention (Ciapryna et al. 2012; Åkermark et al. 2013) whilst emergent literature explores injection therapy (Thomson et al. 2020). However, an evidential void remains regarding non-invasive, conservative care, with only shockwave therapy realising controlled trials (Seok et al. 2016).

1.2. **Treatment strategies for MN**

Optimum treatment strategies for MN continue to command debate. The literature proposes many varied conservative treatment options for MN, including massage (Pérez-Domínguez and Casaña-Granell 2020), orthotics and footwear modification (De Oliveira et al. 2019), exercises (Pérez-Domínguez and Casaña-Granell 2020), corticosteroid injections (CSI) (Santiago et al. 2019) and manipulation (MAN) (Cashley and Cochrane 2015). The latter two options offer the greatest meta-analytical evidence for efficacy, with CSI having the largest body of evidence but inferior clinical benefits (Matthews et al. 2019). Indeed, an exploration of the available literature demonstrates that these are the only two conservative interventions to gain any traction. According to a robustly designed study, CSI efficacy endures for several months but with diminishing benefit month on month (Thomson et al. 2013). The limitations of CSI are emphasised by reports that up to 47% of CSI-treated patients subsequently require surgery (Rasmussen et al. 1996; Markovic et al. 2008; Thomson et al. 2013; Rao et al. 2014). Despite this, CSI remains widely employed in clinical settings (Thomson et al. 2020). This may be due to the relative safety, rapid relief, and potential repeatability of the intervention but this explanation remains untested. Additionally, despite the aforementioned limitations of CSI, it does appear to offer benefits beyond the current alternative conservative therapies. That being the case, it remains a logical choice for those clinicians intervening prior to surgery or in cases where surgery is not an option. What is currently lacking is a protocol or hierarchy of interventions that suggests in what order, or to which individuals, specific conservative interventions could be gainfully employed.

Steroid injection has become a popular line of treatment but the evidence for it is conflicting and limited. Many papers suggest good short-term results but very few studies have reported a long-term follow-up. Of those that have, long-term prognosis for cortisone injection therapy is unsatisfactory. Given the acknowledged limitations of CSI to elicit prolonged mitigation of pain and impaired functionality in MN (Thomson et al. 2013; Choi et al. 2021; Hau et al. 2021), treatment involving targeted MAN may prove crucial to promoting enhanced functional mobility and tissue compliance, leading to more enduring treatment benefits (Cashley and Cochrane 2015). This is based on the evidence that MAN improves motor function (Holt et al. 2021) and joint mobility (Shin et al. 2020). That being the case, mechanical entrapments as described in the aetiology theories are likely to respond well to

MAN, which produces improved mechanical function. It was the initial premise of the author that if MAN is an effective intervention in numerous other entrapment pathologies such as carpal tunnel syndrome (Du et al 2022), radicular low back pain (Trager et al 2023), posterior interosseous nerve syndrome (Saratsiotis & Myriokefalitakis 2010), then it is worthy of exploration in entrapments of the foot and ankle. A literature review produced little of note and therefore the need for this thesis was identified. The decision to focus specifically on MN was borne from personal frustrations at the poor outcomes of current modalities as well as an anecdotal sharing of information amongst colleagues which seemed to indicate that many clinicians were experiencing the same poor outcomes in response to their conservative efforts. Added to this was the realisation that colleagues from other professions – notably chiropractic and physiotherapy – were enjoying greater successes for MN patients than were those employing the more traditional orthoses and steroid injection approach. A desire to enhance the patient experience and improve outcomes in my own clinical setting began the journey toward the creation of this thesis. A more detailed review of the treatments of both CSI and MAN shall be explored further in Chapter three, sections 3.2 and 3.3.

At the current juncture, whilst the evidence base for pharmacological interventions continues to grow, there is no clear evidence or guidelines to assist the clinician in determining which non-pharmacological conservative interventions, if any, should be employed and any form of gold standard conservative care would appear to still be someway distant. It is hoped that this thesis will progress the journey toward understanding optimum treatment interventions and regimes for MN by furthering the current knowledge relating to the effectiveness of MAN and CSI interventions.

Four main aetiological theories have been proposed in relation to MN. These theories are explored in greater detail in Chapter two, section two. Briefly, one theory suggests an ischaemic origin, whilst the other three all implicate some form of entrapment and irritation, either from the metatarsal head at the metatarsophalangeal joint (MTPJ), from the deep transverse metatarsal ligament (DTML) or from an enlarged bursa. In all of the theories, a significant degree of biomechanical involvement is implicated in the development of neuromas as the initial insult is thought to be mechanical stress to the neurovascular bundle. As such, the rationale of MAN is both intuitively and pragmatically appealing because targeted enhancements to functional mobility and tissue stiffness should lead to more

physiologically sustained treatment outcomes. MAN has been shown to deliver both functionally enhanced mobility and a nociceptive dampening effect to reduce pain (Griffiths et al. 2019; Shin et al. 2020; Riaz et al. 2022;). Nevertheless, evidence for MAN in the foot is limited to a case study (Cashley 2000), a clinical audit (Cashley and Cochrane 2015), and one controlled trial (Govender et al. 2007).

1.3. **Diagnosis and evaluation of MN**

Optimum strategies for the diagnosis and evaluation of the effects of MN also command clinical and scientific debate (Padua et al. 2020; Post 2020; Galley et al. 2022). The latter's influence might impact on understanding and perceptions of the efficacy and effectiveness of treatments. For example, with regard to clinical indicators, little has been published regarding the effectiveness of the clinical tests routinely employed to aid the diagnosis of MN. Despite this, MN is a condition generally regarded as having a safe clinical diagnostic specificity (Sharp et al. 2003; Cloke and Greiss 2006; Jain and Mannan 2013; Claassen et al. 2014; Rao et al. 2014), with radiological investigation reserved for equivocal cases and those progressing to surgery (Sharp et al. 2003; Pastides et al. 2012).

There are a number of clinical tests that can be readily employed where MN is suspected and research has shown that a combination of clinical tests is an extremely accurate predictor of MN (Sharp et al. 2003; Owens et al. 2011; Pastides et al. 2012). Research investigating the efficacy of treatment for MN would be expected to mimic these recommendations to confirm the diagnosis of MN and include clinical tests such as the plantar digital nerve stretch test, the webspace tenderness test and the lateral squeeze test. The clinimetric characteristics of such diagnostic tests are considered elsewhere within this thesis (please see Chapter 2, section 2.3).

In attempts to strive for even greater understanding of the effects and impact MN has on those diagnosed with the condition, patient-reported outcome measures (PROMs) may offer important insights. For example, while visual analogue scales (VAS) of patient-perceived pain have previously been deployed within research investigating the influence acute and chronic conditions, including MN (Kim et al. 2016; Mahadevan et al. 2016; Choi et al. 2021), the use of pressure threshold testing (PTT) to assess patients' thresholds of discomfort would represent a novel approach for this condition. Nevertheless, the worthiness of using such PROMs and instrumentation would need to exceed necessary

thresholds of psychometric qualities and patient' acceptability. Please see Chapter 2 and Chapter 5 for a critical overview and consideration of psychometric qualities of selected PROMs for assessments in MN, respectively.

1.4. **Aims of the thesis**

Given the challenges to understanding about optimum treatments and assessments associated with MN, this thesis had the following aims:

The primary aim

The primary aim of this thesis was to investigate the efficacy of MAN as a conservative treatment for adults with MN. This was broken down into the following specific sub-aims/objectives:

Chapter 2 - To contextualise the current understanding of the treatment of MN through a narrative review of the literature.

Chapter 3 - To give context and critical evaluation through the literature to the decision for selecting the interventions of MAN and CSI.

Chapter 4 – To critically evaluate candidate approaches and rationalise methods employed in this study

Chapter 6 – To explore the efficacy of MAN versus CSI in the treatment of MN when assessed using VAS and PTT.

Chapter 7 – To explore the efficacy of MAN versus CSI in the treatment of MN when assessed using MOxFQ, FAAM and SF-36 questionnaires.

Secondary aims

Chapter 5 – The assessment of the selected psychometric qualities of PROMs, specifically the reliability and reproducibility of algometry in adults. Achieved by exploring the intra-session and inter-day reproducibility and single measurement reliability of PTT amongst adults with MN.

Chapter 6 – To assess congruence between inter-day PTT and VAS scoring patterns over time

Chapter 8 – The assessment of the relative importance of factors contributing to the successful treatment of MN.

1.5 **Overview of the thesis' organisation**

This thesis comprised four data-driven chapters offering novel investigations associated with manipulation as a treatment for MN. The latter included a critical appraisal of the clinimetric utility of pressure testing for discomfort thresholds (PTT) as a novel outcome in this context (n = 26; Chapter 5), an exploratory pragmatic controlled trial investigating MAN versus CSI in the treatment of patients with Morton's neuroma focusing on self-reported pain levels (VAS) and PTT (n = 61; Chapter 6) and other PROMs reflecting functionality and health (Chapter 7). A final data chapter (Chapter 8) contributed secondary analyses of data in Chapters 6 and 7 exploring novel factors in enhanced clinical outcomes of non-surgical treatment of Morton's neuroma using descriptive multivariate modelling and discriminant analysis. The key themes pertinent to the thesis' ambitions, and which form the conceptual framework for this research project, are outlined in Figure 1.1.

The primary aim

The overarching aim of this thesis (Chapters 6 and 7) was to investigate the efficacy of MAN as a conservative treatment for patients with MN. Within an explorative pragmatic trial, it was hypothesised that an acute, short dosage (6, weekly episodes) of MAN would show efficacy for improving MN, yielding relevant gains in PROMs such as self-reported pain levels of pain, pressure thresholds of discomfort and functionality compared to usual conservative care (CSI). Additionally, the retention of effects was explored at three, six, nine and twelve months following the cessation of MAN and CSI.

Secondary aims

Secondary aims included assessment of the psychometric qualities of selected PROMs (Chapter 5) and assessing the relative importance of factors contributing to the successful treatment of MN (Chapter 8).

In more detail, the thesis' secondary aim within Chapter 5 was to examine the intra-session and inter-day reproducibility and single measurement reliability of PTT amongst ipsilateral and contralateral metatarsophalangeal articulations associated with MN in adults. Adjunct aims included assessing the influence of test administrator' experience on the latter psychometric characteristics and congruence between inter-day PTT and VAS scores. A further aim of the clinimetric assessments within Chapter 5 involved assessing congruence between inter-day PTT and VAS scores (undertaken and reported within Chapter 6).

The thesis' secondary aim within Chapter 8 was an exploration of antecedent clinical metrics, including patients' history, and PROMs (VAS; PTT; MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS) contributing to subsequent optimum non-surgical clinical outcomes in the treatment of MN.

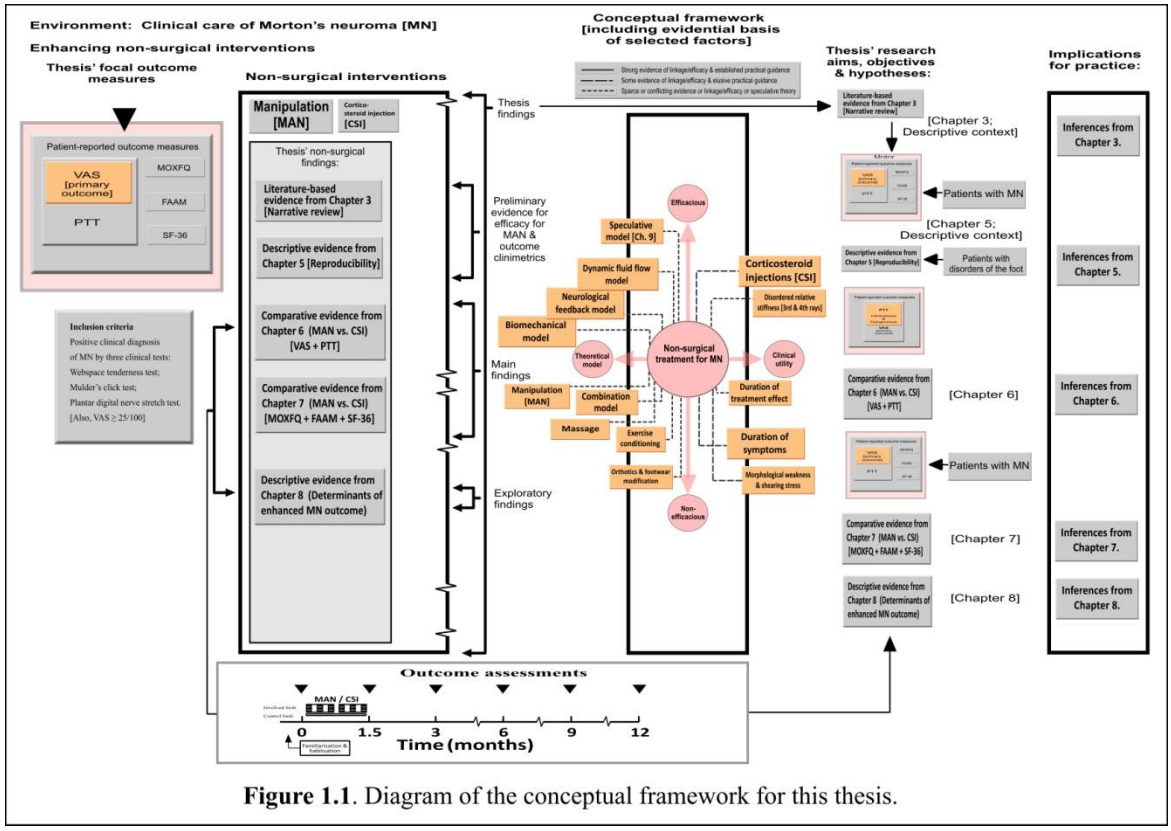

Figure 1.1. Diagram of the conceptual framework for this thesis.

CHAPTER TWO

Narrative review of literature: Morton's neuroma

Aim of chapter – To contextualise the current understanding of the treatment of MN through a narrative review of the literature.

2.1. Introduction and general context

First described by Civinini (Civinini 1835), MN (also known as plantar digital neuritis, Morton's metatarsalgia, Morton's neuritis, Morton's syndrome, inter digital neuroma, forefoot neuroma and inter-metatarsal neuroma) is a common, painful affliction of the forefoot affecting the common plantar digital nerve (Coughlin et al. 2002). In 1876 T. G. Morton, after whom the condition is named, described MN as "a peculiar and painful affection of the 4th metatarsophalangeal articulation" (Morton 1876). Diagnosis in the clinical setting has been shown to be reliable but confirmation is often sought by recourse to ultrasound (USS) or magnetic resonance imaging (MRI) (Chaganti et al. 2012; Sharp et al. 2003; Pastides et al. 2012). For a fuller discussion on these points, the reader is referred to section 2.3. Many authors suggest that conservative interventions should be attempted prior to surgical treatment (Saygi et al. 2005; Valisena et al. 2018; Colo et al. 2020), but this is not a universally held view, with others suggesting that the limitations of conservative care mean that it is more cost and time effective to progress directly to surgery (Gaynor et al. 1989). Some papers have highlighted the short-comings of conservative care (Gaynor et al. 1989; Colo et al. 2020), whilst a number have also shown that surgical correction is not without its failures and complications (Archuleta et al. 2020; Choi et al. 2021; Koti et al. 2022). Furthermore, there is a clear gap in the research literature pertaining to conservative interventions. Padding and strapping and the use of metatarsal domes are commonplace within many podiatric clinics, but the effectiveness of these treatments is entirely untested, and they remain completely absent from the literature. Anecdotally, many practitioners will relate good outcomes using these modalities yet there remains no evidence of their effectiveness. A further complication is encountered when evaluating the prevalence of MN, since there can be no way of determining the number of cases being successfully treated in private practice using conservative interventions and therefore not progressing on to the NHS surgical departments, where they would be added to official statistical records. This means that this condition is, in fact, likely to be significantly more prevalent than is currently estimated.

There is general consensus that MN is a neurological condition with a large element of mechanical involvement. To understand the condition, and grasp the relevant pathological neuroanatomy, the starting point for investigation must be an accurate representation of the normal nervous system of the lower limb. Once this is established, then the pertinent deviations from it, which comprise MN, can be discussed and appreciated.

2.1.1. *Gross neuroanatomy*

The nervous system is the command centre of the body, controlling all functions. It can be broadly sub-divided into two distinct but conjoined systems. These are the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS is formed of the brain and the spinal cord. The CNS is a highly protected structure, with the brain being encased in the cranium whilst the spinal cord is protected by the vertebral column, where it is housed within a large internal tunnel structure, the vertebral foramen. Amongst other roles, the CNS acts as the central processing and response unit for the information that is transmitted to it from the periphery by the PNS. The PNS functions to internalise and transmit information from the external environment and, also, from the internal periphery. Unlike the CNS, the PNS is not afforded the luxury of comprehensive bony protection and is therefore exposed to the dangers of, amongst other threats, mechanical insult. The PNS is comprised of cranial nerves and spinal nerves. They begin life as nerve roots, emerging from the spinal cord. These nerve roots form an interconnecting web with their neighbours to create a mixed nerve formation known as a spinal plexus. The plexus is an amalgam of nerve tissue which merges to become a single nerve as it emigrates from the spinal region. There are thirty-one pairs of spinal nerves which originate at the spinal level as a series of spinal plexuses. They are named according to the vertebral level at which they emerge from the protection of the spine. In the case of the lower limb, the nerve supply originates at the lumbosacral plexus. This plexus can be further subdivided in three: the lumbar plexus, sacral plexus, and the pudendal plexus. The sacral plexus is of particular importance in terms of the neurology of the foot and ankle. It originates in the pelvic region and is a conglomerate of the nerves which arise at the levels of L4, L5, S1, S2, S3, and S4. It provides sensory and motor innervation for the posterior compartment of the upper leg, most of the lower leg and the entire foot. At the level of the pelvis, the sacral plexus gives rise to the sciatic nerve. The sciatic nerve is the thickest and longest nerve in the human body. Following the sciatic nerve distally to the posterior thigh, it bifurcates into the common fibular nerve and the larger tibial nerve. Occasionally, these two nerves can be shown as separate entities as proximal as the plexus itself, but more commonly, they divide in the lower third of the posterior thigh, just superior to the knee. The tibial nerve innervates the triceps surae muscles of the calf and gives off a branch as the sural nerve, which is purely sensory and feeds into the posterior-lateral components of the leg. As it descends, the tibial nerve enters the ankle complex, passing posteriorly, and then inferiorly, to the medial malleolus, where it enters

the tarsal tunnel. At this point, it sits in a relatively superficial position and is at risk of mechanical insult. It is afforded bony protection laterally by the body of the calcaneus and superiorly by the sustentaculum tali, which is an anterio-medial portion of the calcaneus, extending as a shelf to form a roof for the tarsal tunnel. Medially, there is protection only from the flexor retinaculum, which is soft tissue, arising from the medial malleolus and terminating on the medial border of the medial calcaneal tubercle. Once inside the tunnel, the tibial nerve gives off a branch as the medial calcaneal nerve, before bifurcating into the medial and lateral plantar nerves. As they course along the plantar aspect of the foot, these nerves separately create further branches called the common plantar digital nerves (PDN). The PDN lies in the inter-digital cleft, housed in a shallow tunnel with the thicker and more robust flexor digitorum sheaths either side. The floor of the tunnel is a matrix of the globular fat of the plantar fat pad and some distal fibres of the plantar aponeurosis. The tunnel is completed with the deep transverse metatarsal ligament (DTML) making the roof. Each branch of the PDN can be viewed as supplying an inter-digital cleft rather than a digit. This is achieved by means of a further bifurcation within the inter-digital cleft, distal to the DTML. These branches are known as the proper digital nerves. The first proper digital nerve supplies the lateral aspect of the great toe and the medial aspect of the second digit. The second PDN supplies the lateral aspect of the second digit and the medial aspect of the third digit, and so on across all digits. The branches, which arise from the medial plantar nerve, eventually terminate at the apex of the hallux, second and third digits, respectively. The lateral plantar nerve branches terminate at the apex of the fourth and fifth digits. At the third inter-digital cleft, between the third and fourth digits, there is usually found a communicating branch, which joins the medial and lateral branches. This third inter-digital cleft is the most common location in which to find a MN. There has been some discussion around whether the communicating branch and subsequent increased density of neural tissue in this particular cleft, is in some way responsible for the increased incidence of MN at this location, but this is for later discussion. Whilst there is broad agreement that a multitude of variations exist within the neuroanatomy of the human form, the above represents a general schematic of the design, as we currently understand it.

2.1.2. *Intra-neural anatomy of the peripheral nerve*

Intra-neural Anatomy of the peripheral nerve is derived of a number of components. The axon is a single nerve fibre and is the functional component of the nerve. The axon is effectively the body's internal wiring and is used to transmit stimuli by means of electrical

impulses, initiated by chemical triggers known as neurotransmitters. Each axon is wrapped in a layer of connective tissue known as the endoneurium. Axons are bundled together to create a nerve fascicle, which in turn is encased in the perineurium. The perineurium resists tensile loading, offering protection from mechanical stress to the axons. The nerve body consists of a bundle of nerve fascicles bound together under an outer layer of connective tissue known as the epineurium. The epineurium is the outmost layer and is responsible for both protection and the delivery of nutrition to the internal structures (Lee and Wolfe 2000).

2.1.3. *Peripheral neural insult*

Peripheral nerve tissue is amongst the most fragile and easily damaged tissue within the human body. Such neural insult is routinely caused by compression or entrapment, which can in turn, lead to loss of motor function or sensory perception. Injuries to the PNS can be complex and offer up a variety of signs and symptoms in response (Hussain et al. 2020). Disturbances in neural processing are commonplace as the brain is deprived of a communication channel to its target organ. Signal confusion at the site of injury impedes competent communication with the CNS, resulting in paraesthesia, burning, tingling, pain and an array of related symptoms. Because of this, these injuries can have far-reaching effects beyond the locality of insult. They can have an adverse impact on gross mobility and function, as well as perception. On a global level, they can also negatively impact mood, mental health, and behaviour (Hussain et al. 2020).

MN is a particular form of neural insult, but is, in fact, not a neuroma at all. A true neuroma is a result of incomplete regeneration of nervous tissue after insult or injury. When the regenerating tissue from the proximal nerve end is unable to reorganise itself correctly with a distal destination, the stray fibres imbed themselves in the surrounding scar tissue, forming an indiscriminate mass of neural tissue, termed a neuroma (Hetherington 1994; Stokvis et al. 2010). There is no evidence of this process occurring with cases of Morton's neuroma (MN) and therefore, the term Plantar Digital Neuralgia may be more apt. However, despite the absence of a true neuroma, excised nerve tissue has consistently been shown to exhibit signs of degeneration on histological examination (Giannini et al. 2004; Su et al. 2006; Giakoumis et al. 2013). However, Morscher and his research colleagues demonstrated that the same degenerative picture is presented by asymptomatic participants, and they therefore suggest that such findings do not in fact offer a positive indication of pathology (Morscher et al. 2000). In their comparative study, they were able to demonstrate the same degenerative

changes in symptomatic nerve tissue and that of cadaveric nerves with no history of forefoot pathology. They go so far as to suggest that their findings render histology, MRI and USS all redundant for MN, as all rely on identifying nerve changes. Furthermore, although Giakoumis noted a variety of histological changes in all of his neuroma participants, he was unable to identify consistent between-participant histological changes (Giakoumis et al. 2013). These findings confirmed those of an earlier study by Bourke (Bourke et al. 1994). This further throws into question the validity of histological verification of surgically excised tissue for MN and by default, the value of MRI and USS in diagnosis.

Bourke (1994) claimed that the nerves resected during surgery for MN showed no significant characteristics that would differentiate them from the asymptomatic population. He further suggests that the nerve is not the root cause of MN at all. This argument may be supported by the high incidence of recurring symptoms despite surgical intervention. It may be argued that any swelling of the nerve seen on ultrasound or MRI, is secondary to the cause of pain, or potentially even incidental as such changes are commonly seen in the asymptomatic population also. The cause may be mechanical in nature and due purely to dysfunction of the adjacent MTP joint. This argument may be further supported by the research of Zanetti et al., who have demonstrated a high incidence of asymptomatic neuromas on scan (Zanetti et al. 1997). This may also help to explain the patients who have a positive clinical presentation, but a negative radiological one (Di Caprio et al. 2018), as well as the large number of sufferers who continue to have symptoms, from pain to mobility restrictions, after surgical neurectomy (Stamatis and Myerson 2004).

2.2. **Aetiological theories**

Filippo Civinini, an Italian anatomist, was first to describe this pathology, having discovered it in a single cadaver. He reported encountering a peculiar swelling of the plantar digital nerve in the third inter-digital cleft (Civinini 1835; Larson et al. 2005). Some ten years later, the first case in a live patient was reported. Lewis Durlacher, chiropodist to the Royal Household, reported an inter-digital neuralgia, which worsened with lateral compression of the forefoot. The patient in question was King George IV (Durlacher 1845; Larson et al. 2005). This was the first time that lateral compression had been noted as an aggravating, and potentially a causative factor. Subsequently, an orthopaedic surgeon by the name of Thomas Morton, published a case series of surgical correction in 15 cases (Morton 1876). Morton, after whom the condition is now named, also postulated the first

aetiological theory. Despite the passing of over a century, the underlying aetiology of the condition remains contentious (Beech et al. 2000; Giannini et al. 2004; Pace et al. 2010). There is however, general agreement that the condition is a mechanically induced neuropathy, which most commonly occurs in the third inter-digital cleft (Wu 1996; Dockery 1999; Bencardino et al. 2000; Spina et al. 2002; Valente et al. 2008; Lee et al. 2009; Adams 2010). It is thought that this results in degeneration of the local nerve tissue and perineural fibrosis (Chaganti et al. 2012), although the histological evidence for this is, as previously discussed, weak at best. Hassouna and Singh were the first to organise the various papers into a coherent group of theories, which they then named. There has been little change since they did so (Hassouna and Singh 2005).

2.2.1. *Chronic trauma theory*

Morton hypothesised that the plantar digital nerve was undergoing mechanical irritation due to localised trauma arising from dysfunction of the neighbouring metatarsophalangeal joint (MTPJ). The solution he proffered at the time, was to undertake an osteotomy at that joint – a procedure which met with mixed success (Morton 1876). Despite the emergence of a number of newer theories regarding the aetiology of MN, there has to date, been little evidence to challenge or support, Morton's traumatic damage concept. Morton's theory was corroborated by Quinn et al., who found that MN lesions consistently sat at the level of the metatarsal head (Quinn et al. 2000). Quinn et al. were also able to establish that, despite the neurovascular bundle underlying the DTML, the MN lesion never sat plantar to the metatarsal, but in 100% of cases, were dorsal to the plantar border of the neighbouring metatarsal bones. This potentially adds weight to Morton's original postulation regarding entrapment by inadequate movement of the metatarsal head. It is beyond the remit of this thesis to establish which, if any, of the aetiological theories are correct, but the impact of the MAN intervention may be argued to be predominantly upon the MTPJ and therefore, the success of this intervention may add weight to Morton's original traumatic dysfunction theory. Because the goal of the MAN intervention is to increase and normalise the range and quality of motion of the MTPJ, it follows that if Morton was correct in his claim that MTPJ dysfunction was the cause, then corrective MAN would ameliorate the symptoms. It is conceded however, that there currently exists no evidence to support the notion of MTPJ dysfunction in MN. It may be that the PTT data in this thesis can begin the work towards establishing a correlation between the existence of MN and a reduced ability of the MTPJ to withstand loading. That discussion will be explored in Chapter 5.

2.2.2. *Entrapment theory*

Several authors have suggested an entrapment-related aetiology. They theorise that the condition is caused by compression and subsequent irritation of the plantar digital nerve (PDN) as it passes inferiorly to the deep transverse metatarsal ligament (DTML) (Read et al. 1999; Spina et al. 2002; Valente et al. 2008; Lee et al. 2009; Adams 2010). This is thought to be due to increased tension of the DTML or cross-linkages, and adhesions within the soft tissue structure itself. It is postulated that the PDN is either embroiled in the repair of previous ligamentous insult and thereby restricted, or experiences a decrease in available space, as the DTML applies excessive pressure superiorly. When one examines the architecture of the cleft, it is not difficult to perceive a situation whereby the DTML could exert pressure on the dorsal aspect of the neurovascular bundle, whilst ground reaction forces, or shoe gear, exert pressure from the plantar aspect. If these pressures are too great, or too frequent, it is not inconceivable that the traumatised nerve tissue responds with an inflammatory reaction. However, an anatomical dissection and surgical intervention study by Kim et al., disputes this theory (Kim et al. 2016). They used cadavers to establish consistent distances between the bifurcation of the PDN and the DTML. They then used surgical MN cases to establish that the lesion consistently arises at the site of the bifurcation. In their series, as consistent with the literature, all cases of MN arose at the bifurcation. Kim et al. were able to demonstrate that in their cadaveric cases the bifurcation was never closer than 14.6mm distal to the DTML. In their surgical cases they were able to show the mean length of a MN was 7.5 mm, with a range of 6 mm to 11 mm. This would mean that the proximal edge of any MN would tend to be in the region of 7 mm distal to the DTML and even in the case of the largest MN, its proximal border would still be some 3.5 mm beyond the ligament and the centre of the lesion, 9 mm away. This data suggests that the neuroma does not sit at all in the locality of the DTML but more distally. However, the MN consistently sat adjacent to the MTP joint. Given these findings, they argue strongly in favour of Morton's original postulation that the irritation comes from dysfunction at the MTP joint and not an entrapment under the DTML (Kim et al. 2016).

One could imagine that if the DTML was the causative structure, then stretching or elongating it in some fashion, may lead to a reduction in the subsequent force that it applied onto the neurovascular bundle. However, given that the MAN used in this study did not allow for any shearing stress between the neighbouring metatarsals, nor did it directly

impact the DTML itself, it is difficult to conceive how the MAN procedure could produce any meaningful impact on the DTML. Whilst there would have been some momentary, mild dorsiflexion of one metatarsal relative to its neighbour, this would be minimal and no more than if the participant had stepped on a small stone. Since the neighbouring metatarsal was in no way tethered, if the associated soft tissues were in any way tensioned, as described by this theory, then they would more likely have simply pulled the metatarsal to join its neighbour. Much greater velocity and movement was generated around the joint and its capsule and therefore, looking to these locations for the therapeutic effect, is more intuitively satisfying.

2.2.3. *Ischaemic degeneration theory*

A third theory suggests that MN has its origins in ischaemic degeneration of the local vascular bundle. Nissen stated in his discussion that *"...the digital arteries were often so degenerate as to be hardly recognisable. However, serial sections of a number of specimens established the degree, extent, and constancy of the vascular degeneration and suggested strongly- that changes in the nerve were secondary and ischaemic in character."* He found marked degeneration of the arterial wall and thrombosis, both of which preceded any gross thickening of the nerve. In view of this, he claimed that the arterial insufficiency leads to the onset of pain and predates any changes in the neural tissue. He further argued that histological examination of excised nerve tissue showed clear ischaemic damage of the nerve (Nissen 1948). Just two years later, Ringertz and Unander-Scharin argue that these ischaemic changes are in fact, consistent with those found in an asymptomatic population over the age of 40 years. They do concede that it is possible that such vascular changes may lead to subsequent neural fibrosis, but state that such is the frequency of these changes in the general population, that a different aetiology for MN should be explored (Ringertz and Unander-Scharin 1949). Subsequently, the ischaemic theory has enjoyed little exposure in the literature.

A number of papers have demonstrated that MAN is capable of improving local blood flow (Karason and Drysdale 2003; Amatuzzi et al. 2021) and this theory may therefore, explain what is happening at the capillary level. However, such is the weakness in the overall evidence for this theory as it relates to MN, rather than MAN, that it is perhaps the most unlikely candidate of all.

2.2.4. *Bursal complex theory*

A fourth theory postulates a relationship between MN and intermetatarsal bursitis (Bossley and Cairney 1980). Bossley & Cairney noted that in the second and third clefts, the intermetatarsal bursa (IMB) extends beyond the DTML and can come into direct contact with the neurovascular bundle. They also observed that the bursa sits more proximally in the fourth cleft, or can be altogether absent at this location. They argue that this helps to explain the distribution of MN symptoms in the various clefts, especially the almost complete absence of MN in the fourth cleft. In their treatment group, they injected steroid into the IMB, taking care to keep the injection very superficial. The steroid was accompanied by Angiografin (a diagnostic dye agent) in order to facilitate radiographic confirmation of placement. Using this method, they were able to confirm that steroid placement was restricted to the IMB and did not encroach on the neurovascular bundle, which sits significantly inferior to the IMB. Of their eleven participants, four obtained complete and permanent relief, whilst the remaining seven obtained some form of improvement lasting from several days to several months. Five of those eventually had surgical intervention, involving neurectomy, which offered relief in all cases.

There was some weight added to this theory by Zanetti et al., who were able to identify increased bursal fluid within the affected clefts of MN sufferers. Zanetti et al. compared the MRI scans of 16 MN sufferers to the scans of 70 asymptomatic volunteers. The prevalence of neuromas in the asymptomatic population was found to be 30% and intermetatarsal bursal fluid was found in 67% of the asymptomatic group, with 49% of those being in the third cleft, where MN is also most prevalent. The dorsoplantar depth of bursal fluid sat consistently more than double the transverse width and ranged from 2 to 12 mm with a mean of 7.4 mm, 5 mm and 5.2 mm in the 1st, 2nd and 3rd clefts, respectively. There were no incidences of bursal fluid in the 4th cleft, which is consistent with differing anatomy of this particular cleft. There was no statistical correlation between the presence of fluid and the presence of an asymptomatic neuroma in the 1st or 2nd cleft, but there was a statistical correlation in the 3rd cleft. They conclude that there is merit in exploring this theory further, but that their data was not sufficiently robust to support the theory unequivocally (Zanetti et al. 1997).

More recent research has verified the findings of Bossley and Cairney and Zanetti et al., establishing that the intermetatarsal bursa of the second and third cleft consistently protrude

beyond the DTML and show a close proximity to the neurovascular bundle (Theumann et al. 2001). This subsequent research by Theumann et al. demonstrated that in all cases, the bursa progressed distally beyond the DTML to the level of the inter-metatarsophalangeal joint, and they state therefore, that more accurate nomenclature would be inter-metatarsophalangeal joint bursa.

There is a lot to recommend this theory, not least of all, is the consistency of findings that place more distal bursae in the clefts alongside more frequent cases of MN. Additionally, very recent anatomical research notes that as the neurovascular bundle courses beyond the DTML, it then rises dorsally and when the MTP joint is dorsiflexed, the nerve comes into direct contact with the plantar surface of the bursa (Wei et al. 2022). This should not be disconcerting, as the role of the bursa is to ease frictional forces and therefore, some contact is normal. However, excessive forces or duration of contact, could potentially lead to irritation of either or both structures. This theory shows some consistency with the results of the MAN intervention, since the nerve involved sends branches directly into the MTP joint (Wei et al. 2022), meaning that a loss of MTP joint plantarflexion, would result in increased neural tension and therefore, a subsequent increase in the pressure between the nerve and the bursa. Conversely, MAN successfully normalising MTP joint plantarflexion would result in a reduction in tension and a corresponding improvement in symptomology.

2.3. **Methods of assessment and diagnosis of MN**

MN is usually assessed and diagnosed in the clinical environment using a combination of a thorough history and a selection of clinical tests chosen from the plethora available, according to the clinician's personal preferences. Some clinicians also employ a diagnostic nerve block using local anaesthetic infiltration. However, this form of pharmacological test has long been cautioned against, due to its unreliability and the associated risks of infection and anaphylactic shock (Younger and Claridge 1998).

According to the literature, diagnosis of MN is readily established by clinical tests alone (Sharp et al. 2003; Chaganti et al. 2012; Pastides et al. 2012), but since the precise location of the neuroma is poorly identified clinically, the diagnosis is routinely confirmed radiologically in cases which are progressing to surgery (Biasca et al. 1999; Pastides et al.

2012). USS (Irwin et al. 2000; Betts et al. 2003; Sharp et al. 2003; Gomez et al. 2005; Saragas 2006; Gregg et al. 2008; Markovic et al. 2008; Rout et al. 2009; Park et al. 2011; Cho and Wansaicheong 2012; Kele 2012; Morvan et al. 2012; Thomason and Cooke 2012) and MRI (Zanetti et al. 1997; Biasca et al. 1999; Pfirrmann et al. 2002; Pfirrmann et al. 2003; Weishaupt et al. 2003; Espinosa et al. 2010) are both heavily cited in the literature, with little to suggest that one is more accurate than the other (Sharp et al. 2003; Lee et al. 2007). Due to the greater financial burden related to MRI and the relatively good availability of USS, coupled with good outcomes of USS for soft tissue visibility, some authors suggest that USS is the preferred first choice (Kaminsky et al. 1997; Pastides et al. 2012).

There is little contention in the position that a clinical diagnosis is easily, readily and reliably obtained, without the need for radiological intervention, for those individuals not yet contemplating a surgical intervention. To that end, there is an array of clinical tests available to aid the clinician in diagnosis and some limited work has been done to try and establish which tests are the best performers. There are no large-scale studies and the level of evidence provided by the small number of papers on this topic is weak indeed, with no level I or level II evidence currently available in the literature. This makes any critical evaluation of the available tests challenging.

A systematic search of Medline, Pubmed and Science Direct was performed on 08/02/2023. The search parameters were “Morton’s neuroma OR plantar digital neuritis OR forefoot neuroma AND clinical tests.” The search returned a total of 1,147 papers. 85 foreign language papers were excluded. There were 115 papers specifically investigating MN. The remaining 1,032 related to neuromas of the hand, oral medicine, general foot and ankle investigations or commentaries. A large number of them mentioned metatarsalgia, but not MN specifically. There were 28 literature or systematic review papers on MN, but none on clinical testing. There were 37 interventional studies and 19 exploring radiological findings. 8 studies looked at injection therapy and there was 1 Delphi consensus study exploring a new diagnostic tool and 1 pain study. There were 7 case studies and a single e-book on MRI imaging. The remaining four papers were specific to clinical tests for MN (Cloke and Greiss 2006; Owens et al. 2011; Pastides et al. 2012; Mahadevan et al. 2015).

Mahadevan et al. performed a study which looked at seven of the most commonly used tests and found that the webspace tenderness test (which they called the "thumb index finger squeeze test") was the most sensitive, with 96% sensitivity and 100% specificity, followed by Mulder's click test, which has sensitivity of 62% and a 100% specificity (see table 2.1.). Conversely, the remaining tests performed poorly by comparison. All clinical tests enjoyed high positive predictive values of 95% to 100%, but very low negative predictive values of less than 34% (Mahadevan et al. 2015). The authors examined 54 feet and confirmed diagnosis against a reference standard of a positive finding on diagnostic USS. An unfortunate weakness of this paper was that their protocol assumes superiority of USS over clinical tests. This is without justification according to a number of other researchers, who have found clinical tests to be more sensitive than either MRI or USS when compared to post-surgical histology reports (Sharp et al. 2003; Claassen et al. 2014; Raouf et al. 2019). Nonetheless, the clinical tests and USS enjoyed good agreement in Mahadevan et al.'s study and they concluded that clinical tests are comparable to USS for the diagnosis of MN.

Table. 2.1. Operational characteristics of diagnostic clinical tests compared with ultrasonography (From Mahadevan et al. 2015).

Test	Positive Clinical Tests	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy Rate (%)
Thumb index finger squeeze (webspace tenderness test)	51 (96)	96	100	100	33	96
Mulder's click	34 (64)	62	100	100	0	61
Foot squeeze	23 (43)	41	0	95	0	41
Plantar percussion	19 (36)	36	100	100	3	37
Dorsal percussion	17 (32)	26	100	100	3	33
Abnormal light touch	13 (25)	25	100	100	2	26

Test	Positive Clinical Tests	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy Rate (%)
Abnormal pin prick	13 (25)	25	100	100	2	26

Note: Data presented as n (%), unless otherwise noted.

Owens et al. (2011) offered testing against a control group and found webspace tenderness test (WST in Table 2.2.) and the foot squeeze test (SQU) to be the most sensitive (opting to use this lower threshold of proof rather than the Mulder's click test). They state that a combination of positive SQU and WST tests implies a very high probability of MN (see Tables 2.2 and 2.3). They compared 76 feet with MN to 40 with foot pain from a different diagnosis, as ascertained by MRI (Owens et al. 2011). This is a useful comparator as it closely resembles how such tests would be employed in the clinical setting, rather than rating the tests against asymptomatic feet. Therefore, Owens et al.'s results are more readily translated into the clinical environment, where all patients being tested would most likely be complaining of foot pain in some form. Unfortunately, only 16 of these 40 feet reported pathology in the lesser rays of the forefoot. A further weakness to be considered in this paper is the inability to consider false negative tests, as no surgical procedures were performed on those who tested negative for MN.

Table 2.2. Clinical testing in 76 feet treated operatively for Morton's neuroma (from Owens et al. 2011).

Test	Positive	
WST[a]	72/76	95%
SQU[2]	67/76	88%
PLP[c]	47/76	62%
TTSD[d]	37/76	49%

Table 2.3. Statistical analysis: Chi-square test (from Owens et al. 2011).

Clinical tests	**Comparison between groups (*p* values)**			
	A vs. B	**A vs. B1**	**A vs. B2**	**A vs. B3**
WST	0.000	0.000	0.000	0.000
SQU	0.003	0.394	0.166	0.000
PLP	0.000	0.000	0.000	0.000
TTSD	0.007	0.116	0.000	0.000
Any 2	0.000	0.000	0.000	0.000
WST+SQU	0.000	0.000	0.000	0.000
TTSD + any	0.000	0.000	0.000	0.000

Note: Underlined values indicate that differences were non-significant.

In a small study of 22 surgical patients, Cloke and Greiss (Cloke and Greiss 2006) were able to demonstrate excellent sensitivity for three specific MN clinical tests (Table 2.4). They further reported that two of those tests also enjoyed excellent specificity. These excellent results, in one of the very few papers to explore clinical tests, recommended these three tests to this thesis.

Table 2.4. Results from Cloke & Greiss 2006.

	Mulders click	**Webspace pressure**	**Metatarsal approximation**	**Digital nerve stretch test**
Sensitivity	0.95	0.95	0.90	1.00
False negative	0.05	0.05	0.10	0.00
Specificity	1.00	0.00	0.00	0.00
False positive	0.00	1.00	1.00	1.00
PPV	1.00	0.95	0.95	0.95
NPV	0.50	0.00	0.00	0.00

Pastides suggested that a clear history and examination were by far the most sensitive guides to diagnosis of MN, comparing favourably to USS and MRI. They did not offer any data in support of specific clinical tests in their paper, but instead referred only to the fact that the operating surgeon had noted a clinical diagnosis of MN prior to radiological examination. In their retrospective review of 43 MN surgeries, they report 98% sensitivity for clinical diagnosis versus 90% for USS and 88% for MRI (Pastides et al. 2012).

The above is the full extent of the current literature that focuses primarily on clinical tests for MN. The following describes each of those tests and talks to the merits of their use.

2.3.1. *Mulder's click test (Mulder's sign)*

One of the oldest clinical tests still in use today for MN is the Mulder's click test (Mulder 1951). This test is performed with the patient lying in a supine position. The clinician spreads one hand over the dorsum of the patient's forefoot and uses this hand to apply a lateral compression to the foot at the level of the MTP joints. The clinician uses their other hand to simultaneously apply direct plantar pressure to the affected web-space. A reproduction of the sufferers' symptoms, together with an audible or palpable click is a positive finding for MN (Sharp et al. 2003). Pastides found this to be the most sensitive clinical test (98%), detecting 42 of 43 neuromas in their population (Pastides et al. 2012). Conversely, Coughlin et al. found it to be less useful at 45% sensitivity (Coughlin and Pinsonneault 2001).

2.3.2. *Lateral squeeze test*

This is perhaps the most commonly employed clinical test and is a derivative of the previously mentioned Mulder's click test. The only difference between the two tests being a lower threshold of proof for the lateral squeeze test. Mulder's test requires a reproduction of symptoms, together with an audible or palpable click (Mulder 1951; Sharp et al. 2003), whereas subsequent authors have maintained that a reproduction of symptoms alone is sufficient to deem the test positive and the palpable click is largely irrelevant (Wu 1996; Biasca et al. 1999; Dockery 1999). The test is performed by grasping the affected foot around the area of the metatarsal heads and applying gentle, steady lateral pressure. At the

same time the thumb and forefinger of the other hand should be used to apply alternating dorsal and plantar pressure to the affected inter-digital cleft. Care should be taken to use the side of the thumb rather than the pulp as this creates a cushioning effect (Owens et al. 2011). The reproduction of symptoms, which are immediately relieved by the removal of pressure, is a positive finding (Wu 1996).

Wu suggests that this is the single most useful clinical test for MN and Owens et al. report a score of 88% accuracy in identifying positive cases (Wu 1996; Owens et al. 2011). However, both authors also caution that each clinical test can be susceptible to false positives. Encouragingly, their research was able to establish that the accuracy of diagnosis is greatly increased, when using a combination of clinical tests. This was also able to markedly reduce the incidence of false positive tests (Owens et al. 2011).

2.3.3. *Plantar digital nerve stretch test*

The plantar digital nerve stretch test (PDNS test) is performed with the patient in the supine position and both ankles maximally dorsiflexed. The clinician then places his thumbs on the plantar aspect of the digits on either side of the affected digital cleft. This is done on the symptomatic and asymptomatic limbs simultaneously. The toes are then passively taken through their full range of motion into maximal dorsiflexion. The test is considered positive if the patient reports greater pain in the cleft of the affected foot (Cloke and Greiss 2006). This test was first devised and identified as an excellent predictor of MN by Cloke and Greiss (Cloke and Greiss 2006). Later, Pastides et al. also employed this test and they too found it to be sensitive for MN, citing it as one of the most useful indicators currently available (Pastides et al. 2012). There have to date, been no challenges to the findings of these two papers.

2.3.4. *Bratkowski's test*

There is very little written about the Bratkowski's test, but what is available appears to view the test favourably. The test is performed by simultaneously moving both digits either side of the affected cleft, into full extension. With the digits held in this position, the clinician applies pressure to the plantar aspect of the foot with their thumb. The thumb is then rolled back and forth medial to lateral, over the location of the suspected lesion. Reproduction of symptoms is considered a positive finding (Bratkowski 1978; Blitch et al. 2009; Barrett

2011). Unfortunately, there is no statistical data available on the sensitivity of this test to date.

2.3.5. *Plantar Percussion Test (The Tinel-Hoffman sign)*

This test is arguably one of the least useful tests cited in the literature. According to Owens et al., it identified just 62% of lesions correctly (Owens et al. 2011). The procedure is identical to the Digital Nerve Stretch test, except that there is no requirement for ankle dorsiflexion and percussion is applied to the plantar aspect of the involved cleft, whilst the digits are held in full dorsiflexion. Greiss suggests that the lack of ankle flexion removes the nerve stretch element of testing, relying exclusively on percussion. He argues that it is feasible that "inflammatory changes surrounding the nerve are more sensitive to stretching than to percussion" (Greiss 2012). That being the case, this test would appear to offer little or nothing in terms of identifying any involvement of neural tissue in any malady of the forefoot. Furthermore, it is not beyond the realms of possibility that a patient with bursitis, capsulitis or even a stress fracture in this area, will exhibit a pain response to percussion of the area, even in the absence of MN, and thereby give a false positive result for this test.

2.3.6. *Web-space Tenderness Test*

The web-space tenderness test involves applying both dorsal and plantar pressure simultaneously to the involved cleft, in an effort to reproduce symptoms. A study in 2011 reported that this test enjoyed a 95% success rate in identifying positive cases of MN (Owens et al. 2011). With a sound knowledge of the local anatomy, it is possible to position the fingers in such a way as to ensure that one is compressing the nerve when eliciting a pain response. Unfortunately, there is no way by which one can be assured that they are compressing only the nerve and not also other associated structures, such as the deep transverse metatarsal ligament. This being the case, selecting a sister test with which to twin this one, should mean opting for one of the lateral compression tests, which would not stress the ligamentous structures.

2.3.7. *Gauthier's Test*

Gauthier's test is performed by using one hand to laterally compress the metatarsal heads together, whilst simultaneously flexing and extending the digits either side of the affected cleft with the other hand. This motion is done repeatedly for 30 seconds. The test is considered positive if the patient's symptoms are replicated during that time. This test is

highly sensitive according to Vito and Talarico (Vito and Talarico 2003), but the authors cite no evidence for their confidence in it. Conversely, their claim is strongly disputed by Villas et al. and others, who state that the test is inconsistent (Okafor et al. 1997; Villas et al. 2008).

2.3.8. *Sullivan's Sign*

Sullivan's Sign is positive where there is lateral deviation of one of the lesser digits on weight bearing. This can be seen clinically or on radiographs (Sobiesk et al. 1997; Dockery 1999). Sometimes known as the Victory Sign, or the Churchill Sign, there is a visible "V" appearance of the affected cleft. It is not a well reported sign in relation to MN and its diagnostic value is likely limited, as it is not specific to MN (Baron et al. 1997; Miller and Nakra 2001).

Repeated research has demonstrated that the combined clinical tests of the Lateral Squeeze test (Sharp et al. 2003) and the Digital Nerve Stretch test (Cloke and Greiss 2006; Pastides et al. 2012) offer increased precision compared to combined radiological assessments of MRI and ultrasound (Sharp et al. 2003; Owens et al. 2011; Pastides et al. 2012; Mahadevan et al. 2015). In other words, a purely clinical diagnosis of MN is entirely safe and as accurate, or more accurate, than any radiological alternative, or combination of radiological investigations. Whilst this may be counter-intuitive to some, the evidence is convincing that radiological diagnosis is not superior to a clinical one. Indeed, Di Caprio et al. go as far as to state that clinical diagnosis is the current 'gold standard' (Di Caprio et al. 2018).

It is of great encouragement that diagnosis can be readily and reliably confirmed within the clinical setting and with this in mind, the decision was made to make this study as pragmatic as possible, acknowledging the often limited resources available to the foot and ankle practitioner in the clinical realm. In selecting which tests to employ, it was considered that the lateral squeeze test was merely a derivative of the Mulder's click test and therefore, both were not required. Additionally, the PDNS test, Bratkowski's test and the plantar percussion test are also very close relatives and utilising more than one of those could arguably, be considered duplication. Some of the tests apply compressive force dorsal to plantar. This risks adding stress to the DTML and therefore a potential false positive in the presence of ligamentous injury. Other tests, which comprise lateral compression, will not stress the DTML but could potentially compress the intermetatarsal bursa and again, produce a false positive. For this reason, it was deemed necessary to employ a combination

of tests, which delivered forces in competing directions. The reader will recall the high sensitivity and specificity scores attributed to the Mulder's click test and to the web-space tenderness test in Mahadevan's study. Add to this, the assertion by others, that combining the Mulder's click test with another clinical test, yields improved results compared to MRI or USS, or even a combination of MRI and USS (Sharp et al. 2003; Pastides et al. 2012; Claassen et al. 2014) and especially given the familiarity with these tests amongst the healthcare professions (Mahadevan et al. 2015; Archuleta et al. 2020). Due to the weight offered by these findings, Mulder's click test and the web-space tenderness test were selected for involvement in this study. Furthermore, because the PDNS test involved no compression of the inter-digital space in any direction and also reported highly favourable results, with no evidence to the contrary, it was also added. In order to satisfy the inclusion criteria of the study, a participant would be required to return a positive reading for all three of these tests.

2.4. **Visual analogue pain scale (VAS)**

Pain rating scales measure the intensity of pain being experienced by a subject. Pain however, is a multi-faceted experience, of which intensity is only one aspect. In many instances, it could be argued that pain intensity is less important than the emotional context of the pain. For example, in cancer sufferers, the pain itself may be of less significance than the meaning of the pain (Williamson and Hoggart 2005). Fear and anxiety for the future may also lead one to view pain differently and therefore, pain should never be considered using intensity alone. In the treatment and monitoring of Morton's neuroma, pain rating scales are a useful tool and can be given context when used alongside PROM tools. Whilst quality of life is a composite of many factors, pain has been shown to rank as the primary variable to impact overall quality of life (Garip et al. 2011). Because pain is a personal and variable experience, it is most accurately described through self-reporting methods such as pain rating scales (Emshoff et al. 2011).

There are a large number of pain intensity rating scales available for both research and clinical use (Bahreini et al. 2015). The four most commonly found in the literature, are the visual analogue pain scale (VAS), the numerical rating scale (NRS), the verbal rating scale (VRS) and the faces rating scale (FRS) (Ferreira-Valente et al. 2011; Frampton and Hughes-Webb 2011). The validity of all four scales is well established, but VAS and NRS have

consistently been shown to out-perform all other scales in terms of sensitivity to changes in pain perception (Breivik et al. 2000; Ferreira-Valente et al. 2011).

VAS is a bidirectional, unidimensional linear scale used for the self-reporting of pain intensity. It comprises a straight, horizontal line of exactly 100 mm in length, with verbal anchors at either end. The verbal anchor at the beginning of the line reads "no pain", whilst the anchor at the end of the line reads "worst pain ever", or similar wording with the same meaning. The scoring is marked by asking the participant to bisect the horizontal line at the point between "no pain" and "worst pain" which best correlates to the pain in question. The distance from the "no pain" end of the line to the participant's bisection line is then measured and expressed in millimetres. This allows for 101 potential pain scores, from 0 mm to 100 mm (± 0.5 mm precision).

Ahearn writes that the first visual analogue scale was developed as an employee rating device at the Scott Paper Company in 1921. The tool was designed by two employees, Hayes and Patterson, as a means for management to rate staff without needing to employ written terminology, which may have appeared judgemental (Ahearn 1997). The tool was first used to measure pain by Woodforde and Merskey, who modified the verbal anchors to read "no pain at all" and "my pain is the worst imaginable" (Woodforde and Merskey 1972). According to Hjermstad et al (2011), there is now an extensive array of literature pertaining to the use of VAS. They performed a literature review of studies employing pain rating scales and were able to conclude that VAS has been in common usage since the 1950s (Hjermstad, Fayers et al. 2011). They were further able to identify that VAS is the most frequently used of the common pain scales they'd investigated, appearing 50% more frequently than the next most common, VRS. Within their literature review, it was evident that the majority of papers were unable to recommend one tool over another (25 of 54 papers), whilst 18% favoured NRS and 9%, VAS. In other words, 55% of all papers that they reviewed concluded that VAS was as good, or better than, any other pain intensity rating scale.

One of the benefits of using VAS is the ease and speed with which data can be collected (Todd and Funk 1996; Hawker et al. 2011). However, whilst VAS can quickly demonstrate changes in the participant's perception of pain, it is crucial that the researcher understands what magnitude of change is required in order to see a clinically worthwhile change in

symptomology. Statistical significance does not necessarily equate to clinical significance and there is little value in producing statistically significant changes that are of no clinical benefit. Despite the VAS being a linear scale, changes in VAS scores are clinically relevant on a ratio, rather than a linear basis. That is to say, participants with a higher baseline VAS score require a greater decrease in their score, before they report any meaningful improvement (Tubach et al. 2005; ten Klooster et al. 2006). ten Klooster et al. state that the greater the baseline score, the greater the improvement required before the participants registers a meaningful improvement, and because of this, changes are most accurately expressed in percentage terms, with 55% being the cut off at which participants perceive a satisfactory improvement in their condition (ten Klooster et al. 2006).

Tubach et al. were able to demonstrate that participants with moderate pain from osteoarthritis of the knee, required a mean change in VAS of 19.9 mm before they reported any meaningful improvement. In the same study, participants with severe pain, required a VAS shift of at least 36.6 mm (Tubach et al. 2005). In a more recent study, Tashjian et al. found that a smaller shift in VAS was required. They studied participants with rotator cuff injuries of the shoulder and found that a VAS shift of 14 mm was clinically significant (Tashjian et al. 2009). However, the accuracy of their findings may have been compromised by the relatively small sample size of their study. They examined 81 participants as compared to the 1362 of Tubach et al.. Once again, in a small-scale study, Grilo et al. found close agreement with Tubach et al. in that they estimated a 20 mm change as being the minimum required for clinical significance (Grilo et al. 2007). However, they felt that the changes were linear in nature. This difference of opinion may be rooted in the fact that Grilo et al. chose a rather high and arbitrary baseline score of 50/100 mm as an inclusion criterion for their study. This would have served to mask the ratio effect that may exist between participants whose baseline score was below 50 mm and those above it. In a similar study, Kelly also found that the data was linear, but her sample size was very small and the confidence intervals in the data wide, leaving room for a type II statistical error (Kelly 2001). Myles et al. also argue that the VAS is a linear scale, but they excluded all participants with mild pain and also those with severe pain, on the basis that "we considered they could not provide informed consent" (Myles et al. 1999). This seems a rather sweeping generalisation and has consequences for the conclusions the paper draws. It is difficult to conclude with any certainty that the VAS scale is linear, when all participants at either extreme of the scale's recording capabilities have been removed in this way.

In 2001, Gallacher, Liebman and Bijur were able to demonstrate that a shift of 13 mm on the VAS scale represented a clinically significant improvement in symptoms (Gallagher et al. 2001). This is in keeping with the findings of a seminal paper by Todd et al., which also suggested a shift of 13 mm as being the least change of clinical significance. However, they also suggested that depending on how their data were interpreted, this figure may increase to 16 mm (Todd et al. 1996). In an almost identical study, Kelly concluded that the shift should be in the order of at least 9 mm (Kelly 1998). In a later study, Kelly concluded that a shift of 12 mm would be required (Kelly 2001). These findings correlate well with the findings of Jenson, Chen and Brugger (2003), who reported the least meaningful change as being between 9.4 mm and 13.3 mm.

In their reanalysis of two separate clinical trials, Jensen, Chen and Brugger further argued that VAS scores could be used to categorise pain into specific intensity groupings. According to their findings, a VAS score of < 5 mm can be considered no pain, a score of 5 mm to 44 mm, mild pain, 45 mm to 74 mm moderate pain and > 74 mm as severe pain. However, one must be cautious when applying these figures rigidly, since the boundaries between the fields are not well-defined. When one considers the standard deviation within the paper's data, the fields could read as follows; No pain 0 – 4.4 mm, mild pain 17 – 38 mm, moderate pain 46 – 68 mm and severe pain 73 mm upward. One can see that there are many scores that do not fall neatly into any of these categories, but instead, create significant gaps, and therefore caution should be exercised when attributing labels to data that has been gathered.

It is a long-held practice to ensure that all participants in a study examining analgesia, are reporting moderate to severe pain (Collins et al. 1997). This helps to ensure that there is adequate sensitivity in the reporting of changes. According to Jenson and colleagues, that criterion would exclude all participants with a baseline VAS of < 45 mm (Jensen et al. 2003). Other researchers place the figure slightly lower at < 30 mm (Collins et al. 1997), < 42 (Loos et al. 2008), or even as low as < 17 mm (Aicher et al. 2012).

When using multiple VAS scores over staggered time intervals, there is no agreed protocol within the literature. Some papers advocate giving the participant sight of their previous scores (Farrar et al. 2000; Williamson and Hoggart 2005), whilst others ask their

participants to perform each new score blinded from previous scores (Myles et al. 1999; Bijur et al. 2001; Gallagher et al. 2001; Emshoff et al. 2011). Williamson and Hoggart argue that allowing participants to have access to previous scores reduces measurement error and that depriving participants of previous scores, may lead to VAS data that is out of step with other measures of change (Williamson and Hoggart 2005). However, the evidence for this approach is not compelling and the convention to blind participants from all previous scores remains in place for this thesis, as this is in keeping with previous studies of MN.

2.5. **Pressure algometry (PA)**

Pressure algometry (PA) has been in usage since the Victorian era (Keele 1954). It is currently widely used in the assessment of myofascial pain syndromes (Rolke et al. 2005; Park et al. 2011) and is diagnostic for Fibromyalgia (Wolfe et al. 1990). The goal of PA is to give quantification to the individual's experience of pain in a reliable and repeatable fashion.

There are a number of pressure threshold meters readily available on the market and some work has been done to compare the accuracy of an electronic device to the more commonly used manual one (MacDonald and Atkins 1990; Cashley 2015). Although there has not been extensive work in this area, it would appear that both types of algometer are equally sensitive (Cashley 2015). Fischer was the first to report the use of a 1 cm diameter contact probe, which has become the accepted standard (Fischer 1987). However, a recent study by Finocchietti suggests that different probe sizes should be considered depending on the type of tissue being tested (Finocchietti et al. 2012).

A number of studies have examined inter- and intra-tester reliability of the device and have found it to be good to excellent in this regard (Potter et al. 2006; Ylinen et al. 2007; van Wilgen et al. 2011; Nikolajsen et al. 2011; Park et al. 2011). Further studies have looked for differences in scores relating to gender and age (Lautenbacher et al. 2005). In a methodologically robust study, Chesterton et al. found that females repeatedly score significantly lower than males and suggest that this has implications for those wishing to use PA as an outcome measure in a research setting. The authors found however, that PA scores remained stable despite repeated measure or time lapse, suggesting that the tool is reliable and sensitive, but that it should not be used to compare across genders (Chesterton et al. 2003). This was confirmation of earlier findings by Brennum et al. who found that

male scores could be as much as 50% greater than female scores (Brennum et al. 1989). Dawson and List found that gender differences varied according to ethnicity, with those of Swedish origin showing a greater between-gender difference than those of a Middle Eastern origin. They concluded that both gender and ethnicity influence the pain experience. However, these differences were significant only for the higher readings relating to maximum pain tolerance and not for those relating to the pressure/pain threshold (Dawson et al. 2009). Interestingly, Nikolajsen et al found that boys and girls showed no such gender difference (Nikolajsen et al. 2011). However, there are further statistics to consider from this paper. All of the children were under 12 years of age. This would suggest that many differences that develop later in life, were not yet apparent, and this is borne out in the following baseline characteristics. The mean height was identical in both genders at 134.8 cm and the mean weight of the girls was slightly higher than the boys – 30.6 kg as compared to 29.9 kg. As all participants were prepuberty, it is likely that hormonal differences are not yet expressed and that strength, muscle mass and such, are broadly similar across the genders. It is possible that changes in PA scoring will develop as these baseline measurements change. To add to the issue still further, in a study of 300 healthy volunteers, Neziri et al. found that the differences between male and female scores actually diminished with increased age (Neziril et al. 2011). However, there are two confounding factors in Neziri et al.'s paper. Firstly, the study's age categories are simply split into above and below 50 years of age. This may prove to be too great a bandwidth and too few subdivisions to truly reflect any changes accurately within the analysis. Additionally, the author tested not only pressure threshold, but also pain threshold. These are two very different measurements, one measuring the onset of pain and the other measuring the maximum pain that a participant can tolerate. The paper does not make it clear whether both measurements were considered together for data analysis or whether the changes with age relate to only one of these measurements. Lautenbacher et al. differs from Neziri et al. and states that the pressure pain threshold in relation to mechanical pain diminishes with age, meaning that as we age, we feel pain at a lesser threshold.

Taking a very different approach, Komiyama and colleagues investigated ethnic differences in pressure/pain threshold measurement using a variety of measuring tools. They compared Belgian men and women to their Japanese counterparts and whilst they found that some tools were affected by ethnicity, PA was resistant to this variable at the pressure/pain threshold (Komiyama et al. 2007). These results were replicated in a study comparing

Swedes to people from the Middle East, although this study found differences at the pain tolerance threshold (Dawson et al 2009). Interestingly, this study found significant differences in electrically or thermally induced pain, but not in mechanically induced pain. There appears to be moderate consistency within the literature that mechanical PA scores are not affected by ethnicity, but possibly, by age and gender. This has clear implications for study design and for interpretation of results.

The ability of the algometer to identify the location of dysfunction could be a major step forward in the field of manual manipulative therapies. Since several research papers have demonstrated that traditional manual palpation is unreliable (Najm et al. 2003; Robinson et al. 2009), with moderate to poor levels of inter-rater agreement (Billis et al. 2003; Kilby et al. 2012), there is a clear need for an improved method of lesion detection. In a comprehensive annotated bibliography, Haneline et al. reviewed a total of 48 papers and reported that only 11 papers scored inter-rater reliability above "fair" (Haneline et al. 2009). Haas et al. also demonstrated that motion palpation of joint end play (the feel of a joint as it reaches the end of its range of motion), despite being a popular assessment tool in manual therapy, appears to have no bearing on treatment outcome (Haas et al. 2003).

In terms of identifying joint dysfunction, the value of the algometer has been tested against the traditional method of manual palpation and was found to be significantly more sensitive and reliable than palpation by hand (Chaves et al. 2010). When testing in the lower limb, Walsh and Hall found the algometer to have excellent reliability and inter-rater agreement in both symptomatic and asymptomatic participants (Walsh and Hall 2009). They were able to demonstrate that in asymptomatic participants, both limbs showed equal PTMs, but scores in symptomatic limbs were significantly lower than in the contralateral limb. Similar results were reported in a small-scale study using the algometer to diagnose reflex sympathetic dystrophy (Bryan et al. 1991). Chesterton et al. also showed excellent rates of inter-rater reliability for the algometer (Chesterton et al. 2007).

One area of potential bias with the algometer was explored by Ohrbach et al., who found that measurements were consistently lower in instances when the clinician controlling the pressure, expected this site to be painful for the participant. However, they also concluded that the scores at actual sites of pain, remained significantly different to allow for this bias (Ohrbach et al. 1998). Two other areas of potential bias that exist for this tool and possibly

for all pain measurement tools, are the gender and professional standing of the examiner. Kallai, Barke and Voss demonstrated that these variables have a significant impact on the reporting of pain (Kállai et al. 2004). This has marked implications for all study designs that relate to pain measurement. It is imperative that all measurements are recorded by researchers of the same gender and professional standing in order to ensure reliability of measures.

Since the validation of the algometer in the spine, it has been used to assess the magnitude of change brought about by manipulation of the cervical spine (Fernandez-de-las-Pena et al. 2007), the thoracic spine (Fryer et al. 2004), and the lumbar spine (Thomson et al. 2009). It is feasible that the tool could be used in the same way to assess the effectiveness of various podiatric interventions. However, any lower extremity work could at best, be described as being in its infancy. In one of the few studies to employ PA in the lower limb van Wilgen et al. were able to demonstrate that it could play a valuable role in the diagnosis of knee problems, specifically patellar tendinopathy (van Wilgen et al. 2011). Brennum et al. and Neziri et al. did record some scores for the second toe in their studies, but in the case of Brennum et al., they were more focussed on the reliability of repeat measurement than on the use of the tool in the foot specifically (Brennum et al. 1989; Neziril et al. 2011). It is also worthy of note that Walton et al. established that the PTM is a reliable tool even in novice hands, suggesting that it could readily and confidently be applied by any clinician with the most basic of training (Walton et al. 2011).

2.6. **Patient Reported Outcome Measures (PROMS)**

Patient-reported outcome measures (PROMS) serve a variety of functions within healthcare. There is an array of different tools, all of which are primarily designed to facilitate the retrieval of information about how interventions have impacted an individual's condition and quality of life. These tools are by no means passive instruments of data collection. Rather they serve to prompt the participant into a period of reflection and self-assessment, potentially leading to a change in how the individual views their condition (Greenhalgh et al. 2018). The regular employment of PROMS has been shown to promote increased frequency of communication between patient and clinician and in some cases, may also be associated with enhanced symptom control (Kotronoulas et al. 2014). Clinical outcomes, whilst vital, are an incomplete picture of the impact that a given intervention has had on those that receive it. The impact on the individual's quality of life, their ability to

work, exercise and socialise should all be considered in the round also. The patient perspective has become an increasingly integral part of the healthcare landscape in recent years and PROMS have been employed to facilitate the incorporation of this particular facet of the patient journey, especially in the realms of healthcare research. Arming the clinician with information about how clinical interventions are affecting the patient's life, as well as their condition, should lead to better clinical decision-making and improved outcomes (Field et al. 2019).

Choosing the most appropriate PROMS can be a challenging exercise. It is of course imperative that the tools employed are capable of capturing information which is of relevance to the study, and which enhances outcomes. It can also be valuable from a research point of view, to consider whether choosing a specific tool would facilitate better communication of the research to the wider community. In the same vein, the correct choice of instrument can also lead to more fluid comparisons with previous and potentially, future research.

PROMS can either be generic or condition specific but in the case of MN, there are no condition-specific tools currently available. Having established that a generic tool was the only option, it was then essential to ensure that the tools selected would be acceptable to the participants. Given that a number of aspects of symptomology, functionality and quality of life needed to be captured, there was a risk that the document combining the necessary PROMS would be unwieldy or show excessive duplication. For example, the SF-36 questionnaire asks the question "Does your current health status prevent you from walking more than a mile?" and the Manchester-Oxford Foot Questionnaire asks the participant how often they would agree with the statement "I avoid walking long distances because of pain in my foot." Removing duplicate questions (or broadly similar questions) from the various PROMS would risk invalidating the scores obtained and so each tool had to be included in its complete format. In reviewing the various tools which could have been employed, it was imperative that duplication was kept to an absolute minimum. This is in order to ensure that participants' time is respected and also that focus is maintained as well as possible when answering PROMs. Additionally, the participant must be able to understand the logic and reasoning clearly and easily in each question being asked. Ideally, they should also find completion of all required PROMS straightforward and not too time-consuming. Beyond all the above considerations, there is always the need for the instrument to demonstrate

statistical reliability, sensitivity and validity. Without such robustness, the tool is purposeless.

PROMS are health status questionnaires that can be sub-divided into three broad types of instrument - the global rating scale, the disease-specific rating scale and the region-specific rating scale. Each type of instrument has, by design, inbuilt strengths and weaknesses. The global instrument covers a wide range of diseases and dysfunction, regardless of the body-part affected. This allows the capture of information concerning a broad range of maladies in a variety of settings but may also serves to limit the tool's sensitivity to change (Martin et al. 2006; Dawson et al. 2012). Disease-specific instruments are very narrow and specific as regards the data they capture. This allows them to be extremely sensitive to change. Disease-specific instruments have been shown to be more sensitive than region-specific counterparts when used in the foot (Burn et al. 2013). However, to the author's knowledge, there is no disease-specific instrument in use for Morton's neuroma. Region-specific rating scales capture information pertaining to a specific body region. They are less restrictive than disease specific tools but offer information that is more precise and sensitive to change than a global instrument.

According to Button and Pinney, there is no satisfactory rating scale with which to assess foot and ankle problems (Button and Pinney 2004). However, in an effort to understand as much as possible about each participant's state of health and general well-being, this thesis explored the potential use of a number of questionnaires. In 1991, the Foot Function Index (FFI) was introduced as a method of charting the impact of foot pathologies on those with rheumatoid arthritis (Budiman-Mak et al. 1991). However, it was soon clear that such a scale, validated using participants with a mobility limiting disorder, presented problems for the wider use of the tool (Agel et al. 2005). When this tool is used for participants who are more active than those with rheumatoid arthritis, a scoring ceiling is frequently encountered. In other words, the expectation of the tool is set too low in terms of daily physical activity of the general population. Agel et al. concluded that because of this limitation and due to the fact that many questions within the FFI relate to walking aids, which a large portion of foot pain sufferers do not use, "the FFI appears to be a reasonable tool for low-functioning individuals with foot disorders… [but] The FFI should be used with caution in individuals who function above the level of independent activities of daily living" (Agel et al. 2005). In an effort to address these short-comings of the FFI, The American Orthopedic Foot and

Ankle Society (AOFAS) produced a scoring system that more satisfactorily captured a wider range of participants with lower extremity dysfunction (Kitaoka et al. 1994). This tool grew in popularity due to its ease of use and more sophisticated scoring. However, in response to a number of previous papers, which had questioned the validity of the tool (Guyton 2001; Toolan et al. 2001; SooHoo, Shuler et al. 2003; Button and Pinney 2004), the AOFAS released a statement, which concluded that "Scores from the AOFAS Clinical Scoring Systems have not been found to be valid or reliable, and therefore their continued use is not recommended."

In 2005, Martin et al. published a lower limb specific quality of life questionnaire with a musculoskeletal focus. Unlike the previous FFI, their questionnaire was not disease specific. Their Foot and Ankle Ability Measure (FAAM) showed good agreement with other measures of physical function, but a poor relationship with measures of mental function, suggesting that this particular tool should be viewed purely as a measure of the participant's physical abilities (Martin et al. 2005).

The global Short Form 36 (SF-36) will be used to capture a wide perspective of general health status. The Foot and Ankle Ability Measure (FAAM) and the Manchester Oxford Foot Questionnaire (MOxFQ) will be used as region-specific measures of foot health. Although both FAAM and MOxFQ are similar, they do ask slightly different questions and there is no clear evidence within the literature as to which instrument is more sensitive to changes associated with Morton's neuroma.

2.6.1. *Manchester-Oxford foot Questionnaire (MOxFQ)*

The need for better outcome measurements in the treatment of foot pathologies had been identified by Button and Pinney in 2004 (Button and Pinney 2004), Agel et al. in 2005 (Agel et al. 2005) and reiterated by Dawson et al. in 2006 (Dawson et al. 2006). Button and Pinney performed a meta-analysis of 49 different rating scales from within the foot and ankle literature and concluded that "No rating scale was identified that demonstrated reliability, validity, and responsiveness in patients with a variety of foot and ankle conditions" (Button and Pinney 2004). The Manchester-Oxford Foot Questionnaire (MOxFQ) was then devised, validated and first published in 2006 by Jill Dawson and her team. Specifically, this was the first outcome measure to be developed for the foot that had patient input to its design (Dawson et al. 2006). MOxFQ focusses on patient evaluations of change rather than the

opinion of the clinician, thereby giving a more accurate interpretation of the impact that the foot pathology is having on the patient's overall wellbeing and quality of life and minimising potential bias (Dawson et al. 2007). Having established the validity and responsiveness of the MOxFQ, Dawson et al. then established the minimally important change (MIC) scores for the instrument. The MIC allows the tool to be used in the clinical setting, as well as the research one, ensuring that the clinician is aware of when a change is likely to be of value to the patient rather than when it is or is not, statistically significant (Dawson et al. 2007). In a large-scale study of 671 surgery patients the MOxFQ was found to have no floor or ceiling effects in any of the questions and to be equally useful across all regions of the foot, with the possible exception of the midfoot, where little data was available (Dawson et al. 2011).

As a regional rating scale, the MOxFQ gathers very specific information about the musculoskeletal function and disability of the foot, but may miss some of the global impact of foot pain. For this reason, it has been combined with the global rating scale SF-36 in this study.

2.6.2. *Foot and ankle ability measure (FAAM)*

In 2005, Martin et al. published the Foot and Ankle Ability Measure (FAAM), which demonstrated good agreement with other measures of physical function, but a poor relationship with measures of mental function. As previously mentioned, this helped identify the FAAM as an ideal measure of the participant's physical abilities (Martin et al. 2005).

Additionally, Martin et al. found that the Activities of Daily Living (ADL) scale within the FAAM, was more sensitive to changes than the corresponding subscales of a similar questionnaire, the short-form 36 questionnaire (SF-36). The FAAM is a self-reporting rating scale, which was developed from a pre-existing scale known as the foot and ankle disability index (FADI). The only difference is that one sleep-related item and four pain related items have been removed from the FADI to create the FAAM (Donahue et al. 2011).

In a study comparing four different outcome measures, it was established that "The FAAM received the most positive ratings for its clinimetric evaluation… and the FAAM can be

considered as the most appropriate, patient-assessed tool to quantify functional disabilities in patients with chronic ankle instability" (Eechaute et al. 2007). The flexibility of FAAM in terms of including or excluding the sports category, and of participant's being able to exclude questions that they do not feel applicable to their situation, increases the appeal of the tool, as it creates an evaluation that is perceived to be closer to the reality of the participant's actual functional performance (Burn et al. 2013).

2.6.3. *Short form 36 (SF-36)*

Designed in 1989 as part of the Medical Outcomes Study (Tarlov et al. 1989), The Short Form 36 (SF-36) has grown steadily in popularity ever since. It is a global rating scale questionnaire which consists of 36 items which combine to measure an individual's generic health status. Martin et al suggest that the SF-36 enjoys such popularity because early validity research studied a diverse number of pathologies and employed large number of participants, allowing the extrapolation of scores to be generalised. Because the SF36 was validated over a variety of conditions it has been used as a standard instrument against which others are often measured (Martin et al. 2006). While the SF-36 has been shown to be a robust global measurement tool, other rating scales such as FAAM, have been shown to be more sensitive to changes in lower extremity conditions (Martin et al. 2005).

By 1993, the SF-36 questionnaire was proving a useful and well utilised tool for healthcare research within the UK (Jenkinson et al. 1993). Jenkinson, Coulter and Wright used a postal survey of 13,042 participants to explore the internal consistency and validity of the SF-36, finding that the questionnaire performed well in both of these categories (Jenkinson et al. 1993). At around the same time, a similar study comparing symptomatic participants to an asymptomatic population found that "The SF-36 satisfied rigorous psychometric criteria for validity and internal consistency. Clinical validity was shown by the distinctive profiles generated for each condition, each of which differed from that in the general population in a predictable manner" (Garratt et al. 1993). Since then, the SF-36 has grown in popularity and by 2014, it was reported as being the most commonly used quality of life questionnaire amongst researchers into congenital heart disease. Despite researchers utilising upwards of 90 different questionnaires, the SF-36 was used in 29% of all studies (Kahr et al. 2014). Additionally, a systematic review by Hunt and Hurwit found that the SF-36 was used in 13.7% of all foot and ankle articles published in the orthopaedic literature over a ten-year period (Hunt and Hurwit 2013). They were able to state that of the 139 different outcome

tools used within the literature, the SF-36 was the third most popular, behind the AOFAS and VAS. Specifically relating to forefoot disorders, again they were able to demonstrate the same hierarchy of employment (Hunt and Hurwit 2013).

2.7. **Current treatment modalities**

The following is a summation of currently employed interventions to offer the reader a flavour of current practice. The treatments selected for this thesis will be revisited in more depth in a systematic review in Chapter three. Current interventions can be broadly divided into conservative care and surgical intervention. There is a semantic debate regarding where to place injection therapy. If one considers the strict definition of conservative care as "the avoidance of intrusive measures, such as surgery or other invasive procedures" (Adhiyaman 2021), then a third division of pharmacological intervention, is required. However, for this thesis, we shall accept that the pharmacological interventions of injection therapy are, as considered by many, to be an extension of conservative care (Weiss et al. 1994; Bose 2005; Tonks et al. 2007).

Whilst injection therapies enjoy growing attention in the literature, the wider gamut of conservative treatment remains under-reported. Paradoxically, these treatments are most commonly referred to as being the first line of defence, with a progression to pharmaceutical and then to surgical interventions in the case of failure (Åkermark et al. 2013; Colo et al. 2020; Klontzas et al. 2021; Ross et al. 2022). The initial treatments of choice are padding and strapping, footwear modifications and/or orthoses. The only paper to review the effectiveness of padding and strapping is from 1989. It reports 12 cases of padding, with a 100% failure rate. This paper also considered orthotic therapy and injection therapy but concluded that the treatment plan of choice should bypass conservative care altogether, due to such poor outcomes (Gaynor et al. 1989). It should be noted however, that there are a number of weaknesses in this study. Firstly, it was retrospective in nature and the treatment groups were not clearly defined. Furthermore, the design of the given orthotic is not declared and therefore, no assessment of this modality can properly be made by the reader. Additionally, there is no detail of the injection therapy used and not even confirmation that this was the same for each participant, again, weakening the value of the study.

Kilmartin reports that pronation-controlling orthoses are of no benefit in the treatment of MN (Kilmartin and Wallace 1994). However, the orthoses used were not made of standard

materials such as polypropylene or carbon fibre, but instead, were cut from chiropodists felt. Furthermore, there was no mention of any forefoot correction being built into the device, which could perhaps be regarded as a standard practice when treating MN: The latter is after all, a forefoot malady. It is therefore fair to say, that this paper fails to offer sufficient evidence to discount the use of functional foot orthoses in the treatment of MN.

In their systematic review and meta-analysis, Matthews and Hurn bemoan the paucity of high-quality studies into conservative interventions for MN, stating that they found only one high quality study (Matthews et al. 2019).

2.7.1. *Injection therapy*

Injection therapy has been a first-line intervention for MN treatment for several decades now and a 2018 systematic review reported an 81% success rate for radio-frequency ablation, 71% for alcohol injections and a 51% success rate for CSI (Valisena et al. 2018). Another systematic review and meta-analysis reported poorer outcomes for CSI of just a 43% success rate (Lu et al. 2021). Some papers suggest that alcohol injections offer the most promise for all injection therapies, but they have recently come under additional scrutiny, due to the report of serious adverse effects including digital ischaemia (Biz et al. 2022), as well as skin and subcutaneous tissue necrosis with peritendinous exposition (Ortu et al. 2022).

2.7.2. *Corticosteroid injection therapy (CSI)*

In the absence of superior outcomes, CSI is the treatment of choice in MN cases for many podiatrists and is as close to a 'gold standard' for conservative care as currently exists. There is perhaps a logical appeal to delivering an anti-inflammatory drug to the site of an internal inflammatory response, such as is seen in MN, and these factors may account for the intervention's popularity. Additionally, it is estimated that 20% of orthopaedic referrals are for foot and ankle problems, for which CSI is widely performed (Metcalfe and Reilly 2016).

The steroids are a group of naturally occurring hormones that are synthesised in the adrenal cortex and the gonads. The Glucocorticoid steroids are secreted into the circulatory system in response to perceived threats to the body's welfare (Handa and Weiser 2014). They exert their action on carbohydrates and proteins in order to maintain homeostasis. The main glucocorticoid in humans is cortisol (Handa and Weiser 2014). Corticosteroids intervene in

the inflammatory process by binding to the glucocorticoid receptor, creating a corticosteroid-glucocorticoid receptor (CGR) complex. The CGR complex is then translocated to the nucleus, where it increases the expression of anti-inflammatory proteins and also supresses the expression of pro-inflammatory proteins. Interestingly, the CGR has no impact on the synthesis of these proteins, only on their expression (Buttgereit et al. 2004). The CGR complex also inhibits vasodilation, reduces vascular permeability and impedes the migration of leukocytes (Strehl and Buttgereit 2013). This should not be viewed as a switching mechanism that either shuts down or awakens protein expression, but rather as a regulatory mechanism that creates fluctuations in protein response to the hormone rather more like a wave formation than a simple switch (John et al. 2009). Additionally, at least when used in high doses, corticosteroids have been shown to merge into the cell membrane and thereby change the physiology of the membrane itself. This process leads to less calcium and sodium transport activity across the cell membrane and so, encourages a decrease in the inflammatory response (Buttgereit et al. 2004).

Contra-indications to CSI include joint prosthesis, fractures, local infections, unstable joint structures, and previous failed steroid injections. Serious side effects tend to occur more commonly with systemic high dose or long-term use and are not generally associated with local injection therapy (Metcalfe and Reilly 2016). However, there are still side effects associated with local injection of corticosteroids. They have been shown to adversely affect glycaemic control in diabetic patients and can create a steroid flare in some patients. Fat pad atrophy is also a common consequence of steroid injections (Metcalfe and Reilly 2016). Tendon rupture and joint sepsis have been reported in the literature, and Haraldsson et al, report evidence that shows tendon structures being significantly weakened by the introduction of corticosteroids (Haraldsson et al. 2006). A published systematic review confirmed that a number of previous studies have consistently reported collagen necrosis, a loss of collagen synthesis, organisation and tissue viability (Dean et al. 2014). Since the steroid is often mixed with local anaesthetic, the risk of anaphylaxis should also be considered. However, a systematic review which focussed exclusively on extra-articular injections, such as were used in this current study, was able to report that side effects are rare and usually mild in nature, making the extra-articular injection of steroids a relatively safe intervention (Brinks et al. 2010).

The first CSI was reportedly given intramuscularly by Hench and his team at the Mayo Clinic (Hench et al. 1950), rapidly followed by the first intra-articular injection by Thorn in 1950. Thorn injected into the knee of a patient with rheumatoid arthritis and the patient experienced a rapid analgesic effect (Hollander et al. 1951). Since this time, the role of CSI therapy has grown exponentially, and the hydrocortisone esters being used today, have been developed to offer prolonged action with smaller doses and fewer side effects. Steroid injection therapy has become a mainstay of non-surgical intervention in the treatment of musculoskeletal conditions (Tatli and Kapasi 2009).

In the podiatric field, injectable steroid preparations have been in common usage since the 1960s (Rosen 1963; Locke 1967), yet there is still a lack of scientific evidence in support of their efficacy (Markovic et al. 2008) and nothing at all within the literature, promotes their use as a long term solution for foot complaints. Crawford et al, in a randomised control trial, concluded that there was benefit to be enjoyed at a one month follow-up, but this was lost by three months post injection for heel pain (Crawford et al. 1999). However, in the case of Morton's neuroma, the evidence in the literature in favour of any other form of conservative intervention is sadly lacking and CSI has become the non-surgical treatment of choice. Some studies have shown that the duration of symptoms has an impact on the effectiveness of steroid injection therapy, with the success rate dropping to just 13% in those who have suffered pain for more than a year (Markovic et al. 2008). Additionally, authors have reported rates of 21% - 47% of those treated with steroid injection requiring a surgical intervention within one year (Rasmussen et al. 1996; Markovic et al. 2008; Thomson et al. 2013; Rao et al. 2014).

There are two standard methods of delivering steroid injections to the foot – ultrasound-guided and anatomy-guided. Despite the intuitive leaning toward ultrasound-guided steroid injections, the current evidence suggests no difference in clinical outcomes between the two techniques (Sivan et al. 2011; Mahadevan et al. 2016; Bhayana et al. 2018). Morgan et al. do claim in their systematic review that ultrasound guided injections provide better short- and long-term pain relief than anatomy-guided injections (Morgan et al. 2014). However, this claim is not borne out in their data and several assumptions are made to arrive at this conclusion. Most crucially, the time at which pain data is collected is noticeably later for anatomy-guided injections and since several papers point to steroid effects deteriorating over time, this could account for such apparent discrepancies. For example, a paper by

Mozena and Clifford, who analysed data collected after an average of 11 months, was included in the anatomy-guided group (Mozena and Clifford 2007), while Markovic et al., who collected data at 1, 3, 6 and 9 months, were included in the guided analysis (Markovic et al. 2008). Additionally, one of the eight papers included in their anatomy-guided group (Mozena and Clifford 2007), states that "results were reported as resolved, improved or unresolved." However, further into the paper, results are detailed in percentage points of improvement. How these percentage points were calculated was never disclosed and the reader is left to ponder whether this is the operator's assessment, patient feedback, a VAS score or some other form of measurement. Additionally, other included papers such as Dockery (Dockery 1999), were not blinded and therefore, participant to operator expectation bias may have intruded. Including such papers in a systematic literature review makes any conclusions drawn questionable at best. When one takes that research in tandem with the knowledge that the vast majority of podiatrists who treat Morton's neuroma using steroid injection therapy are unlikely to have ready access to US and therefore, will in all probability, perform anatomy-guided injections, the pragmatic decision was taken to follow such a model in this study.

2.7.3. *Surgical interventions*

Surgical intervention has been a mainstay of MN treatment since the pathology was first described (Morton 1876). In a thorough and detailed systematic review, Valisena et al described the outcomes of 17 different surgical studies covering 959 participants (Valisena et al. 2018).

Despite the fact that nerve resection, and the associated loss of function, is not a recommended treatment for any other nerve entrapment syndrome anywhere else in the body, neurectomy is currently the most prominent treatment option cited in the literature specifically for MN. Indeed, it has a long history of involvement in MN care. It was first postulated as an intervention for MN by an American professor of orthopaedic surgery by the name of Hoadley, in 1893. He reported on a single surgical case of MN within a case series of six patients suffering from MN. Interestingly, he reports a successful outcome using conservative management in his other five patients within this series. In the remaining patient, he resected the nerve and reported a "prompt and complete cure" (Hoadley 1893). However, there appears to have been little appetite for this novel surgical approach, or for exploring the apparent success of conservative care that Hoadley reported. Instead, most

citations in the literature contemporary to Hoadley, continue to prefer an osteotomy over neurectomy. Remarkably, it was almost half a century before neurectomy gained any traction. Some studies report good to excellent surgical outcomes, but there is confounding evidence, suggesting that complications such as stump neuromas, localised paraesthesia and destabilisation of MTP joints, all potentially leave the patient unsatisfied with their surgical outcome. Recurrence of the original pain is also often reported.

Many papers report good outcomes from neurectomy, but in one of the few long term follow-up studies (4 - 8 years), Womack et al. established that 10% of neurectomy patients reported fair results, whilst 40% reported poor results (Womack et al. 2008). Such surgical failures and complications are not uncommon and a return of symptoms is often reported (Jain and Mannan 2013; Archuleta et al. 2020). A resected nerve will secrete Nerve Growth Factor as it attempts to regenerate, sprouting additional nerve tissue in search of a distal connection. If such a connection is not made, then this disorganised bunching of new nerve tissue will embed itself locally and recreate symptoms. It is equally feasible that the pain persists because the underlying pathology has not been addressed.

An alternative surgical procedure, which has garnered some support is decompression of the inter-metatarsal cleft by longitudinal separation of the DTML. Intuitively, it makes sense that if the ongoing pain is as a result of localised irritation from neighbouring structures because the nerve tissue is inflamed and fibrosed, then increasing the available space for the neurovascular bundle within the inter digital cleft will likely result in less irritation. This increase is brought about by dissecting the DTML, which binds the metatarsals to each other. This division allows the metatarsals to drift apart somewhat, easing the compression on the nerve tissue. However, Archuleta et al. cast some doubt on the utility of this procedure. In their retrospective case series, they reported that 40% of patients reported poor outcomes and 18.5% required revision surgery (Archuleta et al. 2020).

2.8. **Manipulation**

When one considers the proposed aetiologies of MN as nerve irritation or entrapment from the bony structures of the neighbouring joints, it is intuitively appealing to consider that physical movement of those joints may impact the symptomology of the condition. Investigating whether a mechanical application of force to alter joint motion and increase

neural firing, may change the participants' pain report, is a first step in exploring the relationship between manipulation and MN.

Reference to manipulation can be found in many ancient texts from an array of differing cultures. In the 19th century, the renowned British surgeon James Paget published in the BMJ, urging his colleagues to study the art of "bone-setting" more carefully (Paget 1867). This was soon followed by the medic Wharton Hood, publishing in The Lancet, the reported benefits of manipulation in musculoskeletal medicine. He detailed the many successes of "bone-setters" that he had been studying for several years (Hood 1871). Both men acknowledged the potency of such intervention and cautioned their medical peers against dismissing the procedures merely because the practitioners were uneducated in medicine. However, the interest quickly waned, as Keating described "Class distinctions within British culture encouraged a derogatory view of many 'hands-on' methods that required healers actually to touch their patients. Manipulation and surgery were frowned upon, especially foot surgery. Additionally, the prevalence of tuberculosis, with its attendant risks of injury from manipulation of fragile lesions of bone, further discouraged the use of manual therapies for patients with spinal and other musculoskeletal disorders". That being the case, the practice of manipulation fell out of favour and has been struggling to regain ground ever since (Keating 2003). Only in the last forty years or so, has there been a concerted effort to scientifically explore the potential benefits of such interventions. In recent years much progress has been made, both in terms of acceptance of manipulation as a therapeutic tool, and also in understanding the various mechanisms of its action.

The manipulation manoeuvre used in this study was a single, high velocity, low amplitude thrust technique. This is a mechanical event, employing controlled force and direction to a given joint structure, resulting in soft tissue and neural deformation. An in-depth description of the technique is offered in the methods of Chapter 4, section 4.9, but we shall explore the theories pertaining to its functionality here.

There are several varied models currently invoked to describe the various effects of manipulation. Several of them are succinctly presented, together with the relevant scientific research in Robert Leach's book "The Chiropractic Theories" (Leach 2004). The models that relate to extremity manipulation include the Neurological Feedback Model, the Biomechanical Model and the Dynamic Fluid Flow Model.

2.8.1. *Neurological feedback model*

This model discusses what is happening at a neurological level, when a joint becomes fixated or restricted, and how the body responds to manipulation at such a joint. Firstly, one should consider the neurological make-up of the joint and its associated local structures. Ruffini-type nerve endings are found within the joint capsule and the local ligaments. They are sensitive to stretch and to pressure and are therefore, useful for indicating movement and position of the joint. This is also true of the Golgi tendon organ, which is found in the tendons near the joint (Józefowicz 2003). Additional nociceptive free nerve endings are also found in the articular capsule, the synovial membrane and the collateral ligamentous structures of each joint. Moving away from the joint, beyond the Golgi tendon organs, are the muscle spindle receptors. These are located at the tendomuscular junction. Within the muscle spindle, there is a primary and a secondary receptor. The muscle spindle gives a muscle its afferent innervations, whilst the efferent innervation is supplied by the Gamma motor neurons (GMN), which attach to the same intrafusal muscle fibres as the muscle spindle. Together, the GMN and the muscle spindle comprise the Fusimotor system (Józefowicz 2003).

During muscle function, the stretching of the muscle belly activates the primary receptor within the muscle spindle. This leads to an Alpha Motor Neuron (AMN) response, which causes the same muscle to contract to prevent damage from excess stretching. This contraction in turn, removes the stretch stimulus that initially excited the primary receptor and so, the receptor stops firing, allowing the muscle to relax (Ogawa et al. 2012). This is termed the Stretch Reflex. The secondary receptors tend to discharge as the muscle is stretched toward its maximum physiologic length, but the primary receptor is more sensitive to changes in fibre length and therefore, maintain a low level of activity, even when the muscle is at rest. At the same time, the efferent side of the fusimotor system is working in a similar way. AMNs are responsible for initiating muscle contraction, but are wider in diameter than GMN and therefore, require a greater stimulus to reach their action potential than do GMN (Hunt and Ottoson 1975). This means that when a muscle is at rest, there will be few AMN firing, but some GMN constantly firing, preventing total relaxation of the muscle. This is known as the Gamma Bias. These two arms of the fusimotor system combine to create a background “noise”, which is constantly checking and correcting irregularities in movement and muscle tone (Leach 1994). As far back as 1975, Korr used this constant

muscle reflex contraction brought about by the fusimotor system, to explain how a joint fixation may occur. As a muscle contracts, the slack created at the tendomuscular junction (where the muscle spindle is) is taken up by an increase in GMN activity. This is effectively an increase in the background noise previously discussed. This level of background activity can also be adjusted by the central nervous system (CNS) to vary the performance of the muscle (Korr 1975). Leach (2004) gives the following example of this.

"An athlete swinging a bat in a wide arc will turn down the level of background noise in order to facilitate large changes in muscle length. These changes would be allowed to occur quickly and smoothly because the skeletal muscle will contract gradually due to the decreased GMN activity. Conversely, a tennis player playing at the net will turn up the background noise so that the ball is returned with the minimum of muscle activity. In this case, an increase in the GMN is employed to inhibit motion" (Leach 2004).

Certain influences can result in the muscle spindle sensitivity being set at an inappropriate level. For example, stress may cause it to be set too high, or injury may result in too low a setting. So, whilst the background level is set at low for our wide arc-type motion, a sudden removal or introduction of load on a joint, slackens the muscle spindle and thereby, silences the feedback. The CNS response to this silence is to turn up the background noise, increasing contraction in an already contracted muscle. Meanwhile, the body's effort to return the muscle and joint to its normal mechanical position is opposed by the increased contraction. This creates muscle spasm and a loss of joint function (Leach 1994).

Furthermore, according to Mense, any damaged tissue will release Bradykinin, Prostaglandin, Hydroxytryptamine and Substance P (Mense 1993). These substances all influence neurological activity by lowering the threshold at which nociceptors fire, resulting in previously sub-threshold stimuli now eliciting a pain response (Schaible et al. 2011). Release of these substances also produces oedema with a resultant localised ischemia (Mense 1991). Additionally, these substances recruit the "silent nociceptors" in the periphery, which do not respond to mechanical or thermal noxious stimuli, but respond instead only to inflammation (Schaible et al. 2011). This serves to further lower the threshold at which pain is felt, resulting in allodynia and hyperalgesia (Waters-Banker et al. 2014). This creates a self-maintaining cycle, which continues the dysfunction. The liberation of these substances, the associated oedema and the localised contraction combine

to create an area of uncontrolled metabolism that leads to a rapid depletion of the available Adenosine Triphosphate (ATP) (Better et al. 1990). ATP is required to provide the energy for resetting the muscle spindle and relaxing the muscle. Therefore, as the supply is depleted, there is a progressive failure of the muscle to relax and a subsequent decrease in the range of motion of associated joints. This continued contracture leads to further ischemia and the cycle perpetuates itself.

Manipulation is thought to restore normal background activity in three ways. Firstly, by forcefully stretching the muscle spindle, a barrage of afferent impulses are sent to the CNS, which responds by re-modulating the central nervous system to a lower level of background activity (Pickar and Bolton 2012). Secondly, the forced stretch of the muscle will stimulate the Golgi tendon organs, which in turn, will alter both AMN and GMN activity, thereby leading to muscle relaxation (Leach 1994). To give context to the third mechanism at work, a brief description of pain theory is required. The earliest theories of pain focused on the biological and pathophysiological components of pain. In the 17th century, Descartes conceptualised pain as an exclusive process within the sensory nervous system (Cohen et al. 2011; Moayedi and Davis 2013). Models such as Descartes' Cartesian Dualism, viewed the mind and body as distinct and separate entities, and allowed no place for the mind in the production of painful sensations. According to this theory, pain and pleasure are one and the same thing, distinguished only by the amplitude of the stimulus (Keller and Krames 2009). During this period, disease was understood to be purely biological in nature and all of the evidence of the time suggested that pain signals were transmitted directly to the brain from the skin, without any synapses, modulation or psychosocial interpretation. This viewpoint remained steadfast for almost two hundred years until, towards the end of the 1800s, additional theories arose, providing a deeper understanding of the body's pain mechanisms. Bell and Shaw's Specificity Theory of pain proposed that there were specific receptors uniquely equipped to respond to the different types of sensory stimulus, allowing for sensations such as temperature, light touch, pressure, and pain to be differentiated (Moayedi and Davis 2013). Accordingly, pain was thought to be felt in direct measure to the severity of injury (Melzack 1996).

These theories still failed to explain how and why the body modulated pain and why pain was different for each individual (Melzack and Wall 1967). In the 1960s, Melzack and Wall postulated a more integrative model, The Gate Control Theory of Pain (Melzack and Wall

1965). Although the mechanisms underlying this proposed theory are now known not to be the only processors of nociceptive stimuli (Millan 2002), the principles that this model proposed have been widely accepted. So profound was the impact of Melzack and Wall's paper that it was revised and reprinted two years later and has since been cited over 10,000 times (Melzack and Wall 1967).

The Gate Control Theory states that non-painful stimuli being transmitted at the same time as nociceptive stimuli, will effectively "close the gate" on the nociceptive stimuli and subsequently, no pain will be registered at the CNS level. The reason for this is that non-noxious stimuli activates interneurons, which in turn, inhibit the progress of nociceptive signals. However, we now know that in the periphery, this can be complicated further by the ability of damaged peripheral neural structures to independently produce pain, without recourse to the sensory receptors at all (Millan 1999).

The gate theory predicts that movement, rubbing, massaging and even kissing will lead to a neurological response, which causes presynaptic inhibition of dorsal root nociceptor fibres and which in turn, serves to inhibit the progress of afferent nociceptive to the CNS. In this way, the sensory fibres create a hypothetical "gate" that can open or close the system to pain stimulation. The gate can be forced open by a sufficiently large number of nociceptive action potentials or forced closed by sufficient sensory feedback. In other words, the greater the nociceptive stimulation, the less secure the gate becomes. One can see that this is a balance between the level of sensory information and the level of nociceptive information. The greater the sensory stimulus, the greater the noxious stimuli will have to be, in order to force the gate open and register pain. Following this through, helps us to understand why many patients are often in more pain over-night or first thing in the morning, when little sensory or movement stimulus has occurred, leaving the gate easily opened by a small amount of nociceptive feedback. Additionally, it is clear how manipulation can have an analgesic effect by increasing the range of motion at the site of pain and by increasing the sensory stimulus due to touch, pressure, thermal alteration, stretch and release, thereby increasing the sensory feedback, which in turn, serves to dampen the body's response to nociceptive stimuli, effectively closing the gate. Furthermore, it has been posited that higher cortical functions contribute to this gating mechanism. This allows for psychological phenomena to directly affect the subjective experience of pain.

From a clinical perspective, Gatchel suggests that the psychosocial component in the gate control theory contributes a great deal in treating patients with pain. Negative states of mind - such as helplessness, hopelessness, and anger - tend to amplify the intensity of the sensory input, while strategies focusing on coping and stress reduction help to "close" the gate. Also, behaviours found to facilitate keeping this gate "open", include poor eating habits, smoking, inadequate sleep, and lack of exercise. By promoting positive health choices, the clinician can utilise additional factors that lessen the perception of pain (Gatchel et al. 2008).

2.8.2. *Biomechanical model*

Because collagen is a viscoelastic structure, whose nature and behaviour is altered according to the loading forces applied to it (Wang et al. 2001; Shen et al. 2011), optimum tissue regeneration after injury is dependent on mechanical input during the repair process (Hooley and Cohen 1979). Without this mechanical input, the tissue will have poorer tensile strength and flexibility and the likelihood of complications such as adhesions and soft tissue malformation, are increased (Kharraz et al. 2013).

Tissue response to manual therapy varies according to the type of load applied during the therapy. Manual loading can be sub-divided into two broad categories - tension and compression. Distraction of a joint will apply a tension load to the associated soft tissue structures. Conversely, some massage techniques or joint springing techniques, apply a compression force. Taking a digit through its full range of plantarflexion would apply tension to dorsal structures and compression to plantar structures. It is crucial that we understand when the body will respond favourably to certain stresses and when those same stresses could be detrimental. For example, in the first few days after ligament damage, the new collagen arriving at the injury site forms a weak scaffolding to support the subsequent repair. Tensile loading of this fragile structure can actually cause total failure, or damage the ongoing repair, and delay healing as this still partially injured structure is only able to withstand a small portion of the stress it could cope with pre-injury (Maffulli et al. 2012; Ratcliffe et al. 2015). The importance of this scaffold structure is highlighted by the fact that the poor outcomes associated with anterior cruciate repair of the knee have been linked to the fact that this ligament is the only one in the body which does not utilise this collagen scaffolding approach to repair (Murray and Fleming 2013). However, as the collagen structure becomes increasingly dense and stable, tensile loading will help to arrange the fibres in the optimum position to promote good healing and normal function. This is because

the new collagen is laid down according to the direction of local forces (Eastwood et al. 1998; Arnoczky et al. 2002). The latter means that applying manual load to healing ligaments and tendons can be highly advantageous, leading to a stronger, more flexible repair in the long term. Also working in our favour, is the fact that the effects of manual loading during the repair process last for several days after the loading has ceased. So, despite the manual therapy lasting for only a few minutes or even seconds, its impact continues for days after the event (Fluck et al. 2000).

Amiel et al. were able to demonstrate that adhesions appear rapidly in response to immobilisation of a joint, as the new collagen is laid down in a haphazard manner due to the lack of signalling from manual stress and motion. Those cross linkages then serve to further reduce the range of motion available to the joint (Amiel et al. 1982). These linkages have been shown to break in response to manipulation, demonstrating that manipulative intervention can directly increase joint motion and joint play (Woo et al. 1975). There are a myriad of papers that demonstrate this fact time and again, at a number of different joints throughout the body. Within the neurological feedback model, we also touched on how manipulation can restore normal muscle tone and function. This clearly forms a significant arm of the biomechanical model also, but there is no need to cover the same ground again here. Pickar stated that a biomechanical shift between two joint surfaces brought about by a direct thrust technique, is thought to produce a proprioceptive overload, which alters the signalling potential of the local neural tissues (Pickar 2002). Manipulation then, can alter the sensory and motor input in such a way as to improve physiological function.

Further mechanical effects of manipulation include the direct removal of nerve compression or irritation (Rousseau 2013). Within the lower extremity, such benefits are especially useful in the treatment of conditions such as tarsal tunnel syndrome and Morton's neuroma (Brantingham et al. 1994; Cashley 2000; Govender et al. 2007; Sault et al. 2016). The biomechanical model states that manipulative intervention has the potential to restore normal joint motion and joint play, whilst simultaneously removing cross linkages. Beyond this, manipulation is also thought to produce an increased blood flow locally, which has implications for the removal of debris and the delivery of nutritional products required as part of the healing process, although this apparent increase has yet to be proven (Maigne and Vautravers 2003).

Additionally, immobility leads to a loss of the lubricating materials, both in the joint itself and within tendons and ligaments (Musumeci et al. 2014). This loss of lubrication within the soft tissues leads to abnormal cross linkage formation and poor quality and range of motion. Where tendons lack the correct mobility, their insertion points become weakened and the structure atrophies (Montgomery 1989).

2.8.3. *Dynamic fluid flow model*

The body's predominant constituents are fluids. All body systems and tissues are completely at the mercy of the dynamic flow of fluids for their vitality and health. These same body systems are also reliant on fluids to facilitate normal motion and function. Competent dynamic fluid flow is required more than ever during the healing and repair processes, which occur after insult to the body's integrity. During the repair process, the demands on the fluid flow systems, are numerous. There is an increased need for the delivery of nutrients and repair products and there is an equally great need for the removal of damaged tissue, debris and inflammatory agents from the site of trauma.

When an injury occurs, the effects can spill from the site of trauma into surrounding tissues in a "dropped paint pot" fashion. The most concentrated effects will be seen at the epicentre of the injury, but the impact will not be contained there and instead, spreading non-uniformly throughout surrounding tissues. Fluid flow structures and neurological structures are most susceptible to assault from the splatter debris of injury and are often significantly altered in function as a result. Both joint and soft tissue restrictions can then be detected, as the damage or alteration of their fluid dynamics results in the loss of glide and slide mechanics. Vascular stagnation can also occur when the fluid dynamics are altered. This leads to an increase in tension in local structures. The body's response to this increased tension and decreased glide mechanics, is to compensate by redistribution of load and pressure onto other structures and diminished use of the injured body part.

As can be easily seen in injuries such as sprained ankle ligaments, stagnation is most often initiated in the venous system. One can see how stagnation in the venous system will impede free flow in the arterial system and so, indirectly impair the healing process by decelerating the supply of nutrients. Stagnation is the result of altered fluid dynamics, which may be brought about by direct trauma to the fluid system in question, dysfunction of the neurological system leading to improper command of fluid flow, or dysfunction within the musculoskeletal system leading to a loss of muscle pump activity.

It is feasible that apparent mechanical restrictions are in fact secondary to the loss of proper fluid dynamics, resulting in diminished lubrication of glide and slide. However, such lubrication is stimulated by movement and therefore, localised manual manipulation will likely increase the levels of lubrication and help restore normal function (Lederman 2005).

2.8.4. *Combining the models*

It is important to note that these theories are not mutually exclusive, but rather each tries to explain how manipulation affects a certain segment of the body. In other words, just because we accept that on a biomechanical level, manipulation breaks collagen cross linkages and adhesions, we are not forced to reject the fact that it also has an impact on the neurological system. Indeed, it would be foolhardy to suggest that breaking cross linkages would not elicit a neurological response. Equally, if a manual intervention results in an increase of blood flow to an area, it is hard to see how this happened without some neurological involvement. So, we are required to take these separate models as incomplete explanations of what is happening in response to manipulation and instead, realise that they weave together to create a picture of a whole-body response to the stimulus created.

2.9. *Conclusion*

At this moment in time, CSI remains the conservative treatment of choice in the absence of superior outcomes elsewhere. The rationale of injecting an anti-inflammatory agent into a pathologically enlarged nerve holds some promise and it is likely that CSI will remain a realistic treatment option for MN for the foreseeable future. However, as shall become evident in Chapter three, the need for better long term conservative outcomes, remains. In the following Chapter, the current position within the literature for the interventions employed in this thesis, shall be laid out. It will contextualise the rationale for the interventions chosen and offer the reader insight as to where these interventions each stand in the current literature and why manipulation may offer some respite to the MN sufferer. The specific manipulation technique employed in this study is detailed in Chapter four, sub-section 4.11.

CHAPTER THREE

Narrative review of literature: Joint manipulation and corticosteroid injections

Aim – to give context to the decision for selecting the interventions of MAN and CSI

3.1 Introduction and general context

This chapter shall offer context to the decisions behind selecting MAN and CSI as the interventions of choice for this thesis. It shall explore their current position in the scientific literature and will shed light on why further research is required. In a recent systematic review of interventions for MN, Matthews et al. concluded "Corticosteroid injections and manipulation/mobilisation are the two interventions with the strongest evidence for pain reduction, however high-quality evidence for a gold standard intervention was not found. Although the evidence base is expanding, further high quality RCTs are needed" (Matthews, Hurn et al. 2019). Whilst most would agree with this sentiment, perhaps further high-quality research in all its guises, rather than specifically RCTs, should be encouraged. This being the case, a deeper search of the literature pertaining to these two interventions, will allow the reader insight into the current worth of conservative options for the treatment of MN.

During a pilot trawl of the literature, this thesis also found there to be an absence of high-quality evidence, as discussed by Matthews. The systematic literature review offered such formal parameters, that only a very small and ultimately only moderately informative, number of papers were unearthed.

Broadening the nature of the search led to a fuller appreciation of what evidence exists at all levels and also for the heterogeneity of study design currently being employed. This served to better facilitate decision-making and study design for this thesis.

3.2 **Corticosteroid injection – a narrative review**

CSIs to the foot and ankle have been widely used for several decades and despite support for their long-term effectiveness lacking high quality evidence, they remain the conservative treatment of choice for MN (Thomson et al. 2004).

Two studies have provided good evidence of their effectiveness for up to three months after treatment (Markovic et al. 2008; Thomson et al. 2013). Thomson et al. was a study of extremely robust design but one must exercise caution when reading their short-term results, as there was evidence within the outcomes of this paper that some pain markers were already poorer at three months, than at one month, suggesting that the benefits of steroid injection

may only be short-lived. Specifically, the VAS score and the Manchester Foot Pain and Disability Schedule (MFPDS) work/activities scores had both deteriorated at three months, whilst the MFPDS pain and walking subsets, together with the Foot Health Thermometer, were improved. This would suggest that a longer term follow-up is required in order to establish the nature of these observed changes. Conversely, Markovic et al. followed their participants for 9 months, with more favourable results following a single CSI (Markovic et al. 2008). They were able to confirm that 36% of those who had MN for less than a year, responded favourably to CSI, whilst for those suffering for more than a year, the figure fell to 13%. Furthermore, they stated that just 28% of all participants experienced complete resolution, while 31% of their study population progressed to surgery within nine months. Unfortunately, the Markovic et al. study is severely weakened by the absence of a control group against which to measure the outcomes.

A 2018 systematic review found an 81% success rate for radio-frequency ablation, 71% for alcohol injections and a 51% success rate for CSI (Valisena et al. 2018). They further reported complications in 5% of participants, although this excludes CSI injections, as the data was not available, and a recurrence rate of 14% across all injection therapies. Of these methods, currently only CSI is open to the UK podiatrist. This is a result of the current legislative position and training requirements of the podiatric profession within the UK.

In a more recent systematic review with meta-analysis, the outcomes for CSI were even poorer with just a 43% success rate (Lu et al. 2021). Somewhat puzzling is the fact that these two similar and contemporary studies identified just sixteen papers between them and yet there was crossover between the two studies of just four papers. The search criteria of Valisena et al. appeared to be broader than those used by Lu et al., by a considerable margin. They used only 5 prospective studies and no randomised controlled trials (RCTs). Conversely, Lu et al. found 4 prospective studies and two RCTs. Additionally, they searched seven data bases as compared to five. This perhaps leans more weight in favour of Lu et al.'s findings, as it is possibly a slightly more comprehensive analysis of the scant literature available.

In her systematic review (Thomson et al. 2020), Thomson cited the additional RCT by her namesake, which we referenced above. However, this RCT had a follow up of just three months and showed relatively poor outcomes (Thomson et al. 2013). Analysis within her

systematic review of the three RCTs, one comparative study and a single prospective study, highlighted the following data. The studies followed a total of 325 neuromas, with a mean follow-up of 11.3 months. Some of the studies collected VAS scores. The mean pre-VAS was 66/100 and mean post-VAS was 43/100, with a mean follow-up of 9 months. This only just surpasses the threshold of minimal meaningful clinical difference. Three of the studies reported neuroma excision post-procedure, with the overall combined rate of excision being 33%.

Mathews and Hurn (Matthews et al. 2019) state that five of the seven injection studies in their analysis delivered only one injection. They further inform "Thomas et al reports that multiple injections obtain better results, however this statement is based on low quality studies. There is no high-quality evidence for the number of injections or if multiple injections influence the effect size more than one injection." Aside from these studies, only retrospective reports and case series recommend CSI in the literature.

In a very recent systematic review (Lorenzon et al. 2022), Lorenzon et al. reviewed the literature pertaining to clinical outcomes for infiltrative therapy for MN. Their literature trawl captured all of the CSI papers that were cited in the aforementioned systematic reviews. Likely due to the scarcity of level one evidence, the authors opted to additionally include prospective and retrospective case series, as well as randomised controlled trials. Following the PRISMA guidelines, they reviewed a total of 25 papers (and 2243 MN), which satisfied their inclusion criteria, from an original trawl capturing 1086 papers from electronic databases, including PubMed; MedLine; Cochrane Library. Their search covered the dates from 1976 through to July 2021. The following search headings were applied; Morton's neuroma injection; Morton's neuroma treatment; Morton's neuroma physical therapy; Morton's neuroma alcohol; Morton's neuroma corticosteroid; Morton's neuroma hyaluronic acid; Morton's neuroma conservative. Papers not in English, or where the primary diagnosis was not MN, or where the study population was unclear, were excluded.

The quality of studies identified demonstrates the need for research, with only 6 randomised trials and just 5 having adequate blinding. A variety of injectable pharmaceuticals were employed in the various studies. 10 were CSI; 9 alcohol; 1 phenol; 1 capsaicin; 1botulinum; 1 hyaluronic acid; 2 radiofrequency ablation.

Most papers were neither randomised nor blinded, increasing the risk of bias. Of the papers examining CSI, there were a total of 674 injections administered. The incidence of improved symptomology post injection was estimated to be 58%. Combining the VAS scores that were available (6 studies), saw a pre-CSI VAS of 70 (± 15), drop to 44 (± 11). Five studies, which rated satisfaction, saw 46.7% of participants being satisfied, with reservations, or completely satisfied. Overall, 28.9% of participants progressed to surgery. In studies which present a follow-up of three years or more, CSI was found to be effective in 36% - 49%, in the long-term. Complications were considered to be a rarity and CSI was therefore, recommended as a first line treatment for MN. It was conceded that surgical intervention tends to meet with higher levels of success but is also accompanied by higher levels of risk and complication. The authors noted that post surgery rates of complete pain relief are higher than the rates of complete satisfaction, suggesting that some patients struggle with the after-effects of surgical intervention, even if the condition itself resolves.

The same search criteria used by Lorenzon et al. was repeated for this thesis. It was performed using the same databases and search terms. This new search included dates from 2021 to the present and was performed on the 17th of February 2023. A total of 84 new papers were identified. Of these, 7 were duplicates from Lorenzon et al., caused by overlapping dates in 2021. A further 40 were duplicates within the databases. That left 37 papers. Of these, 23 were commentaries, reviews or relating to conditions other than MN. The remaining 14 were 11 interventional papers and 3 systematic reviews. Of the interventional papers, 9 focused exclusively on surgical intervention and were therefore excluded. One was a mathematical modelling, cost analysis study which involved no patients and so was also excluded. 2 systematic reviews also concerned themselves exclusively with surgical outcomes and so were also excluded. That left 1 systematic review (Edwards et al. 2021) and 1 intervention study (Santiago et al. 2022).

In the one new systematic review identified, Edwards et al. explored the literature for studies employing a single CSI for MN. They drew on ten studies involving 695 participants to conclude that a single CSI appears to be beneficial in the short-to medium-term and is superior to usual conservative care. It was not clear whether CSI performed better than local anaesthetic alone and it was noted to be inferior to surgical intervention. They searched for publications from 1960 to present within the Turning Research Into Practice database; the Cochrane Central Register of Controlled Trials; the Cochrane Bone, Joint and Muscle

Trauma Group Specialised Register; MEDLINE (Ovid); PubMed; Embase; Cumulative Index to Nursing and Allied Health Literature. Study selection criteria was restricted to randomised and nonrandomised controlled trials, where a single corticosteroid injection for MN was investigated. They noted that the quality of all reviewed studies was low and at risk of bias, although they chose not to elucidate regarding the specific forms of bias they were concerned may intrude. Of the ten studies they selected for review, five compared CSI to other conservative care, one compared CSI to local anaesthetic, one examined USS versus anatomically guided CSI, and three compared CSI to surgery. Very few complications were reported in any of the studies, leading Edwards et al. to conclude that CSI is safe and efficacious when used for medium-term control of MN pain (Edwards et al. 2021).

Santiago et al. was the only new intervention study that our search revealed. They compared USS guided to anatomically guided CSI. In their study of 71 patients, 33 received an anatomically guided CSI and 38 a USS guided one. Up to four injections per participant were performed by an experienced orthopaedic surgeon and an experienced radiologist, respectively. They reported that VAS and MOxFQ scores are superior at all measurement intervals in the USS group and that patient satisfaction is also superior at 87.0% as compared to 59.1%, for anatomically guided CSI. They conclude that USS guidance offers greater long-term improvement. However, there are some short comings in this paper that should not be discounted. Firstly, the number of CSI administered, and the timing of that administration, was not standardised within the groups. Additionally, the anatomically guided CSI scores were less impressive than those of other researchers in the literature. Saygi et al. report superior outcomes at one, six, and twelve months post injection (Saygi et al. 2005), and Mahadevan et al. do so at three, six, and twelve months (Mahadevan et al. 2016). Additionally, both of these papers report a one-year follow-up score, which compares favourably to the USS scores reported by Santiago et al. Given that all of the anatomically guided CSI in Santiago et al.'s paper were performed by a single clinician, whose scores were inferior to those reported elsewhere in the literature, one must consider the potential of unconscious incompetence, and/or of researcher bias.

3.3 **Manipulation – a narrative review**

In 1656, Friar Thomas detailed a range of manipulative interventions for the extremities in his book ***"The Complete Bone Setter"*** (Pettman 2007). This was followed in 1871 by the physician Wharton Hood's publication of a paper in the Lancet, which described methods

of extremity manipulation (Hood 1871). Despite these earlier publications, the research and application of manual manipulative therapy has focussed almost exclusively on the spinal column, to the detriment of the extremities, and there is scant reference to lower extremity manipulation within the current literature. However, in 2006, Hoskins published the first extensive systematic literature review of manipulation of the lower extremity (Hoskins et al. 2006). This was subsequently expanded in 2009 by Brantingham et al (Brantingham et al. 2009) and updated again in 2012 (Brantingham et al. 2012). These three reviews searched several databases from their date of inception, finding papers from as far back as 1981 (with one isolated paper from 1906), yet their combined efforts managed to locate just 50 papers that dealt with the subject of foot and ankle manipulation (Hoskins et al. 2006; Brantingham et al. 2009; Brantingham et al. 2012). It is clear then, that MAN of the lower extremity has enjoyed poor coverage in the literature.

In this systematic review, performed on the 18th of February 2023, very few papers were identified. Searches were made of Medline through EBSCOhost; Pubmed; CINAHL. Search terms included Morton's neuroma; plantar digital neuritis; metatarsalgia; manipulation. The dates searched were from database inception to February 2023. The searches yielded a total of 21 papers. Removing duplicates reduced this to 14. Of those, 5 were removed because MN was not the primary condition being considered. This left 9 papers. In the remaining studies, there were 4 case studies. 2 related to HVLAT manipulation and were retained, whilst two were removed – 1 dealing with fascial manipulation and the other, mobilisations. Of the 7 remaining papers, there were 3 systematic reviews that explored various MAN therapies in the lower extremity, including, but not limited to, MN. A manual search of the reference lists within the above papers produced two further references. The first was "Chiropractic management of Morton's metatarsalgia (Morton's neuroma): a review of 29 patients" (Brantingham et al. 1994). Unfortunately, this paper is not available online and the journal is no longer in existence. The lead author was emailed to request a copy of the paper but, to date, no response has been forthcoming. The second paper, "Pain relief with chiropractic care in a case of Morton's interdigital neuroma: a case report" (Hinwood 1990) is again in a defunct journal and the author has unfortunately passed away. Govender et al. referenced this paper and state that although there was immediate relief from the MAN, ultimately, the patient required surgical intervention (Govender et al. 2007). The entirety of the available literature dealing directly with MAN in the treatment of MN, amounted to two case studies and a

randomised controlled trial by Govender et al. plus a clinical audit (Brantingham et al. 1991; Cashley 2000; Govender et al. 2007; Cashley and Cochrane 2015). In the only controlled trial, Govender et al. found a large treatment effect when compared to detuned ultrasound for their 40 participants (Govender et al. 2007). Interestingly, unlike this thesis, Govender et al. chose not to concentrate their efforts at the joints local to the MN. They stated "*Manipulation was then delivered to any areas of restriction found within the ankle and foot joints. The most common fixations found were decreased: frontal plane figure-8 midtarsal joint motion, metatarsal shear, plantar-to-dorsal cuboid, subtalar eversion, and long axis distraction of the talocrural joint.*". There appears to have been no manipulation routinely applied to the MTP joints. There are a number of limitations with this study, including the small sample size, potential researcher bias and potential participant expectation bias. There were also a variety of manipulative techniques coupled with mobilisation techniques used, which make interpretation of the results difficult, as the reader cannot be clear which technique, if any, is best suited to treat the condition. In an extensive literature review, Brantingham et al. found just 1 high, 9 moderate and 3 low quality studies, which examined the efficacy of foot and ankle manipulation. This led the authors to conclude that such research was in its infancy and further, higher quality studies are required (Brantingham et al. 2009). In a parallel study of metatarsalgia, Waldecker found a significant improvement in pain after manipulation in one of her study groups (Waldecker 2004). She studied two groups reporting forefoot pain at the lesser metatarsals. One group had no visible pathology, whilst the other group exhibited digital retraction deformities. Waldecker stated that "*The presence of a Morton's neuroma could be ruled out by the sonographic evaluation of the intermetatarsal interspace. Furthermore, mobilization treatment of a joint would be unable to change a morphologic structure and therefore influence the pain symptomatology of a neuroma.*". While this appears entirely logical, it falters at two hurdles. Firstly, USS is known to have a high number of false negatives in MN detection, and secondly, she makes the assumption that the pain in MN is caused by the morphologic changes to the nerve, whereas there is in fact, no evidence to support this stance. The manipulation delivered by Waldecker resulted in an immediate reduction of 87% in the pain report. She employed the same technique as is used in this thesis – a comprehensive description of which can be found within Chapter 4, at sub-section 4.11. Interestingly, she reported success in MAN where pain was not associated with any visible deformity – as would be the case with MN, but less success where digital retraction and related pathologies were also present. She was also able to report an improvement in joint

range of motion, according to her USS measurements. The passive range of motion of the lesser MTPJs was measured sonographically. The patients' ankle was placed in slight plantarflexion, with the forefoot in neutral. The probe was placed on the dorsum of the foot, lying parallel to the metatarsal in question. In this position the MTPJ, the metatarsal and the proximal phalanx are all clearly visible. The degree of available plantarflexion was calculated by measuring the angle between the longitudinal axis of the metatarsal and that of the proximal phalanx. Within three weeks, Waldecker's participants' pain had returned, but she opted to administer only a solitary bout of MAN.

A further systematic search, this time using the Proquest collection of databases, returned a further 7 papers. The search employed the following headings – "Morton's neuroma OR Morton's neuroma OR plantar digital neuritis OR metatarsalgia OR Morton's metatarsalgia OR Morton's neuralgia OR plantar digital neuralgia AND manipulation OR mobilisation OR manual therapy OR HVLAT". One paper was in German and discussed manual therapy in general terms for a number of maladies, across the entire foot (Ammer 2008). A second paper related to fascial manipulation and was a pilot study with 28 participants. At the three-month conclusion of the pilot, 19 of the 28 participants were lost to follow-up, rendering the data of little value. However, the remaining 9 patients did enjoy significant improvement in their VAS scores (Biz et al. 2021). The third paper was a report on surgical correction of hallux valgus, which mentioned metatarsalgia as a complication, but was not relevant to this thesis (Suh et al 2017). The fourth paper discusses care of the rheumatoid foot and is in Spanish. There appears to be no crossover in relevance to this thesis (Calleja et al. 2018). There was also an abstract from an oral presentation at The Australian Podiatry Conference, which discussed how population data informed the science of foot disorders (Hannan 2019). A surgical paper relating foot problems to intramedullary nailing also featured in the systematic trawl (Maqungo 2014). The final paper was the previously discussed meta-analysis by Matthews et al. (2019). Given the nature of the available literature, a meta-analysis of the current landscape is impractical.

Due to the paucity of literature in support of MAN in the treatment of MN, one is led to look beyond the forefoot for support of MAN as an intervention. A 2007 study was able to demonstrate that manipulation following an ankle sprain injury resulted in a redistribution of the foot load (López-Rodríguez et al. 2007), which correlates with the findings of Grindstaff et al., who found that manipulation of participants with chronic ankle instability resulted in improved muscle activation and neurological responses similar to those observed with cryotherapy (Grindstaff et al. 2011). These studies contrast with the findings of a study into asymptomatic ankles, which found that manipulation did not result in changes to loading (Alburquerque-Sendín et al. 2009). Drawing these studies together may allow a tentative suggestion that manipulation in the foot and ankle can affect progress toward normalisation of function.

Within the lower extremity, the ankle has received more attention than any other structure as regards manipulation. There is some distorting of the lines between manipulation and mobilisation within this literature, as some papers refer to mobilisation, but describe manipulative techniques within their methods (Cuesta-Barriuso et al. 2014), while others refer to thrust and non-thrust manipulation (Whitman et al. 2009) and still others, refer to Maitland graded mobilisations (which include manipulations at the grade 5 level), without explicitly stating which grade of mobilisation was employed (Green et al. 2001). For the purposes of this thesis, manipulation shall be considered as the delivery of a localised high velocity, low amplitude force, directed at a specific joint, resulting in joint motion beyond the current actively-available physiologic range, but within the joint's anatomical range. Mobilisations are low in velocity, but vary in amplitude. They are passive movements within the patient's range of motion and within the patient's tolerance.

Of the studies involving the ankle, a large number have reported improved range of motion (Green et al. 2001; Collins et al. 2004; Venturini et al. 2007; de Souza et al. 2008; Teixeira et al. 2013; Cuesta-Barriuso et al. 2014) and pain relief (Green et al. 2001; Cleland et al. 2013; Cuesta-Barriuso et al. 2014) as a result of manual therapy. Conversely, some studies employing mobilisation, as opposed to manipulation, have shown no change in ankle range of motion (Gilbreath et al. 2014). Interestingly, an alternative study employing the same mobilisation technique and comparing it to manipulation, found that both modalities resulted in an increase in ankle dorsiflexion range of motion (Marrón-Gómez et al. 2015). To confuse the matter still further, manipulation has also been shown to have no impact on

ankle range of motion (Beazell et al. 2012). These papers on ankle mobilisation and manipulation, possibly deliver more questions than answers. The methods by which ankle motion was measured in all papers was crude and inefficient, leaving room for other joints to compensate for the lack of ankle function and thereby, give a false impression of increased range of motion. No study successfully isolated the ankle when measuring dorsiflexion.

Although the quality of the research into manipulation of the ankle may be of a low level, there is no shortage of papers. The same cannot be said of Morton's neuroma. Aside of one controlled study (Govender et al. 2007), a mixed methods case series (Brantingham et al. 1994), a case study of two cases (Cashley 2000), a single case study (Sault et al. 2016) and a retrospective analysis of thirty-eight cases (Cashley and Cochrane 2015), there is little in the literature to recommend manipulation as a treatment for MN. However, these papers do hint at a strong benefit from manipulation. Govender et al. found a large treatment effect compared to detuned ultrasound (Govender et al. 2007) and Cashley claimed complete resolution of the two participants in his case study (Cashley 2000). The retrospective analysis showed 80% of MN sufferers recording a VAS pain score of below 10/100, at six weeks after the start of treatment (see Figure 3.1). This improvement was still evident at a one-year follow-up (Cashley and Cochrane 2015).

There are limitations within these papers, including small sample numbers, potential researcher and participant expectation bias. There were also a variety of manipulative techniques used, making it difficult to clarify which, if any, is best suited to treat MN. So, while the case for manipulation as a treatment of MN is not yet made, there is some evidence suggesting that it may be worthy of further exploration.

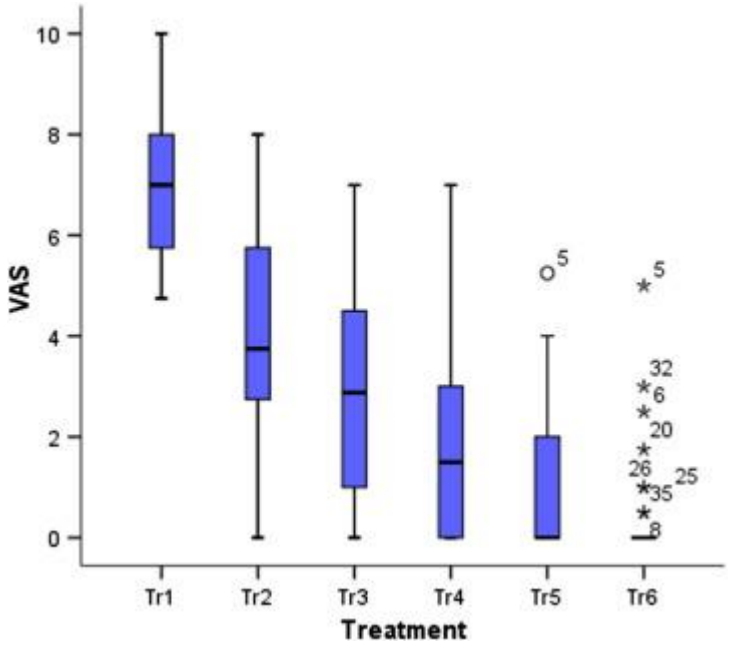

Figure 3.1. Box plot of VAS during treatment (From Cashley and Cochrane 2015).

To date, there is no empirical evidence that directly supports the employment of manipulation in the treatment of foot pathologies. Although there is growing low-level evidence by way of short case studies and a body of support for manipulation at the spinal level, justification for this intervention in the lower extremity remains with limited scientific backing. However, there are a number of studies that have postulated a theoretical basis for the mechanism of action involved in MAN, which shall be expanded in Chapter nine. When insult leads to dysfunction at a joint, the afferent input from the joint proprioceptors reports on the dysfunction and prompts a maladaptive motor response. This serves to further reinforce the dysfunctional motor control of the joint, impeding its functionality and ability to adapt to external influences. Over time, this results in disorder and disease (Haavik and Murphy 2012). This self-limiting cycle can result in chronic dysfunction and pain. The role of MAN in restoring normative proprioception and motor control has been demonstrated in upper extremity research (Haavik and Murphy 2011; Reece et al. 2022) and the same rationale is considered possible in the treatment of MN. Some weight is given to this approach by the success reported in an earlier retrospective study, which offered results on the six-week treatment approach of this thesis (Cashley and Cochrane 2015).

There is a difficulty performing controlled double-blind studies to investigate manipulation, since it is extremely challenging, if not impossible, to blind the participant regarding the intervention, but there is an onus on the employers of extremity manipulation, to find

suitable research strategies in order to determine the effectiveness of such interventions. In this case, a pragmatic, parallel study design was employed, but future studies should explore methods of more effective blinding for both researchers and participants, to enhance scientific rigour.

Within this chapter, a narrative review of the evidence for the efficacy of two candidate treatment interventions (MAN and CSI) has been considered. Previously, MAN has been tentatively explored with some positive findings, but has so far lacked robust data. This tantalising gap in the knowledge base, with strands of evidence that hint at a potentially over-looked intervention, provided the motivation for this thesis. A new platform of robust evidence must be built to explore the potential to which previous papers allude. This thesis begins that work. Given that CSI is the conservative intervention that has historically attracted the most research interest and has been shown in the literature to outperform other conservative strategies, it was an obvious candidate against which to test MAN.

The following Chapter 4 will offer a detailed consideration of general methods and factors affecting the experimental designs within the thesis, including their context and background.

CHAPTER FOUR

General methods

Aim - To critically evaluate candidate approaches and rationalise methods employed in this study.

4.1. **Introduction and general context**

This chapter will offer methods used in general throughout the thesis and provides some context for the study design. Specific methods used in chapters to address relevant aims, have been described separately within the corresponding chapters. There were a number of potential study designs that could have been employed to facilitate the aims of this thesis. For example, manipulation could have been compared to any number of other conservative interventions and thereby, have introduced a new data stream for treatments that currently have little or no data to support them. Whilst this may have been desirable from the viewpoint of widening the debate, it would have also been far more challenging to bring context to any results, without comparison to established pathways of treatment. One apparent solution to this would be to simply add a third intervention arm. Whilst this was considered at length, ultimately it would have made recruitment of sufficient participants non-viable within the timeframe available, due to the required increase in numbers. Furthermore, it would also serve to complicate the study and delivery of findings without any guarantee that the addition of other conservative methods would produce the hoped-for data.

Once a direct comparison between two groups was settled as the preferred study design, the next consideration in methodology was how to ensure that all participants had MN, rather than a masquerading disorder such as inter digital bursitis. At the outset, the intention was to USS all potential participants and include a positive USS as inclusion criteria. However, during the literature review process, it became apparent that the research currently points to clinical diagnosis as being optimal. A number of papers reported equal or greater accuracy of clinical tests versus USS, or MRI, in the detection of MN. The reader will recall a fuller discussion on the area of diagnosis in Chapter two, which covered the current research base and led to the decision to focus purely on clinical diagnosis for this thesis. Additionally, it was felt that opting not to employ radiological diagnostic criteria would result in study findings that could more readily be transferred into the clinical realm, where access to USS and MRI is rarely straightforward, or immediate. The strength of this decision is that it leads the subsequent research in a more pragmatic direction and strengthens its clinical applicability. It is however, acknowledged that this decision also serves to compromise the

robustness of study design and therefore, future, multi-centred randomised control trials will be required to further inform the healthcare community.

4.2. **Aims**

The primary aim of this study was to produce evidence for the efficacy of conservative care, specifically manipulation and CSI. Such evidence should add to the growing body of literature addressing the efficacy of conservative care in the treatment of MN. Secondary aims included assessment of the psychometric qualities of selected PROMs and assessing the relative importance of factors contributing to the outcomes relating to MN.

4.3. **Study design**

The study was a pragmatic, single centre, randomised parallel controlled study, performed at Queen Margaret University, Edinburgh. Participants were both male and female with a clinically confirmed diagnosis of Morton's Neuroma, a minimum age of 18 years old but no upper age limit, and with a washout period of at least three months for those who have previously received treatment for Morton's neuroma.

4.4. **Ethical approval**

An exploratory randomised controlled trial was registered and given research, development and ethical approval from the South-East Scotland Research Ethics Committee (IRAS 129586; REC reference 15/SS/0099 [see appendix I]) and from Queen Margaret University ethics committee. This study conformed to requirements of the Declaration of Helsinki, and the protocol was registered with the Clinical Trials.gov Protocol Registration and Results System (clinicaltrials.gov: NCT02304094).

4.5. **Study sample**

A total sample size of sixty-four was used for the main aspect of the thesis in comparing MAN to CSI. The experimental design sensitivity drives sample size, but in the case of this thesis, there is no previous work to guide a prediction as to the likely efficacy of MAN in the treatment of MN. Considering MCID scores for the primary outcome measure VAS and exploring VAS values observed at week six in a clinical audit of manipulation treatment, aided sample size calculations. Week six was chosen because that specific clinical audit reported successful outcomes on patients whose active intervention lasted six weeks (Cashley and Cochrane 2015). For the purposes of the research, clinical effectiveness of

either intervention was assessed according to changes in the VAS score. An improvement in VAS of 20 mm in either group was considered as the MCID for this study, as this minimum criterion has been identified previously as the important difference in visual analogue pain scales between treatment groups (Hughes and Carr 2002). Furthermore, and for the same reason as above, a difference of 20 mm between the groups was the minimum change required in order to establish a preferred intervention. Sample size calculations were carried out using GPower v3.1 from GPower Software. A total sample of 54 (27 in each arm) was calculated to be required to detect a relative effect size of 0.8 (Cohen's *d*) in a two-sided, independent groups test, with significance level 5% and power of 80%. Allowing for a dropout rate of 15%, 64 participants were recruited, 32 patients to each arm of the study.

In the PTT reliability chapter (Chapter 5), a study sample of 40 was used. It was not possible to pre-empt effect sizes in the reliability data and so, the sample size used was chosen to reflect the ambitions of similar reliability studies.

4.6. **Recruitment of participants**

Clinical staff from the podiatry department of NHS Lothian attended a two-hour event about this study. They were informed of the study design and especially the inclusion and exclusion criteria. The participant information leaflet was discussed at length and copies were left with the staff. Training/refreshing of the correct employment of the relevant diagnostic clinical tests was undertaken with all involved staff. They had an opportunity to ask questions of the lead researcher in order that they felt equipped to recruit participants to the study. After this, staff were asked to identify patients from their existing cohort, who may have been suited to involvement in the study. They invited patients with a clinically confirmed diagnosis of Morton's neuroma to participate in the study. A member of the patient's existing clinical care team checked whether they met the inclusion and exclusion criteria and made the initial approach to invite them to become involved. Those who expressed an interest were given written information in the form of a participant information sheet [Appendix II], which described the study fully in layman's terms. They were then invited to contact the chief investigator, should they choose to become involved.

Detailed information about the study was given by the chief investigator to each potential participant who made contact and they were then given an appointment to attend the Queen

Margaret University (QMU) gait analysis laboratory. As alluded earlier, there was a minimum three months washout period for all participants who'd previously had any treatment for Morton's neuroma.

Those who attended QMU were invited to ask questions about the study and raise any concerns that could be addressed by a researcher, who was independent from the trial. The chief investigator then assessed them against the study's inclusion and exclusion criteria to ensure suitability for involvement in the study.

4.6.1. *Inclusion criteria*

All participants had a pre-intervention screening to establish a positive clinical diagnosis of MN by means of the three clinical tests, web-space tenderness test, Mulder's click test and plantar digital nerve stretch test. These clinical tests are documented in the literature and together provide a safe positive diagnosis of MN. Additional inclusion criteria were a VAS score of 20/100 or greater and a minimum age of 18 years old.

4.6.2. *Exclusion criteria*

Exclusion criteria included previous surgical intervention for MN. Additionally, any existing condition which would prevent CSI was also considered exclusion criteria. This included: active local infection; allergy to Methylprednisolone; allergy to Lidocaine; diabetes mellitus; renal impairment; hepatic impairment; coagulation disorders; needle phobia; recent fracture of less than three months to the affected foot. Additionally, those with contraindications to manipulation were excluded from the study. These included rheumatoid arthritis; osteoporosis; cancers; prosthetic joints in the foot; fixation devices in the foot. Whilst peripheral neuropathy is not a contraindication for either intervention, it would likely so skew VAS and PTT scores and was therefore added to the exclusion criteria. Additionally, although pregnancy is not an absolute contraindication for either treatment, it was considered that the risk of CSI was not warranted, as the risk/benefit ratio could not be justified in the presence of so many other conservative treatment options. The final exclusion criterion was bilateral neuromas. MN is thought to occur bilaterally in approximately ten percent of cases and there is no reason to believe that bilateral cases will respond any differently to MAN or CSI. However, because we were using the contralateral limb for comparative PTT measurements, it was imperative that all participants had only unilateral symptomology.

4.6.3. *Ethical considerations and consent*

Written consent was obtained immediately prior to the first study intervention taking place. The participant had previously discussed the research with a member of their existing clinical care team. They had also received written information about the study from their care team. This occurred at least 24 hours prior to being invited to attend for assessment and inclusion. When the participant first attended QMU, the researcher verbally detailed the study to them again and invited them to ask questions about it. He ensured that they received and understood, the written information sheet and that they were aware of their right to withdraw from the study at any time, without having to declare a reason.

It was stressed to all participants that should they be allocated to the manipulation group then there was a small risk to them in relation to a potential delay in their recovery, if the experimental treatment failed. It was explained that they would subsequently be offered alternative treatment. This could mean a delay in receiving the appropriate conventional care. Additionally, they were informed that they could have access to the standard treatment pathway at any time, should they wish to avail themselves of it. They were then asked if they still wished to participate in the study. If they agreed, they were asked to sign a consent form [Appendix III]. The researcher then gathered further information to include age, gender, duration and location of symptoms. Participants who no longer wished to be involved in the study were invited to either return to the clinic which had initially referred them or continue to receive treatment at QMU, but out-with the study.

All participants were allocated a unique participant identification number (PIN) for the duration of the trial. All documentation within the trial used this reference number alone. Documentation linking the PIN to the personal data of the participant was generated and held by the chief investigator only. Identifiable data was stored in a secure cabinet in the podiatry staff area at QMU, to which only the chief investigator had access. All other data used in the study was link-anonymised and stored on the protected QMU server. Paper copies of questionnaires were stored in the aforementioned secure cabinet. Only the link-anonymised participant identification number was used when recording data.

Each participant was invited to remain in the study for one year to ensure adequate follow-up. Their active treatment in the study lasted for six weeks. All subsequent contact was for

follow-up only. All participants were followed up at six weeks from baseline and then at three monthly intervals thereafter. Follow-ups were a short clinic visit to review changes to their condition and to complete the VAS, PTT and PROM questionnaires.

For those participants whose condition resolved during the course of the study, there was no further need for any treatment. For those participants that did not experience complete resolution, there was a series of treatment options offered. They could either continue with their current treatment that they were receiving during the study, or cross over to receive the treatment that was on offer in the other arm of the study. Regardless of which option they chose, they did not have any further data added to the study, but continued to receive treatment. For those that did not respond to either treatment or did not wish to continue their treatment with the study team, there was an offer of referral to the QMU MSK clinic, or back to the Lothian NHS clinic from where they were originally referred.

4.6.4. *CONSORT enrolment*

The CONSORT protocol helps researchers report methodology and findings clearly, thereby facilitating reading and quality assessment of research. It also provides standards of trial design and interpretation. In other words, it is a valuable tool that enables the researcher to conduct quality research and subsequently helps clinicians to critically appraise the quality of the presented evidence.

CONSORT also encompasses a flow chart which offers information regarding how the trial was conducted. It gives an overview of participant selection and assessment; enrolment; group allocation; follow-up and analysis. It provides a broad view of how the trial was conducted. The following flow chart (Figure 4.1) shows the participants' journey through the trial and details the steps taken to successfully navigate involvement for each participant.

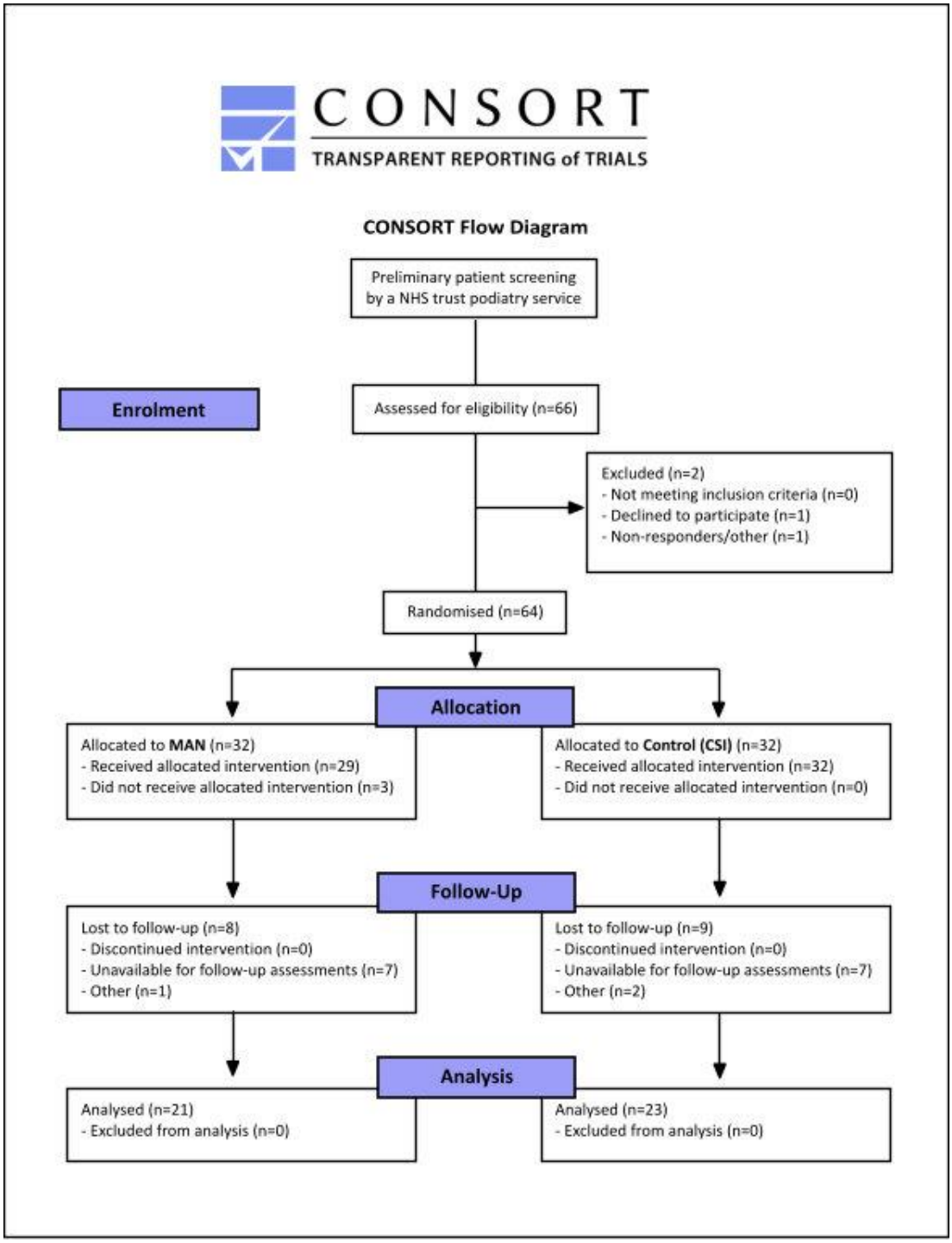

Figure 4.1: Study's flow-chart of participants within the study based on the CONSORT guidelines for longitudinal studies.

4.7. *Group allocation by minimisation*

Once participants provided written consent, their information was entered into the minimisation software for their allocation into a study group. Allocation was to two groups using minimisation, with weighted randomisation. Groups were matched for age, gender,

severity according to VAS score, and duration of symptoms. Greatest weighting was given first to VAS score, then duration of symptoms, followed by gender and finally age. This was performed using the Minim software, which is an MS-DOS program for running minimisation in clinical trials. The authors of the software have allowed its free distribution and use via York University (Evans et al. 2017).

4.8. *Study protocol*

The protocol of the study involved baseline measurement of VAS and PROMS, as well as PTT measurement of both feet. The first baseline session was also used to allow participants to familiarise themselves with the research environment, as well as the study protocol, assessment procedures and tools. This was followed by group allocation and then accordingly, the initial intervention.

Each subsequent session began with the completion of PROMS and then VAS. PTT was then used to evaluate the participants' joint loading capabilities. For the MAN group only, the intervention, VAS and PTT were repeated from weeks two to six, inclusive. At week six, then at months three, six, nine and twelve, the VAS, PTT and PROMS scores were retaken for both groups. The periodisation of review was selected to mirror previous research into MN (Thomson et al. 2013; Santiago et al. 2019; Faulkner et al. 2021; Santiago et al. 2022) and also to try and best capture the expected changes in response to CSI. The measurements were targeted to quantify performance capabilities, pain levels and every-day physical activity since the onset of treatment.

4.9. *Methods of assessment of MN*

The methods of assessment in this pragmatic study were based in clinical practice. They were selected due to their reproducibility in the clinical environment. It was considered paramount that assessment tools could be readily employed, with relevant psychometric precision, and the results rapidly interpreted in any clinical setting so that the findings of this research could be meaningfully applied. They have also been routinely employed in various studies assessing MN (Mahadevan et al. 2016; Song et al. 2019; Wenpeng et al. 2022). Methods have specifically been chosen to reflect the potential impacts of living with MN. This thesis has attempted to capture changes in the primary clinical features of pain and inability to weight-bear appropriately by the employment of VAS and PTT.

Additionally, the impact of MN on daily living, social interaction, well-being and impedance of ambulation has been explored through the use of PROMS.

4.9.1. *Visual analogue pain scale (VAS)*

The VAS can be delivered as a pen and paper scale or as a plastic slide rule, with both options showing good agreement and repeatability (Hagino et al. 1996; Woods and Cumming 2009). However, from a research point of view, pen and paper is preferable in order to ensure a paper chain of data that can be checked and rechecked. Once the plastic slide rule is reset, there can be no rechecking of measurements, increasing the potential for errors in the data. In recent years, electronic versions of the VAS for pain have been validated (Maarj et al. 2022), but at the outset of this research such innovation was in its infancy and although some electronic VAS publications were appearing in the literature, most were related to eating disorders, rather than to pain. Additionally, research has shown a statistically significant (although not clinically significant) difference between scores collected on a mobile device and those by pen and paper (Delgado et al. 2018).

The VAS for this study was conducted using pen and paper. Some authors have cited potential problems in photocopying VAS scales as the line endings may become blurred, making the line either marginally longer or shorter than the 100 mm standard (Johnson 2006; Snow and Kirwan 1988). To avoid this, the paper VAS scales for this study were all individually printed by a professional printer and 50 different printed sheets were randomly checked to ensure that the line was consistently of 100 mm. In all cases, the printing proved accurate (Appendix IV). The VAS scores in this study were all measured using the same ruler to ensure consistency.

VAS scores were collected at baseline, six weeks, then three, six, nine and twelve months. For those in the manipulation group only, additional VAS scores were collected at weeks two through to five, when they attended for their MAN intervention. For all participants, there was a total of at least six VAS scores gathered over a twelve-month period. At each visit, the participant was handed a printed pad of unmarked VAS slips and a pen and were invited to score their pain from the preceding week. No other verbal instructions were offered. The participant marked the pad and returned it to the researcher. The marked slip was removed from the pad and immediately placed in a folder for future analysis. This was repeated every time a participant attended the research centre.

VAS was measured against all of the PROMS used and also, against the pressure threshold scores obtained at the same time as the VAS score. One must exercise caution when interpreting the statistics from the VAS scores of a participant group. Depending on the method of analysis, the reader can be led to conclude that a statistically significant change was arrived at *per participant*, because such change was seen across the group as a whole. However, the potential for widely varying magnitudes of individual pain-reporting means that comparing the mean of a group, may not tell the correct story in its entirety. The question arises, was a significant change detected because there were changes seen across the entire group or because there were very large changes in a small number of participants? Perhaps a more potent statistic would be the total percentage of participants, who achieved a clinically meaningful degree of change. This would allow the clinician to ascertain the potential benefit of a given intervention for his patient group, or for an individual patient (Farrar et al. 2000).

4.9.2. *Pressure Threshold Testing*

The goal of pressure algometry (PA) is to give quantification to the individual's experience of mechanically induced pain in a reliable and repeatable fashion. The pressure threshold meter (PTM) used to provide PA scores, is a simple spring-loaded pressure device that applies increasing pressure to the structure to be tested. The patient is instructed to say stop when the pressure first turns to discomfort. The amount of pressure applied can then be read from the screen on the device. This measurement is known as the pressure/pain threshold. By measuring the score obtained at a given joint, against the neighbouring joints and the contralateral joint of the opposing limb, the clinician can determine whether the joint in question is responding to pressure loading as efficiently as its counterparts. These measurements can also be used to monitor changes over time, and so help to draw conclusions regarding treatment efficacy. At the highest end of the scale, the patient's maximum pain tolerance can be tested. When testing for the pain tolerance threshold, the participant is asked to withstand the discomfort until it becomes too painful to do so. Conversely, the pressure/pain threshold can be identified by asking the participant to say 'stop', as soon as the pressure offers the first instance of discomfort. It is this initial onset of pain (the pressure/pain threshold) that was measured in this study. It should be noted that PA is not a measurement of the patient's pain in the way that, for example, VAS is. VAS gives a quantifiable score to how the patient feels about their pain over a given period of

time – perhaps the last week, or since the last intervention. PA is used to identify areas that may exhibit pathology, even if the patient was previously unaware of any pain at that site. This is similar to a clinician using motion palpation to identify dysfunction in a given structure. The patient may not be aware of any pain in that structure until such time as it is palpated, or pressure is applied. However, it may prove to be that PA scores demonstrate a relationship to VAS scores that would allow PA to be used in place of VAS for determining changes in the patient's condition, whilst simultaneously being applied to identify the location of potential dysfunction. VAS has no power to detect the site of any dysfunction and it is this dual purpose of PA that would create an advantage in its use over VAS.

PA is widely used in the healthcare setting, but rarely in the foot. In order for the PA scores obtained from symptomatic participants to be more meaningful, it would be ideal to establish guideline scores for asymptomatic participants, which will serve as a reference tool in the clinical setting. Beyond this, it is also imperative that the clinician can be confident that the tool is reliable. Measuring the performance of the tool against the performance of another device whose reliability and validity has already been established, allowed clarification as to the reliability and validity of PA. To achieve this, the PA scores obtained were compared to VAS scores obtained at the same point in time, from the same participants.

At each intervention the participant was instructed using the following phrase. "I am going to apply some pressure to the sole of your foot using this meter. You will feel the pressure being applied. As soon as you register the first feeling of discomfort, say 'stop'." All MTP joints of the affected foot were then tested. A small spring loaded digital algometer was placed on the sole of the foot, directly on the MTP joint. The MTP joint was identified by passively, maximally dorsiflexing the digits to expose the metatarsal heads on the plantar aspect of the participant's foot. The meter was placed, directly perpendicular to the sole of the foot at all times and a measurement taken of how much pressure could be applied before the participant registered the pressure as discomfort. At this point, the measurement was considered complete. The measurement was then repeated twice more, so that three measurements of each MTP joint were obtained. Research has shown the third measurement to be the most accurate and so, this was the measurement recorded and used for analysis in this study. At baseline, measurements were taken of all lesser MTP joints of the affected foot. The lowest scoring MTP joint was then used for all subsequent

measurements. Additionally, the corresponding joint of the contralateral limb was also measured at each visit. At every visit, these joints were measured three times and the third measurement used.

Previous studies established the inter/intra-clinician reliability of pressure threshold measuring and have established a normative range of values within the trunk, spine, abdomen and upper body. Since the establishment of these values, pressure threshold testing has been used extensively in the head, neck, shoulders and spine, as a clinical tool and a research aid. There has been little work using it in the lower limb and there are no guideline measurements for the clinician. However, PTM can be employed as a clinical tool to easily and accurately identify areas of dysfunction and to objectively measure the effectiveness of treatment by comparing scores to the contralateral limb. It also allows the clinician to establish and quantify a degree of improvement or deterioration as it occurs in a patient's condition. In one of the few studies performed in the lower limb, Rolke et al. tested the nail bed of the thumb and great toe, the styloid process, the medial malleolus and the abductor halluces muscle, with three repeated measurements at intervals of 1 minute. They were able to conclude *"These data show that assessment of deep pain in distal limbs may become a useful clinical instrument similar to pressure pain testing over truncal structures, which is already well established…"* (Rolke et al. 2005). Participants in another validation study attended for three identical sessions separated by the period of at least a week. The procedure was repeated twice at each session in order to facilitate within-session and between-session reliability testing. The study concluded that both within-day and between-day reliability for normal spinal muscles was good (Potter et al. 2006). These protocols worked well and are similar to many others that have already been tried and tested. It made sense therefore, for this study to closely follow these same protocols.

4.9.3. *Patient reported outcome measures (PROMS)*

To the author's knowledge, there are no PROMS that are condition specific for MN. Having established that a generic tool was the only option, it was then essential to ensure that the tools selected would be acceptable to the participants. In selecting the appropriate PROMS, it was imperative that question duplication was minimised, but that information about symptomology and its impact, was adequately captured. Additionally, the participant should easily understand the logic and reasoning in each question. PROMS should strive to remain as straightforward as possible to minimise lost or inappropriate data, induced by complexity

of the instrument. An error was made in our methodology in this regard, as double-sided printing was used for the paper copies of the PROMS, for participants to complete. It was felt that this would make the document appear less cumbersome and therefore, the task less laborious, but it had the unintended consequence that some participants failed to spot print on the back of the document and therefore, some data was lost to capture.

At baseline, all participants were given a single copy of the PROMS immediately after enrolment in the study. They were escorted to a quiet room and invited to complete the document at their own pace, whilst alone in this space. Once they had completed the document, they were escorted to the clinical area where further baseline information was gathered, and VAS and PTT measurements taken. They were then given a second copy of the PROMS to complete, before any intervention was performed. This allowed for assessment of sensitivity of the PROMS being used.

At subsequent visits (week six, then months three, six, nine and twelve) to the research centre, participants were invited to complete a fresh set of PROMS in the quiet area before being escorted to the clinical area. In all instances, the PROMS were immediately entered into the participant's file for later analysis. The order of the PROMS in the document was consistent at all times and, with hindsight it may have been preferable to randomly adjust the order in which they were presented to the participant.

4.9.3.1. *Manchester-Oxford foot questionnaire (MOxFQ)*

The MOxFQ (appendix V) is a sixteen item PROM initially designed to assess the effectiveness of surgical interventions to the foot and ankle complex. Item content was created through collaborations with patients and validation has been inspected encompassing a range of foot and ankle conditions (Morley et al. 2013). Each item is scored in ascending severity from 0 to 4. Scores are then collated to form three distinct domains. walking/standing contains seven items, foot pain has five items, and the remain four items relate to social interaction. The three domain scores have excellent psychometric properties in terms of reliability, validity and responsiveness (Dawson et al. 2006). As a regional rating scale, the MOxFQ gathers specific information regarding disability of the foot. Conversely, it may fail to identify some elements of the global impact of foot pain. For this reason, it has been combined with the global rating scale SF-36 in this study.

4.9.3.2. *Foot and ankle ability measures (FAAM)*

The FAAM (appendix VI) specifically reports on the physical function and capabilities of those with foot and ankle dysfunction. There are two categories, which together comprise 29 items. The activities of daily living (ADL) category has 21 items and the sports category has 8 items. The sports category is specifically designed for use by athletes and was not included in this current study. The omission of this category does not impact the validity of the instrument (Martin et al. 2009).

Each item on the FAAM is scored from 0-4 or "not applicable". Those that are not applicable are excluded from all scoring calculations. Zero is the poorest rating and 4 is the optimum that participants can allocate to each item. All individual scores (Si) are now added together to create a summary score (Ss). The total number of items that were scored (N) is then multiplied by four. This gives the highest potential score (Sp) available to that participant. The participant's summary score is then divided by the highest potential score and multiplied by 100, so that it is expressed as a percentage.

$$100\left(\frac{\sum Si}{N4}\right) = FAAM\ score$$

Optimum foot health is designated a score of 100% and therefore better foot health should be expressed as a higher percentage score in FAAM. Although this may give a meaningful baseline measurement, the true value of the FAAM is in identifying change over time. Eechaute et al. were able to conclude that a change of 8 percentage points or more in the ADL category of the FAAM, could be interpreted as meaningful change in a clinical context, with a confidence level of 95% (Eechaute et al. 2007).

4.9.3.3. *Short Form-36 (SF-36)*

The SF-36 (Appendix VII) is a global rating scale questionnaire that consists of thirty-six items, combining to measure an individual's generic health status. There are eight separate categories that the participant is asked to score considering their health status in the

preceding four weeks and one which questions health status over the preceding year. Those categories are physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), mental health (MH), energy/vitality (EV), pain (P) and general health (GH). In each category, the participant can score anywhere from zero to 100, with 100 representing optimum health. The individual category scores can be combined to create a summary score. Participants completed the thirty-six multiple choice questions by selecting the printed answer that best reflected their position. The researcher answered any queries relating to ambiguous wording, but no advice was given, and no inference made as to which answer should be selected.

Incomplete questions were imputed as the mean values of the remaining items for the relevant subscales, according to the SF-36 guidelines (Rand Corporation 2022). The thirty-six items were then averaged to create the eight category scores. Scores for each of the eight categories range from 0 ‘extreme symptoms/poor health’ to 100 ‘no symptoms/perfect health’.

One key advantage of the SF-36 over other questionnaires is its global approach, avoiding the narrowness of region-specific or condition-specific questionnaires and instead, capturing a snapshot of the patient’s overall health and well-being at a given point in time. Conversely, this could also overlook information that may be gathered by a more specific questionnaire, which necessitates the employment of the FAAM and MOxFQ in this study.

4.10. **Measurement procedures**

Prior to randomisation, all participants completed their baseline set of visual analogue pain scores (VAS), algometric pressure threshold testing measurements (PTT) and their first set of PROM questionnaires. A duplicate set of PROM questionnaires were completed immediately prior to the participant receiving their first intervention. This helped to explore whether these specific PROMS measurement tools were sufficiently robust, valid and repeatable. Allowing no therapeutic intervention between 1st and 2nd PROMS recording should result in similar scores being obtained on both occasions, thereby inferring that the tools are measuring accurately.

In every case, date-stamped PROMS were completed immediately on arrival at the research location and prior to entering the clinical area and before any intervention. PROMS were used to measure the impact of foot pathology on function in terms of pain, disability and activity restriction and to facilitate systematic review with current literature. Once these were complete, the participant was invited into the clinical area, where their pain was measured using a self-reported VAS scale. Their VAS score was marked on a date-stamped pad. The ability of the involved joints of the foot to withstand pressure was then measured using PTT. Only after all measurements were complete, was any discussion or intervention entered in to.

For all participants, this meant scores recorded at baseline, six weeks, three, six nine and twelve months. Additionally, for those in the MAN group measurements were taken from weeks two through to five. PROM questionnaires were repeated after baseline at six weeks, three months, six months, nine months and twelve months by all participants. Figure 4.2 describes the primary study's experimental design and timeline for MAN and CSI interventions, with associated assessment points.

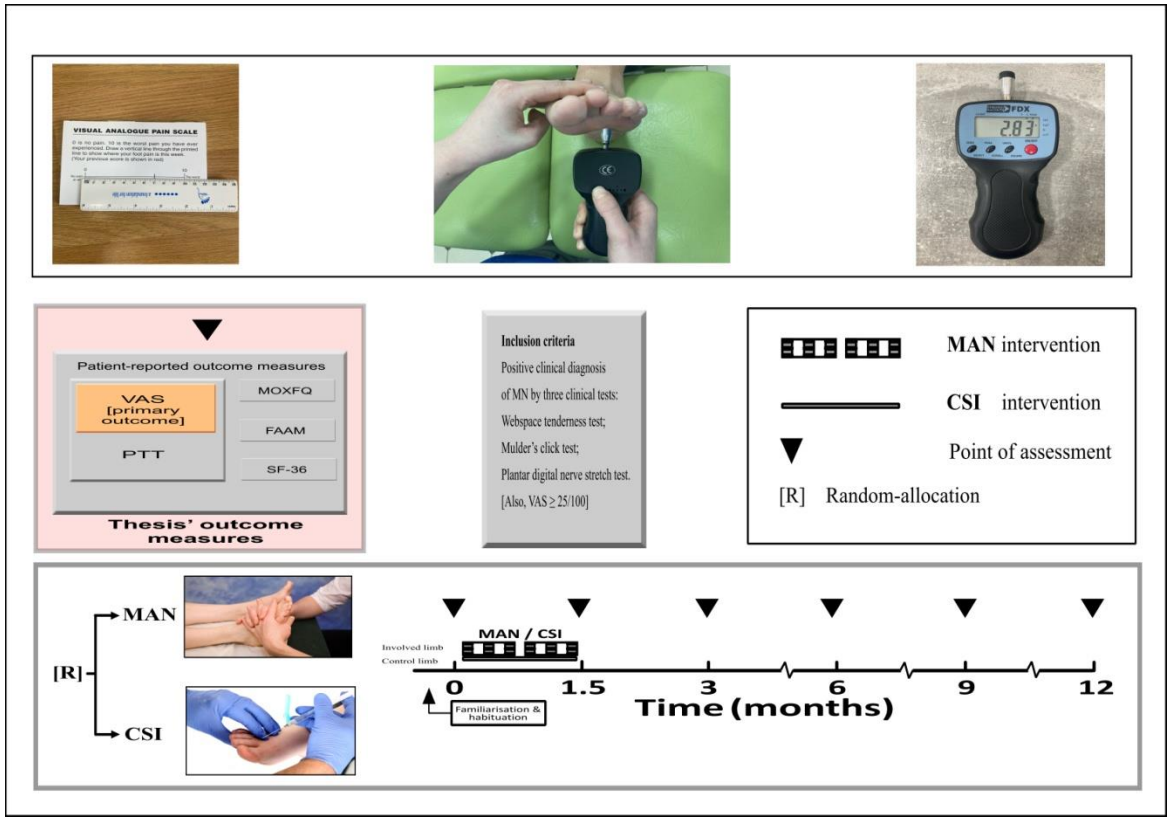

Figure 4.2: Overview of manipulation (MAN) and corticosteroid injection (CSI) intervention characteristics and experimental design. Key: R = Random-allocation to intervention conditions; Closed, inverted triangle = Assessment time-point; MN = Morton's neuroma; VAS = Visual analogue scale (pain); PTT = Pressure threshold testing for discomfort; MOxFQ = Manchester-Oxford foot questionnaire; FAAM = Foot and ankle ability measures; SF-36 = Short Form-36 (generic health status).

4.11. **MAN treatment**

There are a number of different types of manipulative intervention described in the literature. The specific method utilised in this study was a high velocity, low amplitude thrust (HVLAT) technique. The only other controlled study examining MAN and MN used a variety of MAN techniques and was not explicit in which, if any, of these interventions were HVLAT in nature (Govender et al. 2007). The only other papers exploring MAN and MN, use exclusively HVLAT manoeuvres (Cashley and Cochrane 2015; Cashley 2000). It was felt that clarity could be added to our outcomes if both the nature and location of the intervention was offered strict parameters. To that end, all of the lesser MTPJs (MTP joints 2-5) of the affected limb were manipulated at each visit from week one to week six inclusive, for the MAN group. No other manipulative interventions took place, and no further interventions were applied beyond week six. All manipulations were HVLAT in nature. This is a mechanical event employing controlled force and direction to a given joint structure, resulting in soft tissue and neural deformation. The magnitude and velocity of thrust varies significantly from practitioner to practitioner and is therefore, unlikely to be an influencing factor in treatment outcomes (Herzog 2010). Conversely, Herzog argues that thrust direction is likely consistent from one clinician to another and therefore, although this has never been scientifically investigated, is potentially a vital characteristic of treatment success (Herzog 2010).

The manoeuvre took the metatarsal into dorsiflexion and the proximal phalanx into maximal plantarflexion, and was performed by adhering to the following steps:

1. The participant is laid supine on a flat treatment table with all footwear and hosiery removed.

2. They are instructed to relax completely, ensuring that the foot drops into a natural supination and is not being held or supported through ankle dorsiflexion. The entire lower limb should be as relaxed as possible.

3. The manipulation can be performed using either hand. The clinician uses their support hand (the hand which will not perform the manipulation) to lightly hold the forefoot stable and in place on the treatment table. No movement should be permitted, but a tight grasp is not required and is counterproductive. A gentle cupping of the forefoot will suffice.

4. Using their contact hand (the hand which will perform the manipulation), the clinician contacts the plantar aspect of the MTP joint to be manipulated with the radial aspect of the proximal interphalangeal joint of the clinician's index finger. Again, this is placed lightly on the underside of the joint. There is no need for any force or tension to be applied.

5. The clinician, keeping their index finger in place, then rides their thumb up and over to rest on the dorsum of the foot.

6. The palmar surface of the proximal phalanx of the clinician's thumb should now make contact with the dorsal aspect of the participant's proximal phalanx of the digit.

7. The clinician now ensures that the participant's digit rests on the ulnar border of the thenar eminence of the clinician's palm. The digit will usually come to this position quite naturally but taking time to ensure that it rests here properly helps to ensure that there is no requirement for the clinician to grip the digit, causing the participant discomfort. Such discomfort would lead to increased joint tension, making the manipulation more difficult and more painful to perform.

8. The MTP joint is then rotated to its physiologic barrier of plantarflexion. This is achieved by ensuring that the support hand stabilises the rest of the foot effectively, whilst the wrist of the contact hand slowly increases its degree of radial derivation. At

this point, a certain resistance can be felt from the joint and the joint is termed to be 'in tension'. Ensuring that the joint is in tension helps to minimise the discomfort of the subsequent thrust since it then amounts to nothing more than a rapid nudge from this position. Without moving to the position first, the manipulative manoeuvre would be a large, long-levered movement which results in a high degree of discomfort for the participant. This should therefore be avoided at all costs.

9. Next, without allowing the joint to move out of this position of tension, a rapid rotational thrust is delivered from the clinician's index finger (employing radial derivation of the wrist) onto the plantar aspect of the joint. This drives the metatarsal further into dorsiflexion whilst simultaneously plantarflexing the digit, moving the joint beyond its physiologic barrier but remaining within the anatomical range of integrity.

The manipulation was performed in a single rapid movement, lasting less than a second.
A manipulation was considered to be completed successfully if either an audible and/or palpable 'click' was detected, or if a greater degree of joint range of motion could be palpated immediately afterward.

The clinical model for MAN therapy had been derived and adapted from pilot research work, involving a consolidation and integration of neurological feedback, biomechanical and dynamic fluid flow conceptual models (Leach 2004). There was a small risk that some participants would find the manipulation temporarily uncomfortable. They were advised of this risk in advance and informed of steps to take to reduce its impact, should it occur. This happens very rarely and was unlikely to affect the participants of the study, but they were made aware that this does occur on rare occasions. There were no reported cases of adverse effects.

4.12. **CSI treatment**

There are two standard methods of delivering steroid injections to the foot. They are ultrasound-guided and anatomy-guided. Although this is steadily changing, the vast majority of podiatrists in the UK who treat MN using CSI, are currently unlikely to have ready access to USS and therefore, will in all probability, perform anatomy-guided injections. Therefore, the pragmatic decision to follow such a model in this study was taken. All CSI were performed by the same experienced clinician and were anatomically guided.

For the participant receiving CSI, the procedure was as follows. They were taken to the minor surgery clinic at Queen Margaret University. Their medical history was rechecked to ensure there were no contraindications to methylprednisolone (Depo-Medrone) or Lidocaine. Specific enquiries were made of the participant regarding, heart, liver or kidney disease, diabetes, a history of anaphylaxis and any allergies. They were then given the written drug information sheet. Potential complications and reactions to CSI were discussed, including anaphylaxis; facial flushing; tendon weakening; fat pad atrophy; depigmentation; steroid flare; post-injection discomfort; bruising and infection. Informed verbal and written consent were then obtained from the participant.

The drug to be administered was then removed from the locked drug cabinet and signed out to the trial. The clinician then washed their hands and donned a pair of sterile surgical gloves. The pre-mixed vial of 40mg of methylprednisolone in 1 ml of 2% Lidocaine was then drawn up into a syringe and placed on a sterile instrument tray. Once the participant removed their shoe gear and hosiery, they were invited to sit on the treatment chair. The inter-digital cleft to be injected was identified, and the specific site for needle entry was marked with a skin marker. The foot was then prepared by swabbing with a Chloraprep applicator. Whilst the area was drying, the clinician changed the needle on the syringe for a fresh, sterile 23-gauge needle. The injection was then delivered via a dorsal approach, employing aseptic technique in accordance with current national and local guidelines (Reilly 2021). When the needle was removed, a small plaster was applied over the injection site.

With the injection complete, the participant was instructed to remain in the operating chair for a further fifteen minutes to ensure there were no immediate adverse effects. They then reapplied their footwear and were free to leave. There were no adverse events reported.

4.13. **Contralateral limb**

When the MTP joint of the ipsilateral limb with the lowest PTT score had been identified, the corresponding MTP joint of the contralateral limb was also measured using PTT in exactly the same way and with the same frequency as the affected foot. This offered a weak reference point. It could not be considered a control, since the MAN intervention will have a global neurological effect and likely alter pain and sensation responses on the contralateral

limb also. However, since all participants had unilateral MN, it does offer a reference point in a pain-free limb.

4.14. **Feasibility**

The main feasibility constraints were financial and time. Financial constraints prevented a multi-centred approach, and also meant limiting the intervention staff to one member. This had the positive effect of ensuring that all interventions were standardised for experience and ability, but also served to limit the widespread applicability of the findings. Time prevented recruitment of greater numbers, and also therefore, the possibility of exploring further conservative interventions.

4.15. **Statistical analysis' plan**

In order to address the aims of the four data-focused chapters (Chapters 5, 6, 7 and 8), the following statistical procedures, approaches and techniques were utilised to test whether there was sufficient evidence to retain or reject the associated null-hypotheses. In general, this thesis was exploratory in nature and as such, sought to deploy experimental parametric techniques, which offer superior power and efficiency for any given experimental design compared to other (non-parametric) approaches.

4.15.1. *Statistical analyses for Chapter 5 - Examining the intra-session and inter-day reproducibility and single measurement reliability of PTT*

The primary aim with Chapter 5 was to examine the intra-session and inter-day reproducibility and single measurement reliability of PTT amongst ipsilateral and contralateral metatarsophalangeal articulations associated with MN in adults. Secondary aims included assessing the influence of test administrator' experience on the latter psychometric characteristics and congruence between inter-day PTT and VAS scores.

As within Chapters 6, 7 and 8, the primary and secondary outcomes metrics of Chapter 5 (PTT) were described using ordinary statistical procedures (mean [±SD]). One-way repeated measures analysis of variance (ANOVA) was used to check for systematic carry-over effects (learning) effects across trials within each testing session (intra-session) and between days (inter-day). Coefficient of variation (V%) was used to assess variability of indices across the four trials for each intra-session and inter-day. The expression used to calculate V% is shown within the relevant section in Chapter 5.

Single measurement reliability for PTT associated with intra-session and inter-day trials was assessed by computing intra-class correlation coefficients (R_I) and standard error of a single measurement (SEM%) (95% confidence limits). The Spearman–Brown prediction formula was used to predict the measurement reliability that might be expected from the completion and combination of *n* number of neuromuscular tests (Winer, Brown et al. 1971) was used to compute the expected reliability of the mean of multiple measurements for PTT (please see the relevant section within Chapter 5 for computational details).

Variability (V%) associated with intra-session and inter-day assessments of PTT was compared using separate five (metatarsophalangeal joint: 1; 2; 3; 4; 5) by two (time: intra-session; inter-day) by two (test administrator experience: experienced; inexperienced) ANOVAs with repeated-measures on the former two factors. PTT scores associated with ipsilateral and contralateral limbs were assessed separately. Given that the thesis focuses on human responses within environments involving manifold sources of variability, statistical significance within Chapter 5, as within Chapters 6, 7 and 8, was accepted at $p < 0.05$, so as not to make the likelihood of retaining null-hypotheses excessive in such circumstances. The latter would incur an unwanted accompanying loss of exploratory insights that might be properly scrutinised for veracity within further research, or by others subsequently.

In this context, the studies with Chapters 5, 6 and 7 were curated to offer *a priori* experimental design sensitivity estimation offered an approximate statistical power of 0.8 for avoiding intrusion of type-II errors for a medium relative size of change (Cohen's *d*, 0.5) in the study's primary outcomes (V% and VAS, respectively). Chapter 5 required an approximate cohort' sample size of $n = 30$ (www.randomization.com), while Chapters 6 and 7, involving data from the same RCT, required an approximate sample size of $n = 20$ within each group at the study's primary endpoint (1.5 months). Estimates of medium relative sizes of change or difference had been gleaned from amongst pilot work, the contemporary literature or anticipated minimally important clinical differences.

The secondary aim of the clinimetric assessments within Chapter 5 involving congruence between inter-day PTT and VAS scores was undertaken and reported within Chapter 6. Congruence amongst patterns of intra-session and inter-day patient perceived levels of pain

(VAS [primary outcome]) and PTT scoring was examined using participants standardised (z-score) data associated with the intervention conditions (MAN and CSI; please see chapter 6) and an univariate factorial (mode [VAS; PTT] by clinical intervention [MAN; CSI]) ANOVA, with repeated measures on the former factor. *A priori* planned orthogonal difference and polynomial trend analyses characterised the expected patterns of fluctuation in patients' intra-session and inter-day VAS and PTT scoring. For the latter analyses, PTT scores across metatarsophalangeal joints were pooled.

4.15.2. *Statistical analyses for Chapters 6 and 7 - Manipulation versus Steroid Injection in the treatment of patients with Morton's neuroma: An exploratory pragmatic controlled trial focusing on VAS and PTT (Ch.6) and other PROMs reflecting functionality and health (Ch.7).*

In combination, Chapters 6 and 7 report on the insights of ipsilateral responses to MAN in order to characterise its efficacy in patients with MN. It was expected that an acute, short dosage (six, weekly episodes) of MAN would show efficacy for improving MN, yielding relevant gains in self-reported (PROMs) levels of pain, discomfort and functionality compared to usual conservative care (CSI). Additionally, the retention of effects was explored at three, six, nine and twelve months following the cessation of MAN and CSI.

Group means (±SD) and Pearson product-moment correlations described outcome scores and interrelationships. Separate factorial (group [MAN; CSI] x time [baseline; 1.5 mo; 3 mo; 6 mo; 9 mo; 12 mo]) analyses of variance (ANOVAs), with repeated measures for time, tested hypotheses relating to patient-reported levels of pain and discomfort (VAS; PTT [Ch.6]) and relating to patient-reported levels of functionality (MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS [Ch.7]), using *per protocol* analyses (SPSS Vn. 23, IBM SPSS Illinois, USA). *A priori* reverse Helmert orthogonal difference testing located anticipated time-specific effects. Any violations of assumptions underpinning the use of ANOVA were countered using Greenhouse-Geisser ($_{GG}$) adjustments. Statistical significance was accepted at $p < 0.05$. Cohen's *d* quantified relative effect size (ES).

Congruence amongst fluctuating patterns of treatment assessment metrics for self-perceived pain and discomfort (VAS; PTT [Ch.6]) and perceptions of function (Ch.6) were examined using participants standardised (z-score) data. Separate univariate factorial (group: [MAN; CSI]*assessment metric [Ch.6: VAS; PTT; Ch.7: MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS]*time [baseline; 1.5 mo; 3 mo; 6 mo; 9 mo; 12 mo]) ANOVAs, with repeated measures on the latter two factors. Temporal correspondence amongst assessment response patterns was indicated by an absence of factorial interaction.

4.15.3 *Statistical analyses for Chapter 8 - Factors in enhanced outcomes of non-surgical treatment of Morton's neuroma.*

Research within Chapter 8 offered an exploration of antecedent clinical metrics, including patients' history, and PROMs (VAS; PTT; MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS) contributing to subsequent optimum non-surgical clinical outcomes in the treatment of MN. It involved a secondary analysis of data derived from Chapters 6 and 7.

As such, a model consisting of selected factors from amongst the latter candidate variables was tested prospectively and retrospectively in relation to patients demonstrating high and low responses (as measured by patient-reported levels of pain [VAS]) to efficacious non-surgical treatments for MN. The multi-dimensional structures associated with the data prompted the use of a one-way multivariate analysis of variance (MANOVA) was employed to provide a simultaneous comparison of the latter multiple variables, in relation to their response to treatment.

Arbitrarily, it was assumed that the absence of definitive metrics for MCID, high and low threshold levels of response (VAS) to efficacious non-surgical treatments for MN corresponded to upper and lower tertiles, respectively. Consequently, participants were grouped into two categories (high and low responses) on the dependent variable VAS, according to this criterion. Multiple discriminant analysis using a stepwise approach, was used to determine which variables significantly separated high (High-R) and low response (Low-R) groups, and ultimately, whether such a model of statistical discrimination might usefully predict group' belonging. Knowledge of the latter might facilitate understanding

of triage and aspects of beneficial pre-habilitative interventions for variables that are amenable to change.

4.16. **Comments on research paradigm used within the thesis**

The thesis largely reflects a quantitative research paradigm and its philosophical assumptions (Plano-Clark and Ivankova 2016), together with accompanying ontological, epistemological and axiological challenges (Bishop 2015). While other approaches were considered, including mixed methodologies, a quantitative approach was deemed as offering suitable congruency with the ambitions for the research programme within the thesis and facilitating opportunities to learn and advance professionally. Objectivism and positivism are the philosophical foundations of the quantitative worldview (Creswell and Creswell 2017). According to the quantitative paradigm, there is a single, independent reality apart from the researcher's subjective impressions. This perspective maintains that the phenomenon being studied has no effect on the researcher and the researcher should have no effect on the thing being studied. Quantitative studies like those pursued within the thesis, have aimed to establish a numerical value for causal relationships. The quantitative method is grounded on the quantitative research paradigm, follows a deductive approach, and relies on the systematic collection and analysis of numerical data, which is evidenced in Chapters 5, 6, 7 and 8. It is primarily concerned with challenging theories and hypotheses by investigating the connections between numerical factors.

4.17. **Discussion and conclusions**

Two distinct styles of quantitative PROMs measurement were employed within this thesis. This included the unidimensional PROMs of VAS and PTT as well as the multidimensional PROMs of MOxFQ, SF-36 and FAAM. Both VAS and PTT are bidirectional scales which facilitate numerical interpretation and classification of pain (VAS) and individual joint pressure loading capabilities (PTT) by means of a single sliding scale: 0 - 100 mm in the case of VAS and 0 - 10 kg for PTT. Conversely, the questionnaire-based PROMs of MOxFQ, SF-36 and FAAM offer a greater degree of complexity in data gathering and interpretation. They are tools which offer a “best fit” approach through multiple choice questioning. Chapter six shall explore the data from VAS and PTT, whilst chapter seven will discuss the PROMs of MOxFQ, FAAM and SF-36.

Whilst every effort has been made to ensure the study methodology is as robust as possible, it is acknowledged that further, more in-depth research will be required to establish the position of MAN amongst other interventions for MN. Where the option presented itself, this thesis consistently opted for the most pragmatic methods available.

There is a difficulty performing controlled double-blind studies to investigate manipulation, since it is extremely challenging, if not impossible to blind the participant regarding the intervention, but there is an onus on the employers of extremity manipulation to find suitable research strategies in order to determine the effectiveness of such interventions. In this case, a pragmatic, parallel study design was employed but future studies should explore methods of more effectively blinding both researchers and participants to enhance scientific rigour.

CHAPTER FIVE

Single measurement reliability and reproducibility associated with indices of pressure threshold testing using algometry in adults

Aim - The assessment of the selected psychometric qualities of PROMs, specifically the reliability and reproducibility of algometry in adults. Achieved by exploring the intra-session and inter-day reproducibility and single measurement reliability of PTT amongst adults with MN.

5.1. **Introduction**

Contemporary clinical empirical research spans a continuum of demands that include the need for effective evaluation of ipsilateral and contralateral limb competence in functional capacity, performance capabilities or diagnostic signatures within a single test session, and the evaluation of treatment interventions over time. This is important in order to add rigour to the investigation of consistency of measurement and accuracy of captured change over time. Each clinical and research application (e.g. intra-session vs. inter-day) represents specific challenges in the selection of an appropriate test protocol in order to enable sufficient precision of measurement to facilitate discrimination between levels of capacity status confidently (Altman 1990; Mercer and Gleeson 2002).

As alluded to earlier within the thesis' introduction (Chapter One), optimum strategies for the diagnosis and evaluation of the effects of MN continue to command clinical and scientific debate (Thomson et al. 2004). MN is regarded as having a safe clinical diagnostic specificity (Sharp et al. 2003; Cloke and Greiss 2006; Jain and Mannan 2013; Claassen et al. 2014; Rao et al. 2014), especially when a combination of clinical tests is used to offer an

extremely accurate predictor of MN (Sharp et al. 2003; Owens et al. 2011; Pastides et al. 2012). However, relatively little has been published in regards to clinical indicators such as the plantar digital nerve stretch test, the web-space tenderness test and the lateral squeeze test, which have been routinely employed to aid the diagnosis of MN. The clinimetric characteristics of such diagnostic tests are considered elsewhere within this thesis (please see Chapter two, section 2.3).

Patient-reported outcome measures (PROMs), including those relying on intermediary physical instrumentation, may offer other important insights within innovative approaches to MN diagnosis and the evaluation of the condition's effects on sufferers' functional capacity and perceptions of pain (please see Chapter two for a critical overview and consideration of psychometric qualities of selected PROMs for assessments in MN). For example, while visual analogue scales (VAS) of patient-perceived pain have previously been deployed within research investigating the influence of acute and chronic conditions, including MN (Lee et al. 2011; Mahadevan et al. 2016; Samaila et al. 2020), the use of pressure threshold testing (PTT) to assess patients' thresholds of discomfort would represent a novel and relevant joint-specific approach for this condition.

Patient-perceived pain measured using a VAS has received scrutiny for clinimetric robustness. Using a 100 mm scale with verbal anchors (0 mm: 'no pain'; 100 mm: 'worst pain'), changes in scores between approximately 9 mm and 13 mm had been shown to constitute a minimum clinically-important difference (MCID) (Todd et al. 1996; Kelly 1998; Gallagher et al. 2001; Jensen et al. 2003), whereas a VAS score of < 5 mm can be considered as indicating no pain (Jensen et al. 2003). By contrast, although the use of PTT by means of algometry to assess patients' discomfort may offer novel alternative or adjunct information about MN, it has yet to receive clinimetric or psychometric scrutiny.

The need for discrimination of changes in levels of perceived pain or thresholds of discomfort in patients with MN may be relatively demanding of experimental design sensitivity, given that such characteristics might fluctuate by no more than ± 5 % (> 5 mm relative to 100 mm) to indicate symptom absence, symptom progression or condition' diagnosis (Gleeson and Mercer 1992). While participant numbers can be manipulated to achieve a desired level of experimental power for inter-group treatment comparisons

(Lipsey 1990), contemporary clinical practice frequently dictates the necessity for a case-study approach.

Appropriate protocol considerations include patients' accommodation and habituation to the assessment protocol and environment and then subsequently, the number of required inter- and intra-session replicates; estimates of which are calculated on the basis of the reproducibility and reliability characteristics of the performance indices of interest. Calculation of reliability based principally on intra-session measures may overestimate the available precision of measurement and fail to account fully for the biological variability inherent in between-day neuromuscular performance assessments (Gleeson and Mercer 1992; Gleeson et al. 2002).

Indices of patient perceived pain and joint-specific discomfort acquired using inventories and instrumentation such as VAS and pressure algometry, respectively, can provide markers of the limitations to functional capability and the pathophysiology associated with MN. The use of VAS is underpinned by established high levels of reliability for conditions similar to MN. For example, VAS shows high reliability when assessing acute abdominal pain (R_I = 0.99 [95% confidence limits 0.97 to 0.99]) (Gallagher et al. 2002), for knee OA (Alghadir et al. 2018; da Costa et al. 2021), for acute pain (Bijur et al. 2001), low back pain (Shafshak and Elnemr 2021), and moderate to high reliability for disabilities in patients with musculoskeletal pain (Boonstra et al. 2008; Ryan and O'Sullivan 2021). VAS is the second most commonly reported PROM in the foot and ankle literature, after the unvalidated AOFAS and it has been cited in over 300 papers, reporting on in excess of 20,000 participants (Shazadeh et al. 2019). There is a dearth of information available in the contemporary literature regarding the reproducibility and reliability characteristics of indices of PTT when used to assess thresholds of discomfort in MN across the forefoot's metatarsophalangeal articulations. Similarly, information about whether such psychometric qualities associated with PTT are influenced by the level of experience of the test's administrator is currently lacking and would facilitate informed judgement about the test's utility.

The primary aim of this study was to examine the intra-session and inter-day reproducibility and single measurement reliability of PTT amongst ipsilateral and contralateral metatarsophalangeal articulations associated with MN in adults. Secondary aims included

assessing the influence of test administrator' experience on the latter psychometric characteristics and congruence between inter-day PTT and VAS scores.

5.2. **Methods**

The methods employed in this chapter aim to explore evidence regarding the suitability of PTT for use in the foot. Furthermore, they talk to the impact of experience in PTT use on measurement outcomes.

5.2.1. *Participants*

Thirty-six adults (11 men, 25 women; [mean ± SD], age 47.4 ± 10.9 years; height 1.71 ± 0.06 m; body mass 68.9 ± 8.3 kg) gave their informed consent and participated in this single-centre cohort study. Volunteers comprised patients currently attending a podiatry clinic for routine foot care but with no declared lower limb pathology. Inclusion criteria involved patients over 18 years. Patients with a history of foot pain in the last three months, a history of gout, pseudo-gout, Morton's neuroma, metatarsalgia, a history of foot surgery, a diagnosis of any form of arthritis, diabetes mellitus, or a neurological condition were excluded. All participants were undertaking activities of daily living.

Participants were instructed to refrain from strenuous physical activity for the 24 h prior to each test in order to try and minimise any physiological impact that strenuous activity may have on the local tissues. This measure tried to ensure that, immediately prior to testing, activity levels of each participant were broadly similar in an effort to minimise physiological heterogeneity. Four participants of an original sample size of forty had been excluded from the study on the basis that they had not reached validity criteria amongst PTT scores (n = 1) or not been available for all assessment sessions (n = 3). Assessment protocols were approved by the Ethics Committee for Human Testing of Queen Margaret University, Edinburgh.

5.2.2. *Participant orientation and recording of algometric scores*

A Wagner Instruments Force Ten FPX25 digital force gauge with a circular rubber tip (1.0 cm^2) was the PTT algometer selected for use in this study (range: 0.0 kg to 13.0 kg [± 0.01 kg]). All readings were expressed as kilograms per square centimetre ($kg \cdot cm^{-2}$).

The device had been calibrated to the National Institute of Standards and Technology standards prior to the commencement of the study. It was rechecked prior to and at the conclusion of each set of measurements using a standardised 1.0 kg calibration weight applied to its tip under gravitational loading in order to ensure that its precision (± 0.3%) had been maintained. There had been a number of candidate commercially-available pressure threshold meters, with manual and digital offering similar levels of precision and sensitivity (MacDonald and Atkins 1990; Cashley 2015). Although a 1.0 cm^2 contact tip has emerged as a standard for algometry (Fischer 1987), there are arguments for different probe sizes to be considered depending on the type of tissue being tested (Finocchietti et al. 2012).

The PTT device is a simple spring-loaded measuring device that was pressed against each MTP joint in turn. The participant was instructed to say "stop" as soon as they felt the first twinge of discomfort and the corresponding pressure score recorded. The amount of pressure applied could occasionally be sufficient to cause a momentary indentation of the skin persisting for several minutes and so participants were pre-warned of this possibility. Each episode of gently increasing pressure on a MTP joint was delivered at a rate of approximately 10 $N \cdot s^{-1}$ (1.0 $kg \cdot s^{-1}$; test administrator-perceived) and sustained for a period necessary to elicit a PTT score (~ 3 s to 8 s). PTT measurements on MTP joints were separated from the next by 10 seconds. A period of approximately 60 seconds separated the cessation of ipsilateral and contralateral limb measurements. The orientation of the participant during assessments is illustrated schematically in Fig. 5.1.

5.2.3. *Experimental procedures and design*

Following habituation to procedures, participants were secured in a supine position on a clinical plinth. Ambulation to the clinic and waiting area had served as a physiological warm-up of the tissues undergoing algometry. In order to address the study's primary and secondary aims of examining intra-session and inter-day reproducibility and single measurement reliability of PTT amongst metatarsophalangeal articulations associated with MN and assessing the influence of test administrator' experience on the latter psychometric characteristics, the following procedures were undertaken.

Participants had a total of sixteen measurements taken from each metatarsophalangeal joint across both left and right limbs during two inter-day assessment sessions separated by seven days. The order in which the joints were measured was randomised using a computerised random number generator from www.randomization.com. One half of the participants had four intra-session measurements taken of each MTP joint by a clinician experienced in PTT (clinician one: > 10 years of routine clinical PTT; knowledge of relevant contemporary literature). This procedure was then immediately repeated by a clinician who was inexperienced in PTT (clinician two: no clinical PTT; naïve to relevant contemporary literature). The other half of the participants had clinician one immediate follow clinician two in PTT assessment procedures. At the second set of inter-day measurements undertaken one week later, the latter orders of PTT were exactly reversed.

All participants were able to withstand the pressure of the device being applied and none asked to withdraw from the study. Both the participant and the clinicians were blinded to the PTT scores being generated. The PTT scores were read and recorded by the test administrator against a unique trial number for each volunteer, which ensured their anonymity during subsequent processing of data.

Clinician one is a podiatrist who has been using algometric pressure threshold testing routinely for over ten years and was familiar with the literature surrounding the use of the device. Clinician two is a chiropractor who has never used the device in practice and was unfamiliar with any research relating to the use of the device. The reasoning behind using these two clinicians as test administrators was that one could be considered expert in terms of the use of the device and the location of the joints of the forefoot, whilst the second should be able to determine the correct placing of the device but would be considered a novice in its use.

Thus, PTT scores from MTP joints of both left and right limbs were obtained on two separate days. Inter-day assessment sessions were separated by seven days. Within each day of assessment, PTT scores for each MTP joint were recorded on eight separate intra-session occasions, by an experienced and a novice test administrator. Intra-session trends in PTT scores and measurement reproducibility and reliability were estimated by quantifying the performance variability associated with these eight performance scores and was averaged arithmetically over two possible occasions for intra-session audit (2 days).

Similarly, inter-day trends in absolute performance and estimates of reproducibility and reliability were obtained by quantifying differences and performance variability amongst assessment scores on separate days. A description of the experimental protocol is shown in Fig. 5.1.

The secondary aim of assessing congruence between inter-day PTT and VAS scores will be addressed within Chapter 6. Therein, fluctuations in VAS and PTT scores (as primary and secondary outcomes, respectively) in response to clinical interventions have been assessed for congruence amongst clinically relevant changes associated with MN (please see Chapter 6, section 6.4).

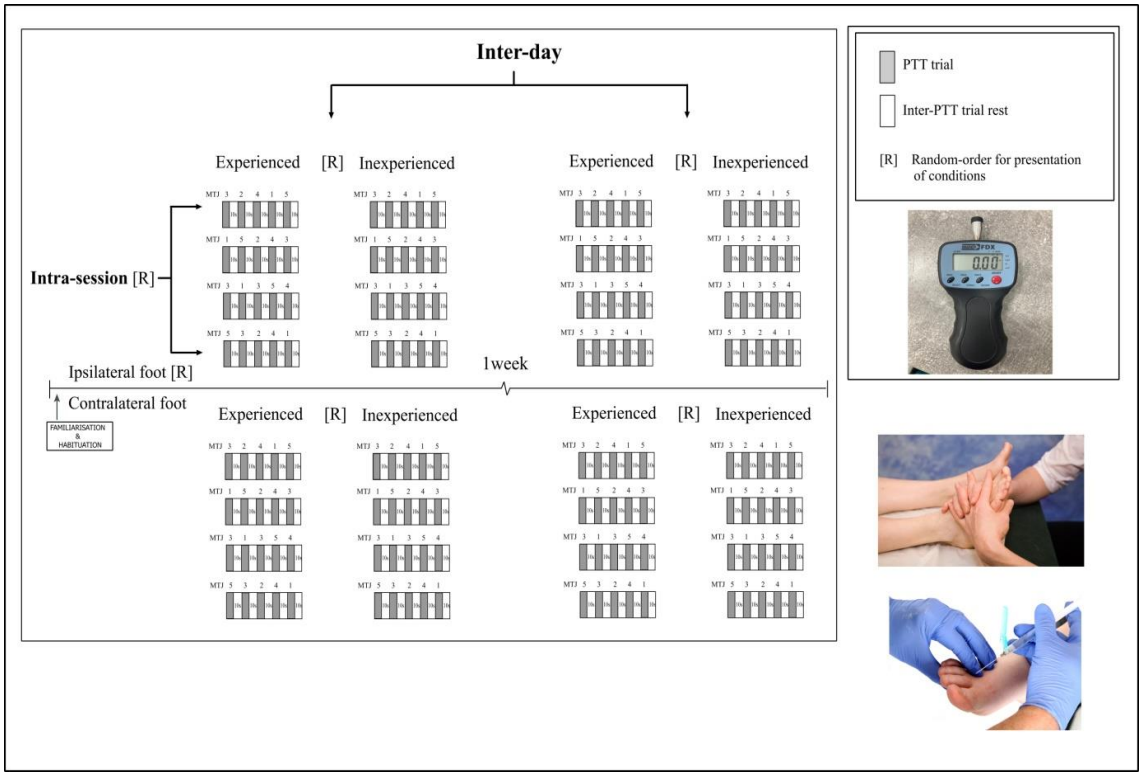

Figure 5.1. Schematic of the protocol for the assessment of intra-session and inter-day measurement reproducibility and reliability for PTT.

5.2.4. *Statistical analyses*

The PTT scores were described using ordinary statistical procedures (mean [±SD]). One-way repeated measures analysis of variance (ANOVA) was used to check for systematic learning effects across trials within each testing session (intra-session) and between days

(inter-day). Coefficient of variation (V%), corrected for small sample bias (Sokal and Rohlf 1981), was used to assess variability of indices across the four trials for each intra-session and inter-day estimate. Coefficient of variation was calculated according to the expression: $(SD \cdot mean^{-1}) \cdot (1 + (1 \cdot [4\ n]^{-1}) \cdot 100$, expressed as a percentage, where n is the number of trials.

Single measurement reliability for PTT associated with intra-session and inter-day trials was assessed by computing intra-class correlation coefficients (R_I) and standard error of a single measurement (SEM%) (95% confidence limits). The latter was expressed as a percentage of the group mean score according to the formula: $((SD \cdot \sqrt{(1 - R_I)}) \cdot mean^{-1}) \cdot 100$ (multiplied by 1.96 to compute 95% confidence limits and assuming a normal distribution of scores). The Spearman–Brown prediction formula ($r_{predicted} = n \cdot r_{current} \cdot (1 + [n - 1] \cdot r_{current})^{-1}$, where $r_{current}$ is the current reliability, $r_{predicted}$ is the predicted reliability that might be expected from the completion and combination of n number of neuromuscular tests (Winer et al. 1971) was used to compute the expected reliability of the mean of multiple measurements for PTT.

Variability (V%) associated with intra-session and inter-day assessments of PTT was compared using separate five (metatarsophalangeal joint: 1; 2; 3; 4; 5) by two (time: intra-session; inter-day) by two (test administrator experience: experienced; inexperienced) ANOVAs with repeated- measures on the former two factors. PTT scores associated with ipsilateral and contralateral limbs were assessed separately. Statistical significance was accepted at $p < 0.05$.

A priori experimental design sensitivity estimation offered an approximate statistical power of 0.8 for avoiding intrusion of type-II errors for a medium relative size of change (Cohen's *d*, 0.5) in the study's primary outcome, V%, requiring an approximate cohort' sample size of $n = 30$ (www.randomization.com).

The secondary aim of assessing congruence between inter-day PTT and VAS scores was undertaken and reported within Chapter 6. Congruence amongst patterns of intra-session and inter-day patient perceived levels of pain (VAS [primary outcome]) and PTT scoring was examined using participants' standardised (z-score) data associated with the

intervention conditions (MAN and CSI; please see chapter 6, section 6.4) and an univariate factorial (mode [VAS; PTT] by clinical intervention [MAN; CSI]) ANOVA, with repeated measures on the former factor. *A priori* planned orthogonal difference and polynomial trend analyses characterised the expected patterns of fluctuation in patients' intra-session and inter-day VAS and PTT scoring. For the latter analyses, PTT scores across metatarsophalangeal joints were pooled.

5.3. **Results**

One-way repeated measures ANOVAs revealed that intra-session systematic or learning effects had intruded, with PTT trial one at a lower threshold compared to subsequent trials ($F_{[1,11]}$ = 6.5 to 12.1, $p < 0.01$). This observation prevailed amongst comparisons of intra-session, inter-day, test administrator' experience and metatarsophalangeal joints. As such, single-measurement reliability and reproducibility of PTT was estimated using trials two to four where no systematic changes had occurred (*ns*) and amongst which, changes in performance can be attributed to random technical error and biological variation.

5.3.1. *Results of reproducibility analyses*

Absolute group mean intra-session and inter-day scores for PTT are shown in Table 5.1. Table 5.2 shows intra-session and inter-day group mean V%, R_I and SEM% values for all indices of PTT. Significant main effects within the repeated measures ANOVAs revealed greater variability of PTT across days (inter-day) by comparison to intra-session assessments ($F_{[1,34]}$ = 85.6, $p < 0.0005$) and for inexperienced compared to experienced test administrators ($F_{[1,34]}$ = 10.5, $p < 0.005$) (see Table 5.2). No differences in variability were noted between PTT scores associated with ipsilateral and contralateral limbs and amongst metatarsophalangeal joints (*ns*).

Table 5.1. Absolute group mean intra-session and inter-day scores for PTT measured by means of algometry and experienced and inexperienced assessors. Scores reflect mean data amongst metatarsophalangeal joints (1-5) and ipsilateral and contralateral feet, which had shown statistically similar scores (*ns*).

	Intra-session		Inter-day	
	Experienced	Inexperienced	Experienced	Inexperienced
PTT (kg)	5.2 ± 2.4	4.8 ± 2.1	6.4 ± 2.6	4.6 ± 1.9

5.3.2. *Results of single measurement reliability analyses*

The R_I during intra-session measures for PTT either closely approached ([range: 0.76 – 0.79] within 5 of 40 intra-session comparisons amongst metatarsophalangeal joints, intra-session and inter-day epochs, two levels of test administrator experience and ipsilateral and contralateral limbs) or had exceeded a clinically acceptable reliability coefficient threshold of greater than 0.80 (Currier 1984). Nevertheless, some group mean SEM% scores, an index of measurement reliability that compensates for potential overestimation of reliability by taking account of the group heterogeneity, indicated a limited capability to discriminate performance changes based on single-trial assessments associated with intra-group comparisons (Gleeson and Mercer 1996) (range: 9.7 ± 4.8% – 15.6 ± 7.8% [group mean SEM% ± 95% confidence limits]; see Table 2).

Table 5.2. Intra-session and inter-day group mean coefficient of variation (V%), intra-class correlation coefficient (R_I) and standard error of the measurement (SEM%) (95% confidence levels, expressed as a percentage of the mean group score) (mean ± SD) for PTT measured by means of algometry and experienced and inexperienced assessors. Scores reflect mean data amongst metatarsophalangeal joints (1-5) and ipsilateral and contralateral feet, which had shown statistically similar scores (*ns*).

	Intra-session			Inter-day		
	V%	R_I	SEM%	V%	R_I	SEM%
Experienced	6.8 ± 4.8	0.85[a]	9.5 ± 3.9	11.1 ± 6.9	0.83[b]	16.3 ± 5.6
Inexperienced	8.4 ± 5.1	0.83[c]	11.4 ± 3.2	13.6 ± 7.8	0.82[d]	15.9 ± 5.9

Note: [a] 0.67 - 0.92 [95% confidence limits]; [b] 0.59 - 0.89; [c] 0.64 - 0.96; [d] 0.59 - 0.89.

5.4. **Discussion**

5.4.1. *Precision of measurement associated with intra-session estimates of performance*

The group mean intra-session variability of PTT associated with the ipsilateral and contralateral feet in the present study (V%: 6.8% and 8.4% for experienced and inexperienced test administrators, respectively) is similar to previously reported coefficients of variation of VAS indices of perceived pain associated with MN-affected feet (V%: 7.9%). Group mean inter-day variability of PTT (V%: 11.1% and 13.6% for experienced and inexperienced test administrators, respectively) exceeded the latter estimates and suggested compromised precision amongst serial measurements of PTT over extended periods of time. It was interesting to note that the patterns of difference in PTT variability shown amongst the varied conditions of intra-session, inter-day and test administrator experience were maintained between ipsilateral and contralateral limbs and amongst metatarsophalangeal joints. For example, the latter suggested that an experienced PTT test administrator might conduct intra-session contralateral limb comparisons for any affected metatarsophalangeal joint with known levels of measurement precision.

An important contributing factor to the greater measurement variability observed under either inter-day compared to intra-session conditions or delivery of testing by inexperienced versus experienced administrators may include relatively different proportional contributions of random technical error to overall error variability. Within the latter

scenarios for assessment, either longer duration between serial measurements (i.e. minutes versus days within intra-session and inter-day comparisons, respectively) or subtly greater fluctuations within influential factors of the testing procedures associated with inexperienced administrators (e.g. algometry loading rates amongst metatarsophalangeal joints) might present greater opportunities for inflated overall error variability to affect measurement variability adversely.

Similarly, relatively different proportional contributions of random technical error to overall error variability may differentially affect PTT measurements undertaken *in extremis* of MN symptoms, such as in low and high levels of algometry loading associated with obvious and subtle prognostic indications. For example, the random error associated with the electrical noise of the algometer (noted previously as < ± 3.0% of 1.0 kg loading, 95% confidence limits) contributes to an error variance of 3.0% at relatively low levels of loading compared to 0.3% at higher levels of physiologically-relevant loading; i.e. ± 0.03 kg as a percentage of 1.0 kg and 10.0 kg, respectively (group mean intra-session data [Table 5.1]). Thus, even if random biological variability associated with both assessment conditions were to remain equivalent, the coupled effects of both technical and biological variability would inevitably provoke the increased overall V% scores in conditions of relatively low levels of algometry loading. The latter would be associated with detection of minimum clinically-important differences during the quantification of symptoms of MN using PTT.

PTT measured under conditions of an intra-session assessment by an experienced algometer is associated with superior measurement reproducibility compared to other scenarios considered within this study. The latter scenarios for algometry in particular demonstrate a compromised capability to discriminate subtle changes in discomfort' thresholds during intra-individual comparisons, with V% scores of up to ± 8.4%. Calculation of 95% confidence limits (Thomas et al. 2015), revealed an overall error of at best, ± 13.6% for PTT when based on a single estimate of threshold and measured under the favourable conditions described previously. At worst, under unfavourable conditions, error for PTT might be elevated to ± 27.2%. Very few intra-individual comparisons within a particular test session might be expected to demonstrate threshold differences that would be so large as to confidently exceed such high levels of measurement error of 54.4% (± 27.2%). These results would challenge the utility of single-trial protocols for the assessment of intra-individual

PTT differences and the efficacy of diagnosing MN pathology when utilising the asymptomatic contralateral forefoot as a comparison. Using a criterion associated with an expectation that the estimated error of the mean score of an independent sample of multiple intra-individual replicates would vary inversely with the square root of the number of trials (Winer et al. 1971), in some circumstances the mean score of as many as 15 intra-individual replicates or more would be required to achieve an arbitrarily acceptable level of measurement precision of better than ± 10% within intra-session assessments (*c.f.* 14 mm of a 100 mm VAS identified as a MCID for VAS whilst the patient acceptable symptom state (PASS score) is the score below which patients consider themselves well. Early research into PASS for VAS set this threshold at 30 mm of 100 mm (Tashjian et al. 2009) but more recent work places it at 25mm (Menendez et al. 2022) Caution should be exercised when extrapolating these findings for MN because no work has as yet taken place specifically for foot pain). The equivalent threshold number of trials to achieve a level of measurement precision of better than ± 10% for inter-day PTT assessments is 20 (see Fig. 5.2). Despite the R_I scores approaching or exceeding a clinically acceptable reliability coefficient of greater than 0.80 (Currier 1984), SEM% results indicate a limited capability to discriminate differences in thresholds of discomfort based on the achievement of an intra-group average separation between scores of 10 % of the group mean score. This is the case for all conditions in which PTT has been measured within this study.

In scenarios involving inter-group treatment comparisons, where participant numbers can be manipulated to achieve a desired level of experimental power (Lipsey 1990), single-trial threshold assessments may be acceptable. However, identification of subpopulations within a group to which limited clinical or scientific resources can be effectively targeted would require a much higher level of measurement precision. This would only currently be afforded by using a mean score of multiple trials as the basis for estimating PTT in order to reduce measurement error (Mercer and Gleeson 2002). The Spearman–Brown prophecy formula used in conjunction with the calculation of SEM%, suggests that PTT offers some practical utility in its capability to discriminate properly between individuals within a group, requiring the mean scores of 10 intra-individual trials to detect differences in threshold scores of better than ± 10%.

5.4.2. *Precision of measurement associated with inter-day estimates of performance*

All indices of performance were associated with significantly greater variability (V%) during inter-day compared to intra-session assessments. Discrimination of an individual's PTT change of ± 10% can be achieved on the basis of 5 trials acquired within the same test session (95% confidence limits), whereas > 15 trials (Winer et al. 1971), respectively are required to achieve this equivalent level of measurement precision during inter-day performance comparisons (see Fig. 5.2.).

The SEM% scores, which ranged between 9.5% ± 3.9% and 16.3% ± 5.6% (95% confidence limits) showed a limited capability to discriminate PTT differences based on single-trial assessments and an average separation between scores of ± 10%. It is predicted that the mean of > 10 inter-day trials would be required to achieve a level of measurement precision better than ± 10%.

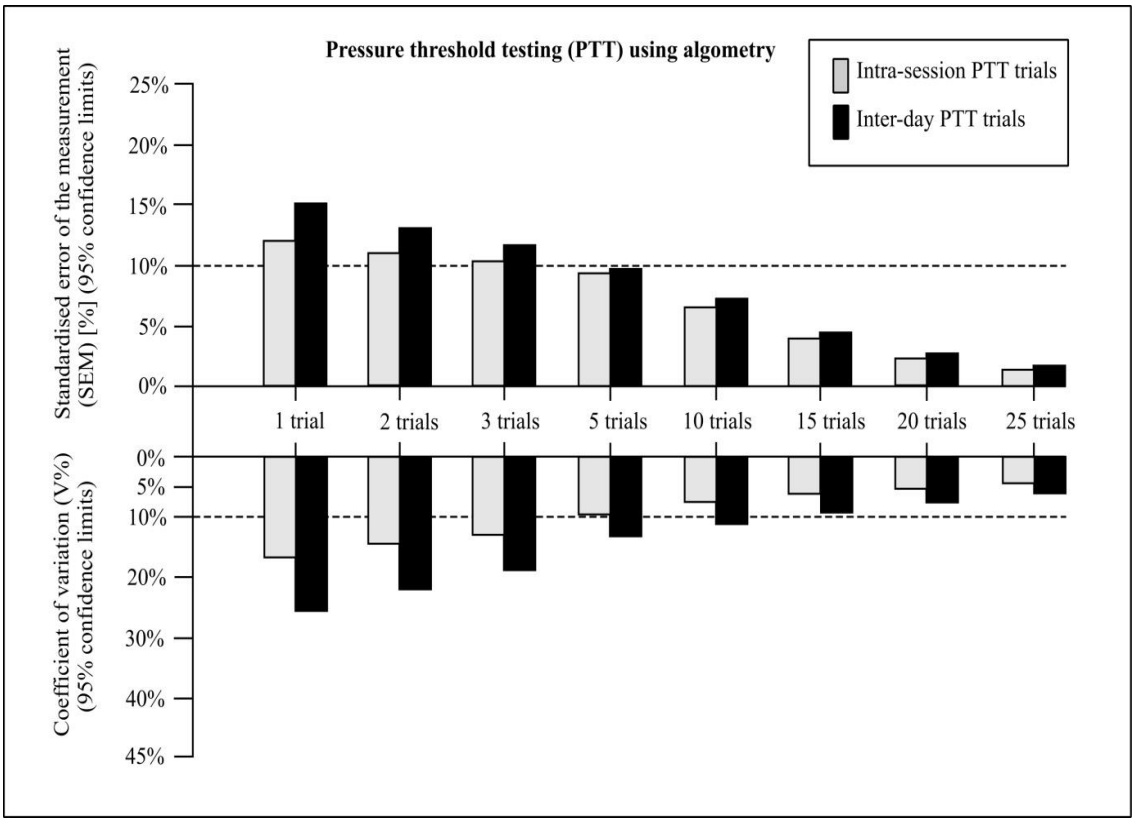

Figure 5.2. Error associated with the intra-session (open bars) and inter-day (closed bars) assessment of PTT using 1 to 25 intra-session trials: coefficient of variation (V% [95% confidence limits]) and standard error of the measurement (SEM% [95% confidence limits]).

5.4.3. *Implications for research and clinical practice*

In general, comparisons of the modes of delivery for PTT show that algometry offered statistically at least as good if not better equivalent levels of measurement reproducibility compared to other traditional methods of assessment such as VAS and inventories of function, during intra-session and inter-day assessments. As such, the current data lends support to the assessment of MN by means of algometry. There are clear and inherent advantages associated with using algometry in the assessment of thresholds of discomfort over the use of traditional methods, particularly on occasions where information is required about an individual's specific metatarsophalangeal joint or the latter's affected by intra-articular effusion as studies have shown good reliability in PTT measurements comparing right and left sides in homologous body sites (Fischer 1987; Prushansky et al. 2004). However, the efficacy of measurements associated with this technology must be further evaluated by researchers and clinicians, particularly when algometry assessments might be undertaken as a diagnostic tool by administrators of varying experience and over different assessment epochs, such as those reflecting measurements within single or serial clinical appointments. For example, it may be wholly appropriate to demand very high levels of measurement precision (perhaps better than 5% error) to confidently discriminate important changes in thresholds of discomfort amongst subtle prognostic and sub-clinical markers of dysfunction in patient populations. As many as 15 trials or more may be required to achieve this level of precision to distinguish changes in an individual's PTT scores. Unless the intended research involves a group-design, these within-participant kinanthropometric issues must be an overriding concern for investigators designing effective assessment protocols.

Some of these challenges to the utility of this technique may be overcome by an experimental protocol that has been designed to permit the clinician investigator to accrue the required number of estimates of PTT over time. This might be particularly relevant given the relative ease by which multiple trials can be obtained during algometry. For example, several assessment sessions for PTT could be conducted within any given testing day to facilitate measurement precision and to enable the accurate discrimination of subtle differences within an individual's joint-specific tolerance to discomfort. Furthermore, flexibility in the amount of error to be tolerated would have the effect of reducing the number of repeat trials required by a considerable margin (see Fig. 5.2).

5.4.4. *Conclusions*

Intra-session systematic or learning effects are likely to intrude within any PTT assessment and as such, the first trial should be excluded from analyses and considered to represent habituation or accommodation to test procedures.

Greater measurement variability of PTT was noted across days (inter-day) by comparison to intra-session assessments. Similarly, PTT undertaken by inexperienced compared to experienced test administrators of algometry provoked greater measurement variability. No differences in measurement variability were noted between PTT scores associated with ipsilateral and contralateral limbs and amongst metatarsophalangeal joints.

Although single measurement reliability of PTT amongst ipsilateral and contralateral metatarsophalangeal articulations scores approached or exceeded clinically acceptable reliability criteria, intra-session and inter-day reproducibility, which exceeded ± 15% (95% confidence limits) indicate a limited capability to discriminate differences in thresholds of discomfort based on a single PTT.

CHAPTER SIX

An exploratory pragmatic controlled trial of the efficacy of manipulation versus steroid injection in the treatment of patients with Morton's neuroma assessed using VAS and PTT

Aim - To assess the efficacy of MAN versus CSI using VAS and PTT and to explore congruence between inter-day PTT and VAS.

6.1. **Introduction**

Optimum treatment strategies for plantar digital neuralgia, otherwise known as Morton's neuroma (MN), a prevalent compressive neuropathy (87 in 100,000; Latinovic et al. 2006) still commands clinical debate. Legacy qualms about the limited evidential basis for treatment efficacy prevail (Thomson et al. 2004). Simple case series and a small number of controlled trials demonstrate the value of surgical intervention (Ciapryna et al. 2012; Åkermark et al. 2013) and emergent literature explores injection therapy (Thomson et al. 2020). However, an evidential void remains regarding non-invasive care, with only extracorporeal shockwave therapy realising controlled trials (Seok et al. 2016).

Non-surgical treatments proposed for MN include massage (Pérez-Domínguez and Casaña-Granell 2020), orthotics and footwear modification (de Oliveira et al. 2019), exercises (Pérez-Domínguez and Casaña-Granell 2020), corticosteroid injections (CSI) (Santiago et al. 2019) and manipulation (Cashley and Cochrane 2015). The two latter treatments offer the greatest meta-analytical evidence for efficacy, with CSI benefitting from the largest body of evidence but inferior clinical benefits (Matthews et al. 2019). According to a robustly designed study, CSI efficacy endures for several months but with diminishing benefit compared to that at one month, as measured by pain visual analogue scale (VAS) and Manchester Oxford Foot Pain and Disability Schedule (MFPDS) work/activities scores (Thomson et al. 2013). The limitations of CSI are emphasised by reports that 21% to 47% of CSI-treated patients require surgery within one year (Rasmussen et al. 1996; Markovic et al. 2008; Thomson et al. 2013; Rao et al. 2014). Despite this, CSI remains widely employed and promoted in the clinical setting (Thomson et al. 2020).

Biomechanical aetiologies have been implicated in the development of neuromas, with irritation from shearing stress of the plantar digital nerve due to disordered relative stiffness of the 3rd and 4th rays and the comparative mobility of the 1st and 5th tarsometatarsal joints provoking increased third interdigital cleft occurrence (Danesi et al. 2012). An unfavourable interaction amongst the relatively increased mobility of the 4th ray around its articulation with the cuboid compared to the 3rd ray's articulation with the lateral cuneiform, in a tight-packed central aspect of the midtarsal may exacerbate the latter effects.

As such, manipulative therapy's (MAN) rationale is both intuitively and pragmatically appealing because targeted enhancements to functional mobility and tissue stiffness should lead to patients experiencing better and more physiologically-sustained treatment outcomes. Research exploring the neurological response to manipulation has demonstrated that the force generated results in a temporary arrest of local gamma motoneuron firing, thereby producing a relaxation of the soft tissues and an immediate increased freedom of motion of the manipulated joint (Pickar and Wheeler 2001). Nevertheless, evidence regarding the effectiveness of MAN is limited to a small case study (Cashley 2000), a clinical audit (Cashley and Cochrane 2015), and one controlled trial that reported a large treatment effect, albeit with limitations including small sample size, potential expectation bias and heterogeneity amongst MAN techniques potentially masking optimal effect and responses (Govender et al. 2007). Given that there is a very small body of work, much of which is by a single author, who is also the author of this thesis, caution should be exercised in the interpretation of the available information.

Notwithstanding the challenges of testing for MN, in which combined clinical tests, such as Lateral Squeeze (Sharp et al. 2003) and Digital Nerve Stretch tests (Cloke and Greiss 2006; Pastides et al. 2012) offer increased precision than combined radiological assessments of MRI and ultrasound (Sharp et al. 2003; Pastideset al. 2012; Owens et al. 2011; Mahadevan et al. 2015), a re-envisioning to contemporary practices for treatment might consider a retreat from the current prescribing of CSI towards MAN, with the intention of increasing the density of stimuli for beneficial neuromuscular adaptation. Lund et al have demonstrated these neural imbalances between the excitatory and inhibitory influences over muscle activation around painful tendons in the lower extremity that result in or from an apparently protective adaptation (Lund et al. 1991). Rio et al have expanded on this theory relating to recurrent musculoskeletal pain (Rio et al. 2016). Because of this, we envisage that manipulation will yield improved efficacy and effectiveness whilst delivering cost-utility benefits at the same time as being well tolerated by patients.

Given the apparent limitations of CSI prescriptions to elicit prolonged mitigation of self-reported pain and impaired functionality in MN, promoting treatment involving targeted neurological and biomechanical manipulations of relevant joints, characterised by single high-velocity thrusts taking a joint beyond the physiological barrier into the

paraphysiological space, may be crucial to promoting enhanced functional mobility and tissue compliance, leading to more enduring treatment benefits for patients (Cashley and Cochrane 2015).

This chapter reports on the insights of ipsilateral responses to MAN in order to characterise its efficacy in patients with MN. Our hypothesis was that an acute, short dosage (6, weekly episodes) of physiologically-principled MAN, featuring 'single, high-velocity supra-physiological barrier thrusting manoeuvres' (as described in chapter 4.11) would show efficacy for improving MN, yielding relevant gains in self-reported levels of pain, discomfort and functionality compared to usual conservative care (CSI). Additionally, the retention of effects was explored at 3, 6, 9 and 12 months following the cessation of MAN and CSI.

6.2. **Methods**

The methods employed in this chapter aim to explore evidence regarding the efficacy of conservative care for MN, and to facilitate the assessment of the psychometric qualities of specific PROMs.

6.2.1. *Study design and participants*

This represented a primary analyses of data elicited from patients with MN (n = 61) and described fully in Chapter Four (General methods). In summary, sixty-one patients with MN (please see Table 6.1) gave their informed consent and participated in this UK single-centre clinical pragmatic, exploratory randomised controlled trial. The trial was registered (clinicaltrial.gov: NCT02304094), and given research, development and ethical approval by the South East Scotland Research Ethics Committee 01 (IRAS 129586; REC reference 15/SS/0099).

In brief, the initial screening of patients was undertaken within the podiatry department of NHS Lothian and then again at the research centre by the clinician having oversight (DC). Inclusion criteria involved patients over 18 years, with clinically confirmed MN (positive Lateral Squeeze and Digital Nerve Stretch tests, with pain VAS score of > 25/100). Patients recording previous surgical intervention for MN, active local infection, rheumatoid arthritis, recent fracture to the affected foot, peripheral neuropathy, pregnancy, allergy to methylprednisolone or lidocaine, diabetes mellitus, ulcerative colitis, diverticulitis,

hypothyroidism, osteoporosis, renal or hepatic impairment, coagulation disorders, needle phobia, or undergoing treatment for diseases other than MN, were excluded. A 'wash-out' period of three months was used to isolate the effects of any antecedent treatment for MN.

Patients gave written informed consent prior to baseline assessment. Allocation was to one of two groups using minimisation with weighted randomisation; groups matched for age, gender, severity, and duration of symptoms. This was performed using the Minim software from the University of York.

Table 6.1: Participant characteristics at baseline

Characteristic	**All** (n = 61)	**MAN** (n = 29)	**Control** (CSI; n = 32)†
Age (years)	53.6 ±15.1	53.9 ±16.9	53.4 ±13.3
Gender (female [male])	47 [14]	23 [6]	24 [8]
Duration of pain (weeks)	199.8 ±219.8	258.9 ±251.0	147.0 ±168.4
Foot affected (right [left])	22 [39]	13 [16]	9 [23]
Cleft affected ('2'; '3'; '4')	25; 35; 1	14; 15; 0	11; 20; 1
Pain severity (VAS, mm)	65.6 ±18.9	68.9 ±18.1	62.6 ±19.3

Note: † No significant differences noted amongst characteristics (MAN *vs*. CSI: $\chi^2_{[1]} = 0.01$ to 1.8; *ns*, and $F_{[1,59]} = 0.016$ to 1.9; *ns*, for categorical and continuous variables, respectively).

The MAN group (n = 29) underwent experimental intervention to the ipsilateral foot, receiving six focal manipulation sessions delivered (one session·week^{-1}) during a six week period, with clinical oversight (DC). The CSI group (n = 32) followed contemporary practice. Primary and secondary outcome measures were recorded at baseline, one and a half months (immediately after completion of all MAN and in keeping with contemporary initial review following CSI interventions) and then during follow-up at three months, six months, nine months and at one year.

6.2.2. *Manipulative therapy (MAN)*

Manipulation of the lesser metatarsophalangeal joints was performed weekly for six weeks. The procedure was a high velocity, low amplitude thrust technique taking the metatarsal into dorsiflexion and the proximal phalanx into maximal plantarflexion. This was achieved by contacting the plantar aspect of the joint to be manipulated with the radial aspect of the proximal interphalangeal joint of the clinician's index finger whilst simultaneously contacting the dorsal aspect of the proximal phalanx of the digit with the palmar surface of the distal phalanx of the clinician's thumb. The participant's digit now rests on the medial border of the thenar eminence of the clinician's palm. The metatarsophalangeal joint was then rotated to its physiologic barrier of plantarflexion. Next, a rapid rotational thrust drove the metatarsal into dorsiflexion whilst further plantarflexing the digit, moving the joint beyond its physiologic barrier but remaining within the anatomical range of integrity. The manipulation was performed in a single movement. The clinical model for MAN therapy had been derived and adapted from pilot research work involving a consolidation and integration of neurological feedback and biomechanical conceptual models. There were no reported adverse effects.

6.2.3. *Pharmacological therapy (CSI)*

Participants from the CSI group received an anatomically guided injection of pre-mixed depo-medrone and lidocaine (40 mg in 1.0 ml) directly to the interdigital site of the MN via a dorsal approach employing aseptic technique. There were no adverse events reported.

6.2.4. *Patient-reported indices of pain and discomfort thresholds*.

The primary outcome measure was the visual analogue scale (VAS) for pain (*100 mm*), which offers robust sensitivity to changes in pain perception (Ferreira-Valente et al. 2011). The scoring was marked by asking the participant to bisect a horizontal line at the point between verbal anchor markers of "no pain" *(0 mm)* and "worst pain" *(100 mm)* that best correlates to the self-perceived level of pain. Secondary outcomes included pressure threshold testing (PTT) using a compact digital algometer (Wagner Instruments FPX *25*, Greenwich, CT, USA) and examining the ability of the involved joints to comfortably withstand directly applied pressure.

PTT has been used previously in the discrimination of myofascial pain syndromes (Park et al. 2011) and diagnostically for fibromyalgia (Wolfe et al. 1990), but not yet routinely in MN. The recorded score corresponded to the point at which the participant had been required to say 'stop' when the progressively increasing pressure produced by the simple spring-loaded device on the structure being tested, first turned to discomfort. The clinimetric and psychometric utility of PTT has been evaluated critically within Chapter Five.

6.2.5. *Statistical analysis*

Group means (±SD) and Pearson product-moment correlations described outcome scores and interrelationships. Separate factorial (group [MAN; CSI] x time [baseline; 1.5 months; 3 months; 6 months; 9 months; 12 months]) analyses of variance (ANOVAs), with repeated measures for time, tested hypotheses relating to in patient-reported levels of pain and discomfort (VAS; PTT) using *per protocol* analyses (SPSS Vn. 23, IBM SPSS Illinois, USA). *A priori* reverse Helmert orthogonal difference testing located anticipated time-specific effects. Any violations of assumptions underpinning the use of ANOVA were countered using Greenhouse-Geisser ($_{GG}$) adjustments. Statistical significance was accepted at $p < 0.05$. Cohen's *d* quantified relative effect size (ES). *A priori* experimental design sensitivity estimation offered an approximate statistical power of 0.8 for avoiding intrusion of type-II errors for a medium relative effect size (Cohen's *d* , 0.5) in the study's primary outcome, VAS, and at its end-point (1.5 months), requiring an approximate sample size of $n = 20$ within each group.

Congruence amongst fluctuating patterns of treatment assessment metrics for self-perceived pain and discomfort (VAS; PTT) and perceptions of function were examined using participants standardised (z-score) data. Separate univariate factorial (group: [MAN; CSI]*assessment metric [VAS; PTT]*time [baseline; 1.5 months; 3 months; 6 months; 9 months; 12 months]) ANOVAs, with repeated measures on the latter two factors. Temporal correspondence amongst assessment response patterns was indicated by an absence of factorial interaction.

6.3. **Results**

Sixty-one participants from sixty-four candidates participated. Statistical analyses were undertaken on data from at least 44 participants who completed the study protocol (see chapter four section 4.6.4 "CONSORT enrolment"). Participants' characteristics at baseline are shown in Table 6.1. The latter were not correlated with the study's outcome metrics and variations merely contributed random error to the study's findings. The study's primary outcome metric of patient-reported severity of pain (VAS) showed no relationship at baseline with pressure threshold for discomfort perceptions (PTT) perceptions of functional capacity (r = - 0·12; *ns*), with each outcome capable of contributing information independently within the study. There was no significant differences at baseline between the study's outcome metrics for participants lost-to-follow-up and those completing all assessments ($F_{(1,57)}$ = 0·6 to 1.7; *ns*) suggesting minimal intrusion of attrition bias.

6.3.1. *Patient-reported levels of pain (VAS) and thresholds of discomfort (PTT)*

Figure 6.1 shows the group mean pain responses over time as self-reported using VAS (Figure 6.1 [a]). Additionally, it details the corresponding ability of the MTPJ local to the MN to withstand pressure without pain, as reported by PTT (Figure 6.1 [b]). As is evident, the MAN group demonstrates immediate and sustained improvement which betters that of the CSI group. Factorial interactions showed group mean ipsilateral patient-reported pain (VAS [$F_{(5,265)}$ = 12·4; p < 0·0005]) and pressure threshold testing (PTT [$F_{(5,285)}$ = 17·4; p < 0·0005]) were significantly improved immediately following MAN, but to a lesser extent following CSI (Figures 6.1[a] and 6.1[b)], respectively). Performance improvements between baseline and immediately after MAN (VAS [MAN: Cohen's *d*, 3·3; 84·4%; CSI: Cohen's *d*, 1·0; 38·6%; $F_{(1,53}$ = 27·8; p < 0·0005, *a priori* difference contrast]; PTT [MAN: *d*, 2·3; 147·0%; CSI: Cohen's *d*, 0·9; 45·9%; $F_{(1,57)}$ = 33·9; p < 0·0005]) were prominent, favoured MAN, and contributed most to overall ANOVA interactions. The latter treatment improvements were retained substantively at 12 months after MAN's cessation (VAS [MAN: Cohen's *d*, 3·4; 83·6%; PTT [MAN: *d*, 2·0; 152·3%), but not for CSI (VAS [Control: Cohen's *d*, 0·6; 21·9%; $F_{(1,53)}$ = 12·8; p < 0·001]; PTT [CSI: Cohen's d, 0·2; 7·1%; $F_{(1,57)}$ = 8·2; p < 0·01]).

The trend demonstrated in the VAS score of the MAN group leans toward a stability which is not evident in the CSI group, suggesting that the long-term benefits enjoyed by the MAN group may prevail for a longer period of time. VAS and PTT scores enjoy an inverse relationship as the joint appears to be able to comfortably withstand greater applied pressure as the pain report diminishes. Once again there is a trend in the data which shows the PTT of the CSI group peaking at the three month point and then steadily decreasing over time whilst the MAN group demonstrates no such slippage. For CSI, this steady decline in VAS (and PTT) is consistent with much (Lizano-Díez et al. 2017; Markovic et al. 2008), although not all (Saygi et al. 2005) reports in the literature. This new data suggests that MAN may prove to enjoy more profound and stable outcomes than CSI, with its beneficial impact enduring.

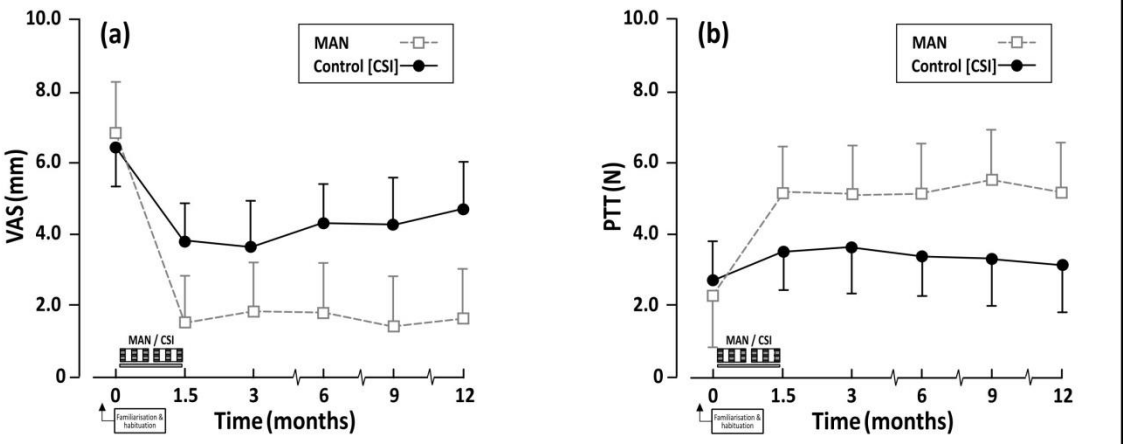

Figure 6.1: Group mean perceptions (±SD; MAN, n = 21; Control, n = 23) of the severity of pain (VAS; primary outcome [a]) and pressure threshold testing (PTT; [b]) assessed in the ipsilateral foot in response to manual (MAN) and corticosteroid injection (CSI) therapies for MN and shown at baseline [0 months], immediately after therapy [1.5 months] and at subsequent follow-up assessments [3, 6, 9 and 12 months].

6.3.2. *Asymptomatic status and patterns of recovery*

Intra-study point prevalence (% of group) for the achievement of asymptomatic status (VAS < 10/100 mm) amongst patients in response to MAN and CSI therapies for MN favoured MAN immediately after therapy [1.5 months: MAN, 62%; CSI, 7%] and at all subsequent follow-up assessments (3 [MAN, 57%; CSI, 18%], 6 [MAN, 61%%; CSI, 8%], 9 [MAN, 62%; CSI, 9%] and 12 [MAN, 59%; CSI, 10%] months) (Figure 6.2; $\chi^2_{[1]} = 6{\cdot}1$ to $21{\cdot}5$; $p < 0{\cdot}05$ to $p < 0{\cdot}0005$, respectively). This gives an indication that there is benefit for the

individual as well as for the MAN group. Since clinical outcomes are relevant at the individual level rather than the group level, these data lend weight to the clinical applicability of MAN over CSI in both the short term (57% - 62% of MAN versus 7% -18% of CSI pain-free) and the long term (59% of MAN versus 10% of CSI pain-free).

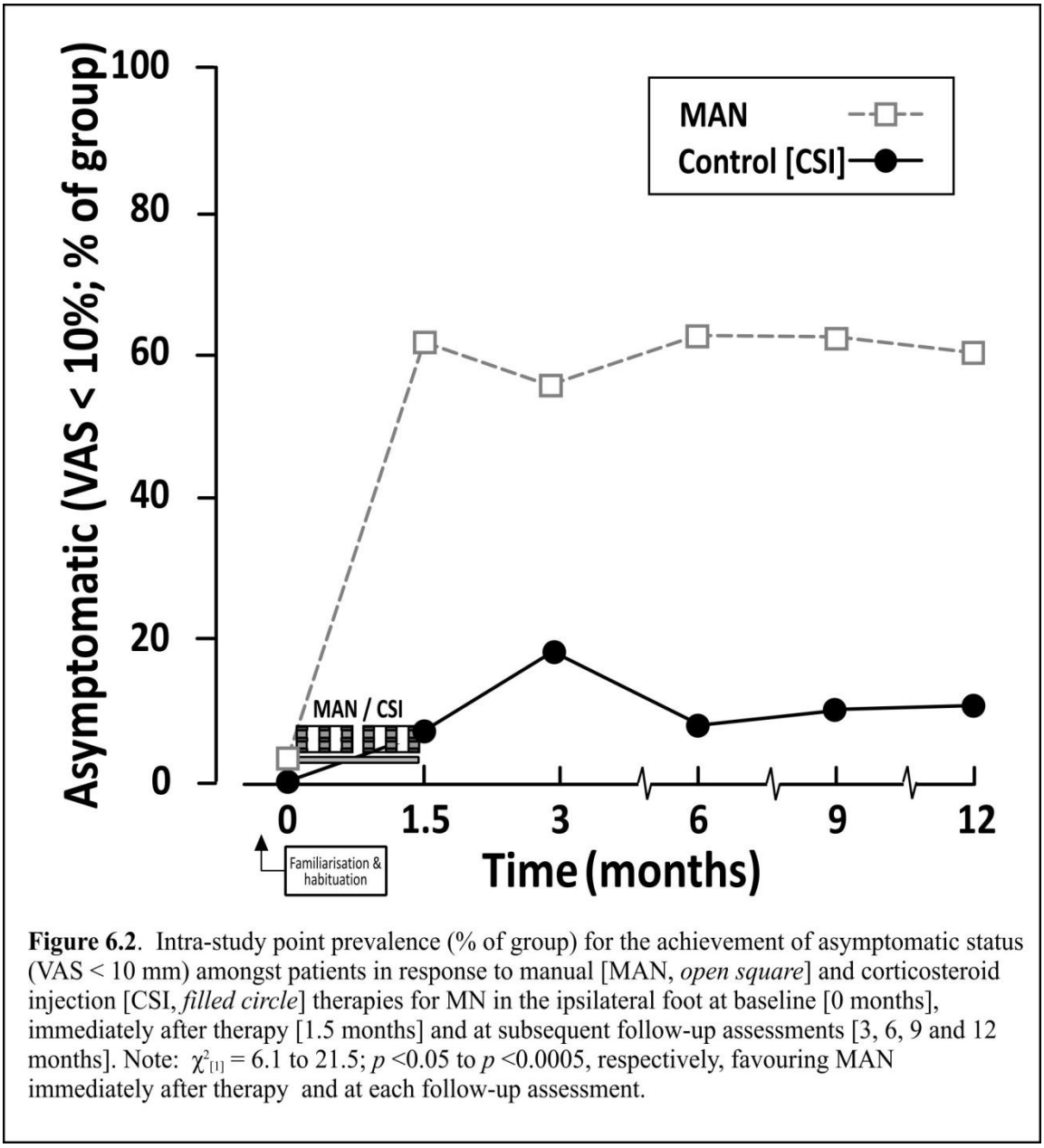

Figure 6.2. Intra-study point prevalence (% of group) for the achievement of asymptomatic status (VAS < 10 mm) amongst patients in response to manual [MAN, *open square*] and corticosteroid injection [CSI, *filled circle*] therapies for MN in the ipsilateral foot at baseline [0 months], immediately after therapy [1.5 months] and at subsequent follow-up assessments [3, 6, 9 and 12 months]. Note: $\chi^2_{[1]} = 6.1$ to 21.5; $p < 0.05$ to $p < 0.0005$, respectively, favouring MAN immediately after therapy and at each follow-up assessment.

6.4. **Discussion**

This study of manipulative therapy for MN showed the protocol's efficacy for improving a primary outcome of patient-reported severity of pain and secondary outcomes of pressure threshold for discomfort and perceptions of functional capacity. There were substantial gains elicited by MAN immediately after intervention (VAS [Cohen's *d*, 3·3; 84·4%]; PTT

[*d*, 2·3; 147·0%]). Concomitant gains for participants acting as controls were modest (*d*, 0·4 to 1·0; 16·6% to 45·9%) and reflected responses elicited by contemporary practice involving corticosteroid injections.

Optimum dose-response characteristics for MAN await scrutiny, but this formulation involving an acute, short dosage (6, weekly episodes) of physiologically principled treatment provoked immediate responses exceeding statistical, precision and reliability criteria for the selected outcome metrics (VAS; PTT; ~ 4% - 10% [95 % confidence limits]) and appears to offer important clinical relevance in counteracting symptoms of MN.

MAN's capability for improving independent facets relating to MN (no significant relationship between outcome metrics) could be deployed usefully as a strategic alternative to contemporary treatment or serve as a specific non-invasive augmentation. It was notable that the immediate gains for all MAN participants exceeded a minimum clinically important difference (MCID) criterion for VAS (10 mm; estimated from likely minimum detectable change scores, with definitive evidence lacking, but realistically might ease upwards towards 20 mm to reflect contemporary clinical practice [also, please see Chapter 2]) and the performance changes of many control participants (Figure 6.3). Retention of improvement in the perception of pain following MAN's cessation (VAS [Cohen's *d*, 3·4; 83·6%, *proportion of gain as a percentage*) was substantial, significantly better than baseline scores and consistently exceeded those for CSI ($p < 0{\cdot}001$).

Recovery to asymptomatic status (VAS < 10mm/100 mm; point prevalence; % of group) in response to MAN and CSI similarly favoured MAN immediately after therapy (62% vs. 7%, respectively) and at each follow-up assessment (57% to 62% vs. 8% to 18%, respectively; $p < 0{\cdot}05$ to $p < 0{\cdot}0005$; Figure 6.2). Acknowledging the pragmatic nature of this thesis, a greater number of participants from the MAN group reporting being asymptomatic may likely translate into the clinical setting, leading to increased numbers of MN sufferers enjoying better outcomes and a subsequent reduction in onward referral to surgical colleagues.

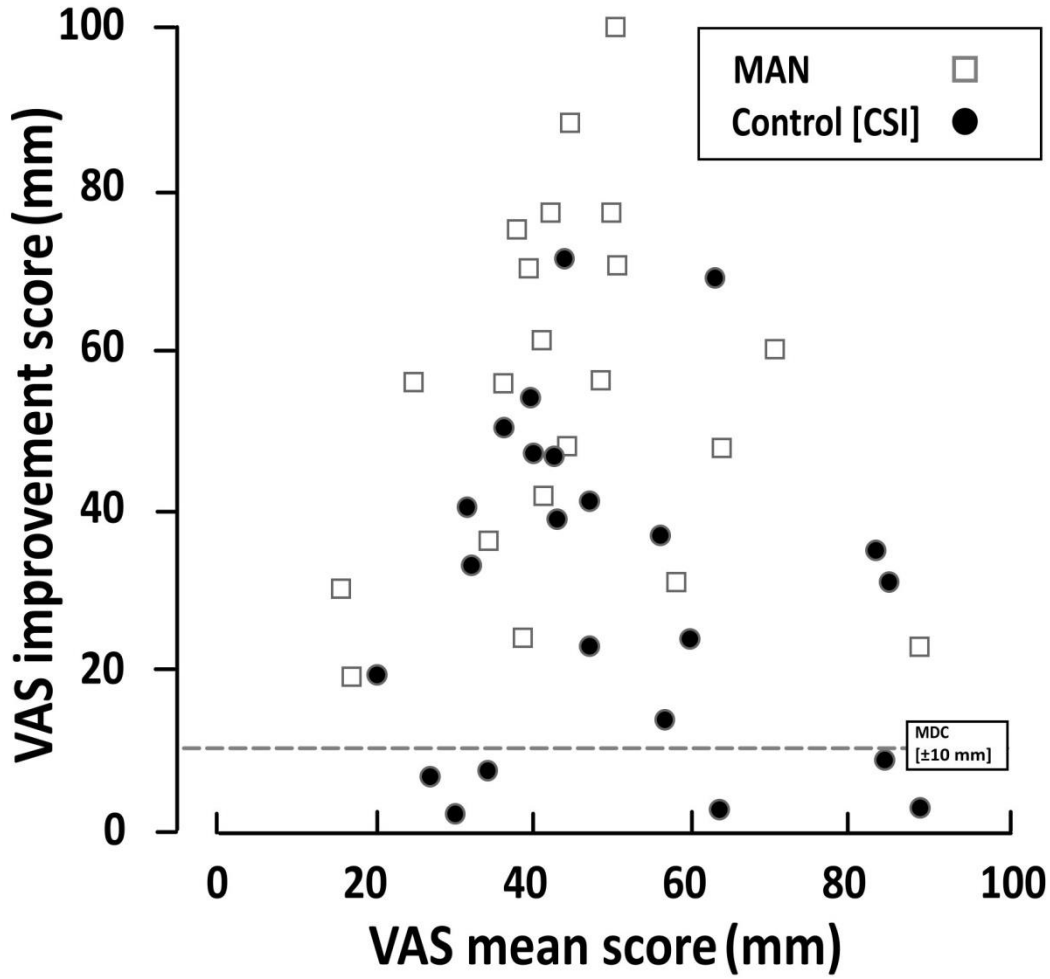

Figure 6.3: Patients' individual perceived improvement scores (±SD; MAN, n = 21; Control, n = 23) of the severity of pain (VAS; primary outcome) assessed in the ipsilateral foot in response to manual (MAN) and corticosteroid injection (CSI) therapies for MN. Results are shown from baseline to the end of MAN/CSI (absolute reduction in the severity of pain [vertical axis: mm] plotted relative to the corresponding mean score associated with baseline and 1.5-month assessments [horizontal axis: mm]). Asymptomatic criteria (< 10 mm of maximum VAS [100 mm]) was used as a proxy for minimum clinically important difference (MCID) and is superimposed for comparison.

Overall, targeted manipulations (Cashley and Cochrane 2015) such as those used in this thesis appear capable of counteracting specific patho-neuromechanical aspects within aetiologies for MN (Danesi et al. 2012; Lund et al. 1991; Rio et al. 2016) and of sustaining substantive beneficial changes for at least 12 months. By contrast, recovery trajectories for CSI were consistent with reports of CSI's efficacy lasting only months (Thomson et al. 2013; Lizano-Díez et al. 2017), with subsequent surgery required by many (Markovic et al. 2008; Thomson et al. 2013; Rao et al. 2014). Importantly, the absence of correlation

between pain duration (circa 200 weeks; Table 6.1) and VAS, suggests that the efficacy of MAN might prevail usefully for acute and chronic MN.

One of the research questions posed within Chapter 5, as a secondary aim, involved assessing congruence between inter-day PTT and VAS scores (as primary and secondary outcomes, respectively) as a notional indicator of PTT's psychometric concurrent validity. The patterns of response of both indices to clinical interventions for MN were assessed for congruence. Figure 6.4 shows the patterns of fluctuation over time amongst group mean intra-study period standardised scores for indices of perceived severity of pain (VAS [thesis' primary outcome]) and patient-reported threshold of discomfort to pressure (PTT) associated with the ipsilateral foot in response to manual (MAN) and corticosteroid injection (CSI) therapies for MN. Despite some aspects the anticipated time-related inverse congruence of responses between PTT and VAS (due to their respective systems of scoring), with the latter's responses to MAN typically showing the largest response excursions, significant outcome (PTT; VAS) by time (baseline to 12 months) by treatment (MAN; CSI) interaction remained ($F_{[5,265]} = 11.1$; $p < 0.0005$) and suggesting that concurrent validity between PTT and VAS may not be assured (Figure 6.4). Furthermore, there had been no statistically significant relationship at baseline between PTT and VAS (Pearson product-moment correlation, [*r*], *ns*), which suggested that each outcome measure would have been assessing a different physiological response to MN, and which tended to corroborate the latter interpretation.

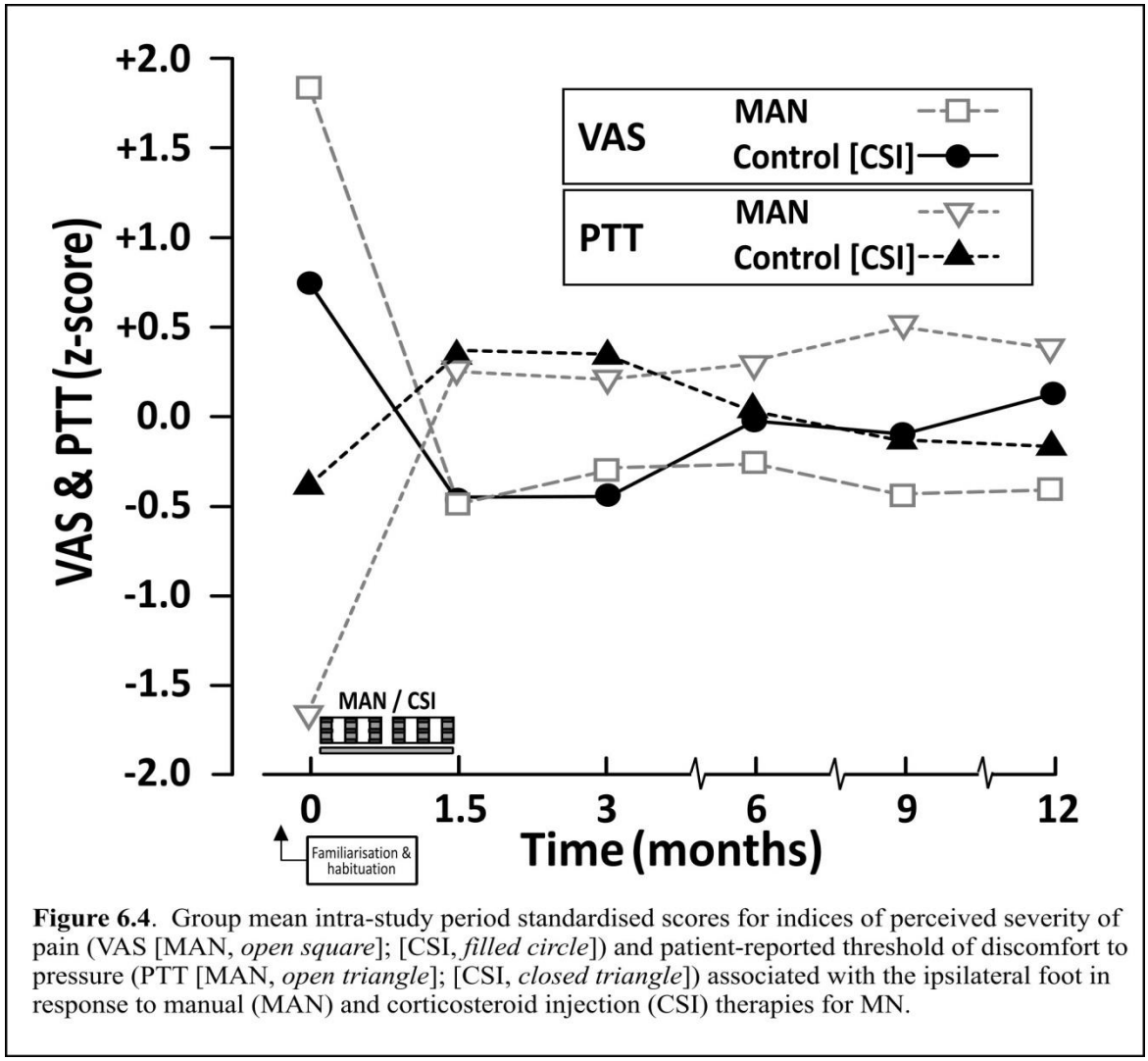

Figure 6.4. Group mean intra-study period standardised scores for indices of perceived severity of pain (VAS [MAN, *open square*]; [CSI, *filled circle*]) and patient-reported threshold of discomfort to pressure (PTT [MAN, *open triangle*]; [CSI, *closed triangle*]) associated with the ipsilateral foot in response to manual (MAN) and corticosteroid injection (CSI) therapies for MN.

Importantly, the absence of correlation between the antecedent duration over which patients had endured MN-related pain (circa 200 weeks; Table 6.1) and VAS as the study's primary outcome, suggests that the efficacy of MAN might prevail usefully for acute and chronic expressions of MN.

Limitations to this study were related to its delivery and design. Logistical and ethical constraints had precluded routine assessment by means of medical imaging. Similarly, experimental controls in this trial were focused on an extended period of longitudinal evaluation of the performance capabilities of the ipsilateral foot and differential inter-group responses, rather than on those of the contralateral foot. Other limitations included that group allocation could not be concealed from participants or from those overseeing the

participants testing administration and treatment as it was evident to all whether one was receiving a injection or not.

Similarly, physical activity behaviors associated with travel to and from the MAN's venue for its delivery and assessments were not monitored directly and varied physical activity might have elicited heterogeneous carry-over effects amongst the patients' responses to MAN. Participants self-perceived pain assessments within the MAN protocol had been monitored, but not reported here. Furthermore, while the patient's compliance with the MAN's treatment prescription was monitored directly, this approach that may not be facilitated in all environments, such as within self-managed care. Nevertheless, future studies could aim to identify optimised MAN dosing and approaches for its scalability and delivery amongst varied care environments. This study's findings were derived from a modestly sized sample of participants (n = 61), aged ~53 years, with a female gender bias (77%; Table 6.1), which might preclude generalisation. Observed Type II error rates were modest (≤ 0.12) and appeared to offer suitable experimental design sensitivity and statistical power amongst the selected indices of participants' perceptions about functional capacity amongst concomitant pain and discomfort.

Further research will be required in a number of key areas to progress this body of work further. Optimum dose-response characteristics for MAN should be explored in order to ensure maximum treatment potency and most efficacious resource employment. Additionally, given that VAS and PTM appear to be measuring related but separate physiological responses, some effort to establish which is more pertinent for MN sufferers may be rewarded with better symptom tracking and ultimately potentially more accurate outcome prediction. In conclusion, both VAS and PTT outcome measures employed here agreed that MAN offers more immediate and more robust outcomes than CSI as an intervention for MN.

6.5. *Conclusions*

This study of acute, short dosage (six, weekly episodes), physiologically-principled MAN in patients electing unilateral treatment of MN suggested that the protocol may be efficacious for improving self-reported levels of pain and discomfort (*d*, 2.3 – 3.3; 84.4% - 147.0%). Gains prevailed beyond the cessation of MAN. In addition, concurrent validity between PTT and VAS may not be assured as indicated by compromised congruence

amongst patterns of response to treatments over time, with no statistically significant relationship at baseline between PTT and VAS suggesting that each outcome measure would have been assessing a different physiological response.

CHAPTER SEVEN

An exploratory pragmatic controlled trial of the influence of manipulation versus steroid injection on MOxFQ, FAAM and SF-36 in the treatment of patients with Morton's neuroma

Aim – To explore the efficacy of MAN versus CSI assessed using MOxFQ, FAAM and SF-36 questionnaires.

7.1. **Introduction**

Within many medical disciplines, clinicians and researchers have embraced a common vocabulary and language for thinking and speaking about the process of disablement (Jette 2006). Several disablement models (Nagi Disablement Model [Nagi Model], National Centre for Medical Rehabilitation Research Disablement Model [NCMMR], and World Health Organization International Classification of Functioning Model [WHO-ICF]) have now been introduced, which allow healthcare professionals to communicate with one another and to speak in a common language across related professional disciplines, regarding overall health status of patients (Jette 2009). In general, disablement models represent conceptual frameworks that form the basic architecture for clinical practice and research, as well as healthcare policy (Kaplan 2007).

In the context of MN, the ICF disablement model provides for a continuum of outcome measures that reflects body function and structure and those reflecting a patient's capability for activity and participation (Michener 2011). In the former regard, tests that have been performed by a clinician (Chapter 4; web-space tenderness test, Mulder's click test, and plantar digital nerve stretch test) and which have in this thesis, been used to define inclusion criteria, rather than treatment progression, may be considered as so-called clinician-based outcome measures. By contrast, the latter capabilities for activity and participation and related patient status have been reflected in patient-based or patient-reported outcome measures such as MOxFQ, FAAM and SF-36 inventories. Although metrics such as VAS (Chapter 6; study's primary outcome) for pain tends to be classified within the latter patient-reported outcome measures (Roberts et al. 2007), it could be argued that PTT, which is reliant on both expertise for its delivery by the clinician and on the perceptions of discomfort by the patient, straddles both extremes of the classification continuum. Thus, the thesis is served by both clinician- and patient-reported metrics, but the latter are emphasised within the adjunct evaluation and comparisons of MAN's and CSI's efficacy and will enable an understanding of a patient's overall health status (Snyder et al. 2008). In this context, disablement models serve as a framework from which clinical outcome assessments from across a patient- and clinician-based continuum can be used to examine the effectiveness of

healthcare interventions such as MAN, upon one or more dimensions of disablement. Furthermore, PBOMs may be incorporated into a treatment plan to supplement Clin-BOMs. Such approaches allow a more complete assessment of a patient's perception of their own health status (Michener 2011).

This chapter reports on responses to MAN and CSI as captured by the outcome measures of MOxFQ, FAAM and SF-36 in patients with MN. It explores data pertaining to the impact MN has on quality of life, performance of everyday tasks, social and sporting interactions and general well-being and explores relevant gains in efficacy for MAN as compared to usual conservative care (CSI). Additionally, the retention of effects as reported by MOxFQ, FAAM and SF-36 are explored at 3, 6, 9 and 12 months following the cessation of MAN and CSI. The chapter offers adjunct data to that offered with Chapter 6 that focused on the outcome measures of VAS and PTT.

7.2. **Methods**

The methods employed here were targeted to produce evidence for the efficacy of conservative care, specifically manipulation, and to facilitate the assessment of the psychometric qualities of selected PROMs, assessing the relative importance of factors contributing to the successful treatment of MN.

7.2.1. *Study design and participants*

This represented a data analyses of metrics from patients with MN (n = 61) and described fully in Chapter 4 (General methods). It offers a partnering study of PROMs involving established functionality inventories (Manchester-Oxford Foot Questionnaire [MOxFQ]; Foot and Ankle Ability Measure [FAAM] and Short Form 36 [SF-36]) to those (VAS; PTT) considered within Chapter 6.

In summary, sixty-one patients with MN (please see Table 6.1) gave their informed consent and participated in this UK single-centre clinical pragmatic, exploratory randomised controlled trial was registered (clinicaltrial.gov: NCT02304094), and given research, development and ethical approval by the South East Scotland Research Ethics Committee 01 (IRAS 129586; REC reference 15/SS/0099). Initial patient screening was undertaken by NHS Lothian and then again at the research centre by the clinician having oversight (DC). Inclusion and inclusion criteria have been described elsewhere in detail (Chapter Four:

General Methods) and briefly (Chapter Six). Allocation was to one of two groups using minimisation with weighted randomisation; groups matched for age, gender, severity and duration of symptoms.

The MAN group (n = 29) underwent experimental intervention to the ipsilateral foot, receiving six focal manipulation-sessions delivered (one session·week^{-1}) during a six week period, with clinical oversight (DC). The CSI group (n = 32) followed contemporary practice. Primary and secondary outcome measures were recorded at baseline, one and a half months (immediately after completion of all MAN and in keeping with contemporary initial review following CSI interventions) and then during follow-up at three months, six months, nine months and at one year. Manipulative (MAN) and Pharmacological (corticosteroid injection; CSI) therapies have been described previously (Chapters 4 and 6).

7.2.2. *Patient-reported inventories of functionality*

Full details of outcome measures used in this study can be found elsewhere (Chapter Four; General Methods), including critical consideration of their relevant clinimetric characteristics (Chapter 2).

In summary, the MOxFQ is a regional rating scale of the musculoskeletal function and disability of the foot (16 items; 0 – 100 metric, 100 most severe), focusing on walking and standing (MOxFQws), pain (MOxFQp) and social interaction (MOxFQsi), with established validity, responsiveness and minimally important change scores (Dawson, Boller et al. 2011). Similarly, the FAAM specifically reports on the physical function and capabilities of individuals with foot and ankle dysfunction, with an emphasis on sensitivity to changes in activities of daily living and participation in sports (FAAMdl and FAAMspt, respectively), but not on foot pain. This study required participants to complete an abridged but validated version of FAAM comprising 21 items, in which each with applicability to a patient is scored from 0 (lowest rating) to 4 (highest rating) (Martin, Hutt et al. 2009). The FAAM score is recorded as the ratio of the sum of applicable item scores relative to the corresponding highest potential score, expressed as a percentage, with optimum foot health designated a score of 100%. The short form (SF-36) of the General Health Questionnaire is a global rating scale questionnaire consisting of thirty-six items that combine to measure an

individual's generic health status (Rand Corporation 2022). Eight separate categories including physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), mental health (MH), energy/vitality (EV), pain (P) and general health (GH) can be collated within summary physical (PCS) and mental (MCS) component scores. Participants can score anywhere from zero to 100, with 100 representing optimum health.

7.2.3. *Statistical analysis*

Group means (±SD) and Pearson product-moment correlations described outcome scores and interrelationships. Separate factorial (group [MAN; CSI] x time [baseline; 1.5 mo; 3 mo; 6 mo; 9 mo; 12 mo]) analyses of variance (ANOVAs), with repeated measures for time, tested hypotheses relating to patient-reported levels of functionality (MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS), using *per protocol* analyses (SPSS Vn. 23, IBM SPSS Illinois, USA).

A priori reverse Helmert orthogonal difference testing located anticipated time-specific effects. Any violations of assumptions underpinning the use of ANOVA were countered using Greenhouse-Geisser ($_{GG}$) adjustments. Chi-square tests explored hypotheses involving categorical data. Statistical significance was accepted at $p < 0.05$. Cohen's d quantified relative effect size (ES). *A priori* experimental design sensitivity estimation offered an approximate statistical power of 0.8 for avoiding intrusion of type-II errors for a medium relative effect size (Cohen's d , 0.5) in the study's primary outcome, VAS, and at its end-point (1.5 mo), requiring an approximate sample size of $n = 20$ within each group.

Congruence amongst fluctuating patterns of treatment assessment metrics for self-perceived pain and discomfort (VAS and PTT, reported in Chapter Six) and perceptions of function (MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS) were examined using participants standardised (z-score) data. Separate univariate factorial (group: [MAN; CSI]*assessment metric [MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS]*time [baseline; 1.5 mo; 3 mo; 6 mo; 9 mo; 12 mo])

ANOVAs, with repeated measures on the latter two factors. Temporal correspondence amongst assessment response patterns was indicated by an absence of factorial interaction. *A priori* planned polynomial trend analyses characterised the expected oscillatory patterns of fluctuation in participants' responses to treatment and concomitant perceptions of pain and discomfort.

7.3. **Results**

Sixty-one participants from sixty-four candidates participated. Statistical analyses were undertaken on data from at least 44 participants who completed the study protocol. Participants' characteristics at baseline are shown in Table 6.1 of the previous chapter. Those baseline characteristics demonstrated no correlation with the study's outcome metrics and variations merely contributed random error to the study's findings. The study's primary outcome metric of patient-reported severity of pain (VAS; Chapter 6) showed modest interrelationships at baseline with perceptions of functional capacity (MOxFQws, r = 0·38; p < 0·01; MOxFQp, r = 0·48; p < 0·005; FAAMdl, r = 0·33; p < 0·01; FAAMspt, r = -0·35; p < 0·005), involving pooled shared variances of < 23% and limited collinearity, with each outcome capable of contributing information independently within the study. Corresponding interrelationships for pressure threshold for discomfort perceptions (PTT; described in Chapter 6) (MOxFQws, r = -0·28; p < 0·05; MOxFQp, r = -0·37; p < 0·005; MOxFQsi, r = -0·25; p < 0·05) were similarly limited (r^2 < 14%). There was no significant differences at baseline between the study's outcome metrics for participants lost-to-follow-up and those completing all assessments ($F_{(1,57)}$ = 0·7 to 2·1; *ns*) suggesting minimal intrusion of attrition bias.

7.3.1. *Patient-reported functional capacity (MOxFQ; FAAM)*

Factorial interactions associated with MOxFQ showed group mean functional capacity associated with walking and standing (MOxFQws [$F_{(5,210)}$ = 3·6; p < 0.01]), pain (MOxFQp [$F_{(5,205)}$ = 3·8; p < 0·01]) and social interaction (MOxFQsi [$F_{(5,195)}$ = 3·1; p < 0·05]) were significantly improved immediately following MAN, but to a lesser extent following CSI (Figures 7.1[a], 7.1[b] and 7.1[c], respectively).

Performance improvements between baseline and immediately after treatment (MOxFQws [MAN: Cohen's *d*, 1·4; 52·8%; CSI: Cohen's *d*, 0·7; 28·2%; $F_{(1,42}$ = 4·7; p < 0·05, *a priori*

difference contrast]; MOxFQp [MAN: *d*, 1·3; 45·5%; CSI: Cohen's *d*, 0·5; 16·1%; $F_{(1,41)}$ = 7·4; $p < 0·01$]; MOxFQsi [MAN: *d*, 0·9; 39·2%; CSI: Cohen's *d*, 0·4; 20·6%; $F_{(1,41)}$ = 2·7; *ns*]) were prominent and mostly favoured MAN. The latter treatment improvements were retained substantively at 12 months after MAN's cessation (MOxFQws [MAN: Cohen's *d*, 1·7; 65·2%; MOxFQp [MAN: *d*, 2·0; 68·3%; MOxFQsi [MAN: *d*, 1·1; 52·1%), but not always for CSI (MOxFQws [CSI: Cohen's *d*, 0·43; 20·0%; $F_{(1,42)}$ = 5·6; $p < 0·05$]), where instead, perceptions about social interaction (MOxFQsi) showed that the relative difference between perceptions at 12 months and preceding scores favoured MAN over CSI [CSI: Cohen's d, 0·03; 1·5%; $F_{(1,39)}$ = 5·3; $p < 0·01$]).

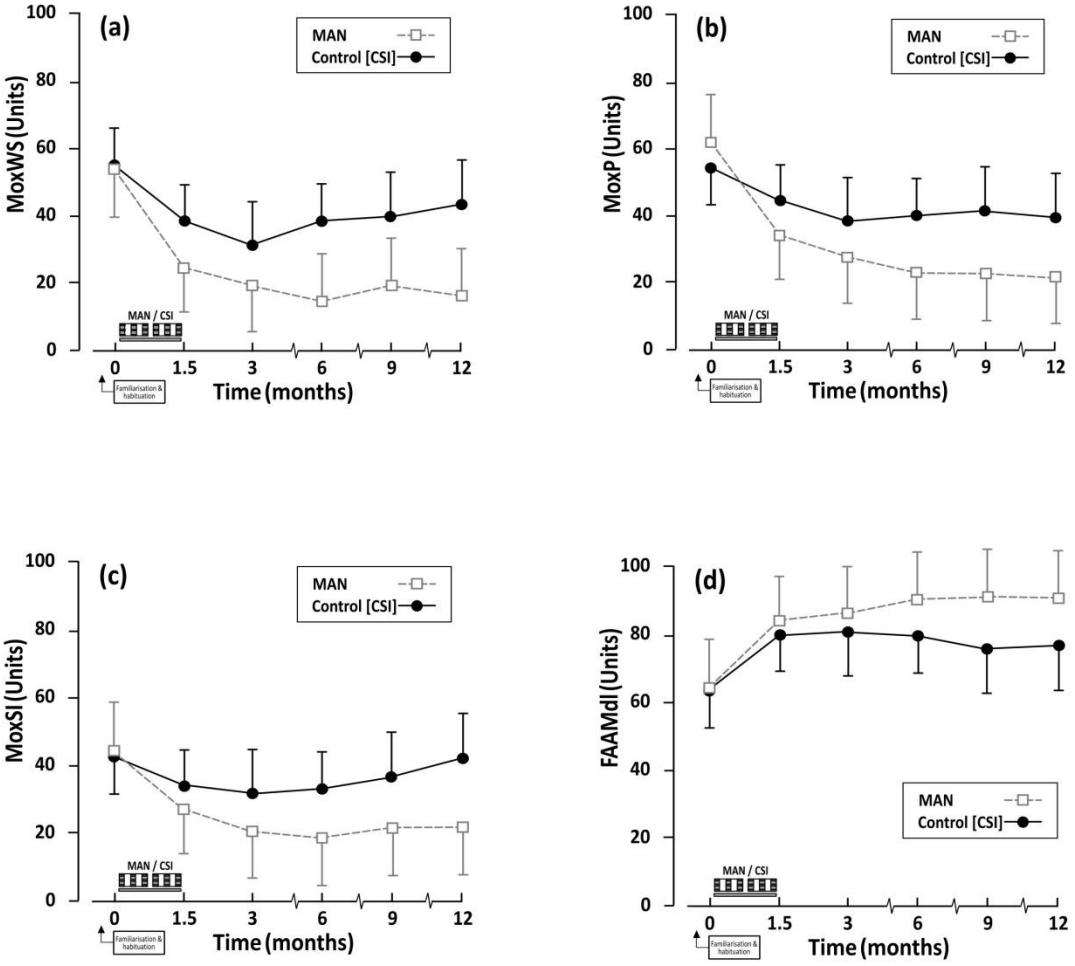

Figure 7.1: Group mean perceptions (±SD; MAN, n = 21; Control, n = 23) of functional capability (MOxFQws [a]; MOxFQp [b]; MOxFQsi [c]; FAAMdl [d]) are shown at baseline [0 months], immediately after therapy [1.5 months] and at subsequent follow-up assessments [3, 6, 9 and 12 months] in response to manual (MAN) and corticosteroid injection (CSI) therapies for MN.

While both treatments elicited significantly improved FAAMdl ($F_{(5,220}$ = 2·7; $p < 0·05$) and FAAMspt ratings ($F_{(5,220)}$ = 2·4; $p < 0·01$), MAN provoked greater improvements than CSI

for both aspects of functional capacity (Figures 7.1[d] and 7.1[e], respectively). Perceptions about functional capability during activities of daily living and during sports participation showed that relatively greater gains accumulated for MAN compared to CSI at 12 months (FAAMdl; $F_{(1,44} = 10{\cdot}7$; $p < 0{\cdot}01$) and at 9 months (FAAMspt; $F_{(1,44} = 10{\cdot}7$; $p < 0{\cdot}01$) compared to the preceding scores, respectively, contributed most to the overall ANOVA interactions. Peak gains in FAAMdl (MAN: *d*, 2·2; 40·8%; CSI: Cohen's *d*, 0·8; 19·8%) and FAAMspt (MAN: *d*, 1·5; 66·1%; [12 months]; CSI: Cohen's *d*, 0·6; 23·1%; [3 months]) favoured MAN as a treatment intervention.

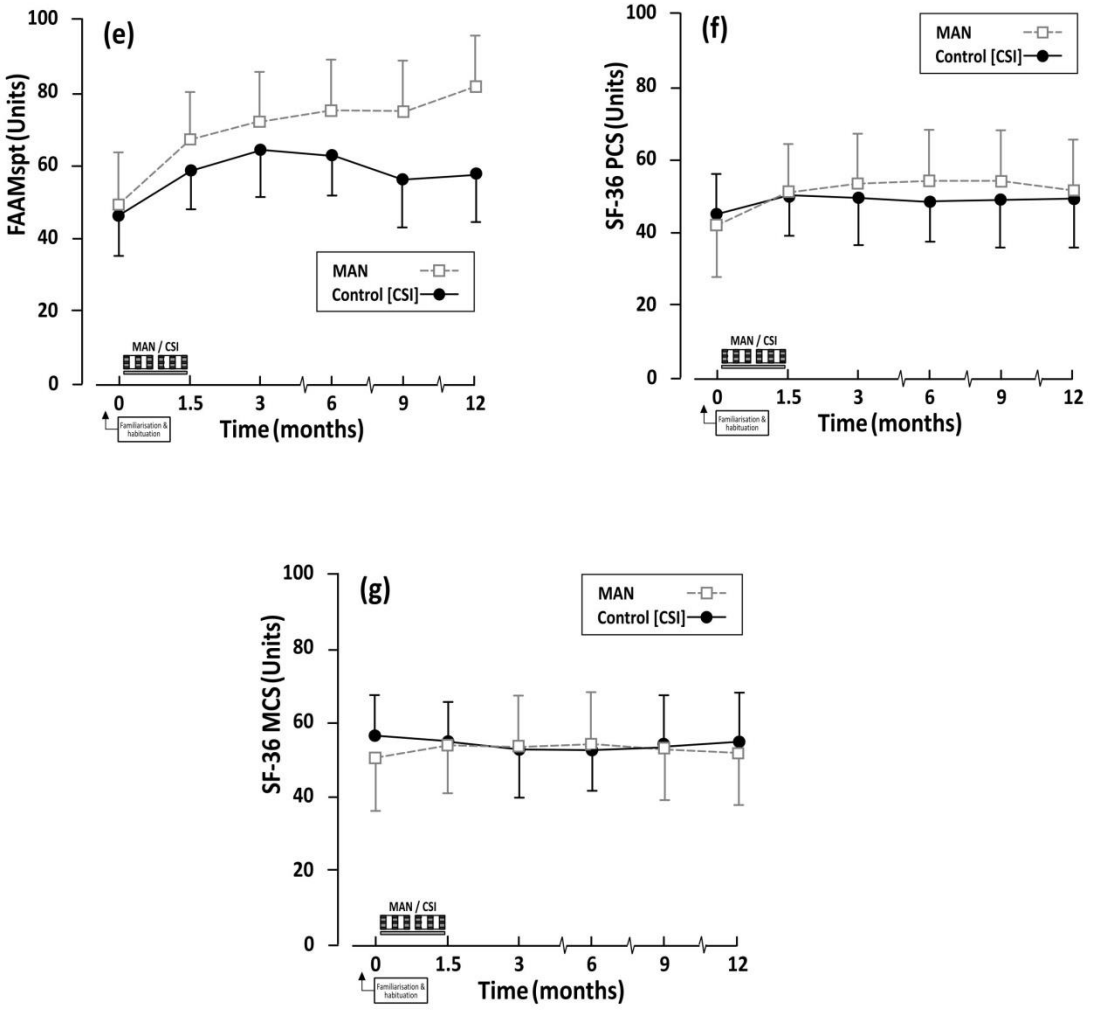

Figure 7.1 (continued): Group mean perceptions (±SD; MAN, n = 21; Control, n = 23) of functional capability and general health (FAAMspt [e]; SF-36 PCS [f]; SF-36 MCS [g]) are shown at baseline [0 months], immediately after therapy [1.5 months] and at subsequent follow-up assessments [3, 6, 9 and 12 months] in response to manual (MAN) and corticosteroid injection (CSI) therapies for MN.

Patient-reported general health (SF-36 PCS and SF-36 MCS)

Factorial interactions associated with GHQ SF-36 showed group mean perceptions of general health associated with patients' physicality (SF-36 PCS [$F_{(5,210)} = 4{\cdot}0$; $p < 0.01$]) and mentality (SF-36 MCS [$F_{(5,210)} = 3{\cdot}0$; $p < 0{\cdot}05$]) were significantly improved following MAN, but to a lesser extent (PCS), or not at all (MCS), following CSI (Figures 7.1[f] and 7.1[g]).

Patients' mental health improvements between baseline and immediately after MAN (SF-36 MCS [MAN: Cohen's *d*, 0.4; 18·8%; CSI: Cohen's *d*, - 0·12; - 6·2%; $F_{(1,42} = 3{\cdot}3$; $p < 0{\cdot}05$, *a priori* difference contrast]) were prominent and favoured MAN. By contrast, patients' perceptions of physical aspects of health (SF-36 PCS [MAN: Cohen's *d*, 1·3; 28·2%; CSI: Cohen's *d*, 0·11; 8·6%; $F_{(1,42)} = 4{\cdot}2$; $p < 0{\cdot}05$]) showed that the relative difference between perceptions at 6 months and preceding scores favoured MAN over CSI and contributed most to the overall significant ANOVA result.

7.3.2. *Asymptomatic status and patterns of recovery*

Participants standardised (z-score) data was used to explore for congruence amongst fluctuating patterns of recovery for patient-reported severity of pain and pressure threshold for discomfort perceptions following the treatment interventions (Chapter 6) and concomitant functional capacity responses. The presence of factorial interaction in separate analyses for both VAS and PTT (described within Chapter 6) with MOxFQws (Figure 7.2 shows the relationship between VAS and MOxFQws, as an exemplar: $F_{(5,205)} = 3{\cdot}1$; $p < 0{\cdot}01$ and $F_{(5,205)} = 2{\cdot}9$; $p < 0{\cdot}01$, respectively), MOxFQp ($F_{(5,205)} = 5{\cdot}1$; $p < 0{\cdot}0005$ and $F_{(5,220)} = 2{\cdot}9$; $p < 0{\cdot}05$, respectively), MOxFQsi ($F_{(5,195)} = 3{\cdot}7$; $p < 0{\cdot}01$ and $F_{(5,195)} = 2{\cdot}5$; $p < 0{\cdot}05$, respectively), FAAMdl ($F_{(5,220)} = 7{\cdot}9$; $p < 0{\cdot}0005$ and $F_{(5,220)} = 9{\cdot}1$; $p < 0{\cdot}0005$, respectively) and FAAMspt ($F_{(5,215)} = 7{\cdot}5$; $p < 0{\cdot}0005$ and $F_{(5,215)} = 8{\cdot}2$; $p < 0{\cdot}0005$, respectively) showed that patterns of intra-study fluctuation amongst indices of pain, pressure thresholds for discomfort and perceived functional capacity were dissimilar over time. *A priori* planned polynomial trend analyses characterised the intra-study period oscillatory patterns in patients' perceptions about their functional capacity and concomitant pain and discomfort as featuring linear, third- and fourth-order responses ($F_{(1,43)} = 7{\cdot}2$ to $19{\cdot}5$; $p < 0{\cdot}01$ and $F_{(1,43)} = 8{\cdot}7$ to $18{\cdot}4$; $p < 0{\cdot}01$, respectively).

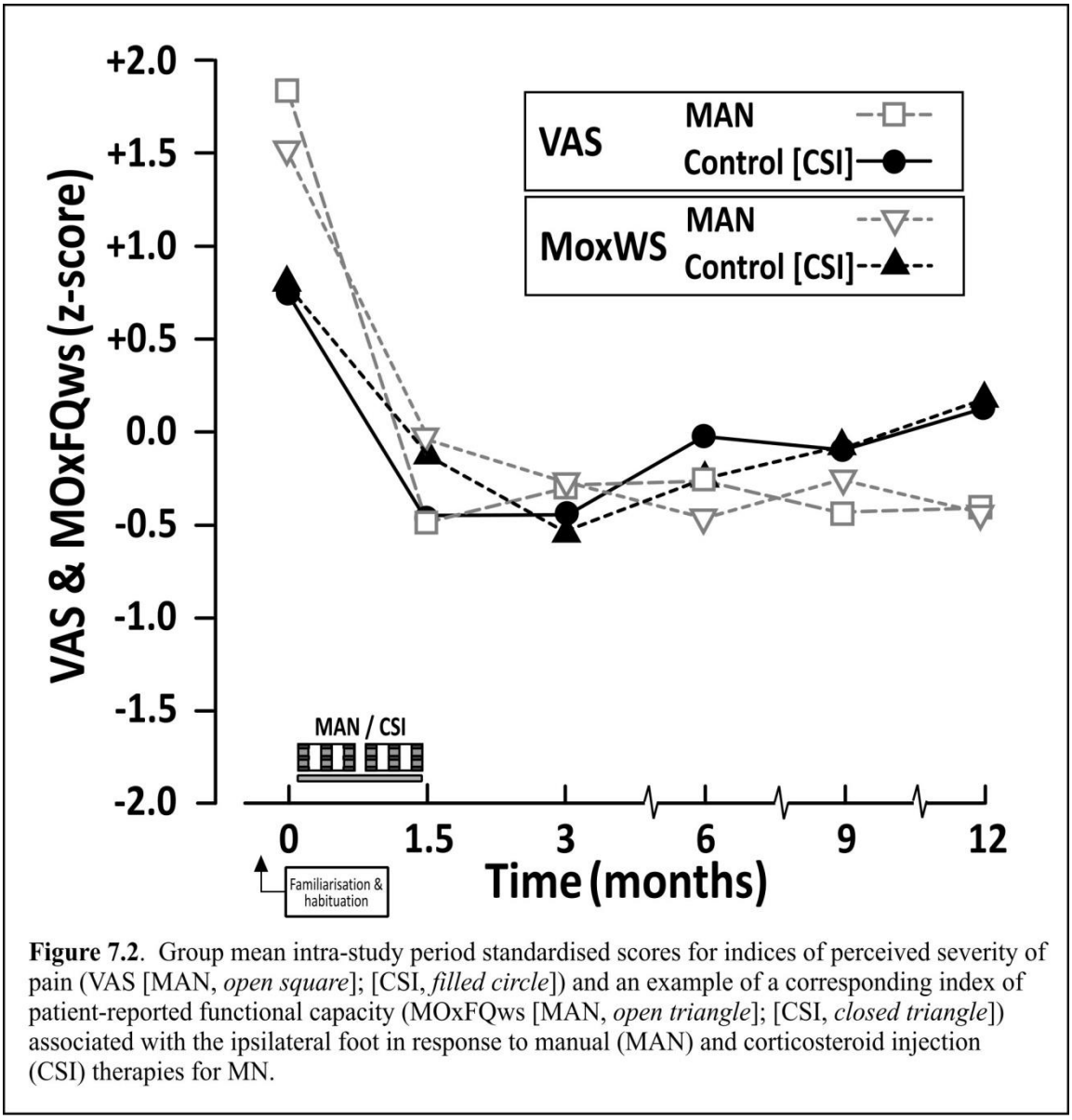

Figure 7.2. Group mean intra-study period standardised scores for indices of perceived severity of pain (VAS [MAN, *open square*]; [CSI, *filled circle*]) and an example of a corresponding index of patient-reported functional capacity (MOxFQws [MAN, *open triangle*]; [CSI, *closed triangle*]) associated with the ipsilateral foot in response to manual (MAN) and corticosteroid injection (CSI) therapies for MN.

7.4. **Discussion**

This thesis has investigated the efficacy of MAN for improving a primary outcome of patient-reported severity of pain (please see Chapter 6) and its influence on the thesis' secondary outcomes of patients' perceptions of functional capacity. With regard to the latter patient-reported outcome measures, there were substantial gains elicited by MAN immediately after intervention MOxFQws [*d*, 1·4; 52·8%]; MOxFQp [*d*, 1·3; 45·5%]; MOxFQsi [*d*, 0·9; 39·2%]) or accumulated during follow-up (FAAMdl [*d*, 2·2; 40·8%]; FAAMspt [*d*, 1·5; 66·1%]). Concomitant gains for participants in the CSI group were modest by comparison (*d*, 0·4 to 1·0; 16·6% to 45·9%) and reflected responses elicited by contemporary practice involving corticosteroid injections.

As alluded to in Chapter 6, optimum dose-response characteristics for MAN remain unquantified, but the protocol employed in this thesis provoked immediate responses of PROMs that surpassed statistical, precision and reliability criteria for the selected outcome metrics (~ 4% - 10%; please see Chapters 2 and 5). From these results, it would appear that MAN may prove to be a useful addition to the armamentarium of the clinician battling MN with the sufferer.

MAN's ability to improve multiple independent facets of MN symptomology (coefficient of determination amongst outcome metrics, at baseline: $r^2 \leq 0{\cdot}23$) could be gainfully harnessed in a number of different treatment methodologies and protocols. These results focusing on PROMs, corroborate the findings with Chapter 6 that demonstrate a potential for MAN as a successful stand-alone first line intervention for MN. However, it could equally well be employed as an adjunct to any of the contemporary treatments currently being employed against MN, since its use creates no barriers to concurrent or subsequent alternate interventions, including conservative, pharmacological or surgical approaches.

It was notable that the retention over 12 months' follow-up of treatment-related gains for PROM metrics largely mimicked the pattern for PROM (VAS [primary outcome]) and clinician-reported (PTT) metrics discussed in chapter six, favouring MAN (PTT, MOxFQws, MOxFQp, MOxFQsi, FAAMdl and FAAMspt [*d*, 1·1 to 2·2; 40·8% to 152·3%]) over CSI.

Overall, the targeted manual manipulations (Cashley and Cochrane 2015) provoked findings corroborating those within Chapter 6 in which the treatment is capable of counteracting specific patho-neuromechanical aspects within aetiologies for MN (Lund et al. 1991; Danesi et al. 2012; Rio et al. 2016) and of preserving those favourable changes for a considerable period afterward (up to 12 months). Conversely, recovery patterns for CSI were consistent with reports of CSI's efficacy being more transitory (Thomson et al. 2013) and involving a significant proportion of MN sufferers progressing to surgery (Markovic et al. 2008; Thomson et al. 2013; Rao et al. 2014).

The results of the SF-36 questionnaire showed modest responsiveness to changes within the participants of both treatment groups. Figures 7.1[f] and 7.1[g] show that baseline scores fluctuated only modestly throughout the entire twelve months of the study. In other words,

SF-36 failed to capture many of the fluctuations observed by the other PROMS employed in this thesis. Figure 7.1 serves to demonstrate a considerable lag between the dynamic treatment-related fluctuations of the MOxFQ and FAAM responses compared to the relative flat-lining of the trailing SF-36 responses by the same participants. This interpretation is similar to the reports of some other researchers exploring MN, although it is by no means a clear picture, as some research teams have seen significant changes in at least one subscale of the SF-36 inventory in response to injection therapy for MN (Pabinger et al. 2020). While it is plausible that the relatively muted and unresponsive metrics of the SF-36 in this study truly reflect patients' correspondingly quiescent perceptions of mentality and physicality, on the basis of the data explored within this thesis, SF-36 might not be best recommended as a suitable tool with which to monitor changes in function or symptomology in response to conservative interventions for sufferers of MN. This may prove to be unique to the particular demographic of the population being studied here, and it must certainly be stressed that the same would appear to be strictly true only in cases where conservative management was being researched. For those papers that report on outcomes of surgical intervention for MN, the SF-36 does appear to offer some measure of change sensitivity. However, even in this environment of potentially greater variations in pain and functionality through pre, peri and post-surgical time periods, it has been reported that SF-36 continues to lag behind alternative PROMS in terms of responsiveness and sensitivity (Rungpra et al. 2015). Whilst it is beyond the remit of this thesis to state the value of SF-36, on the basis of the data gathered, one must be led to question its utility for those with MN. All other PROMS, both those which are more or less clinician- or patient-reported within the ICF of disablement, outperformed the SF-36 and therefore the clinician should look to these tools to inform decision making for MN. Limitations for this study essentially mimicked those reported in Chapter 6 (please see section 6.4). The observed Type II error rates were similarly modest (≤ 0.18), appearing to offer suitable experimental design sensitivity and statistical power amongst the selected indices of participants' perceptions about functional capacity and health associated with their physicality and mentality.

7.5. **Conclusions and implications for clinical practice**

This study explored a pragmatic controlled trial of the influence of manipulation versus steroid injection on MOxFQ, FAAM and SF-36 in the treatment of patients with Morton's neuroma and showed that the former treatment was capable of improving patient's self-reported metrics such as quality of life, performance of everyday tasks, social and sporting interactions and general well-being (*d*, 0.9 – 2.0; 39.2% - 68.3%). The gains were sustained for 10.5 months beyond the cessation of MAN.

By contrast to findings within Chapter 6 involving a PROM (VAS; thesis' primary outcome) and a clinician-reported outcome measure (PTT) within the ICF of disablement, MAN's treatment-related gains on MOxFQ, FAAM and SF-36 were more muted. However, they were similarly superior to the responses to contemporary treatment practice involving CSI. Sustained gains were not enjoyed by the CSI group, whose corresponding metrics suffered a definitive reversal away from early improvements at the three-month point.

Thus, within the context of implications for clinical practice, all PROMs within Chapter 7, with the partial exception of SF-36, favoured MAN over CSI in all dimensions and at all time points. Overall, the PROMS discussed in this chapter (MOxFQ, FAAM and SF-36) showed more heterogeneous responses compared to VAS and PTT and potentially as such, compromised utility in their contributions to understanding clinical outcomes. Furthermore, despite the fact that PROMs such as MOxFQ, FAAM and SF-36 encapsulate information about symptomology and its impact on daily living, which is not captured by VAS and PTT as counterparts, their use in the clinical realm will be subject to time pressures and additional patient burden. Therefore, the clinician must weigh whether there is justification in their use along with, or instead of other tools on offer. Whilst they undoubtedly retain value in the research setting, the clinical value over VAS and PTT, at least for MN, is much less certain.

Chapter 8 will consider the relative importance of factors and selected outcome metrics in predicting enhanced outcomes of non-surgical treatment of Morton's neuroma.

CHAPTER EIGHT

Factors in enhanced outcomes of non-surgical treatment of Morton's neuroma

Aim – To explore the assessment of the relative importance of factors contributing to the successful treatment of MN.

8.1. **Introduction**

As alluded to earlier within the thesis' introduction (Chapter 1), optimum strategies for the non-invasive treatment of MN continue to command clinical debate and about which this thesis has been curated. The outcomes of the thesis' data analysis chapters (Chapters Six and Seven) in particular have shown that manipulation therapy offers efficacy in treating MN and betters the capability of CSI, which has been preferred until now in contemporary podiatric practice, both in terms of potency and sustainability of favourable effects. The scope of this thesis did not permit evaluation of either optimum dose-response characteristics for MAN or indeed, the mechanisms by which MAN has been capable of delivering impressive levels of efficacy. Furthermore, although the sample of patients within the thesis may be representative of patients presenting to NHS podiatry clinics, the antecedent factors that might be conducive to facilitating MAN and indeed CSI, have also not received systematic scrutiny within the thesis.

For example, in order to minimise the differential influence of extraneous factors that might have masked the relative efficacy of treatments, the sample's groupings that undertook MAN and CSI treatment interventions had been 'matched' on factors that had been expected to be clinically influential. Groups were matched for age, gender, severity of MN symptoms according to VAS score and duration of symptoms.

Underpinning concern about influential factors is the debate amongst theoretical bases for the origins of MN (Chapters 1 and 3), together with the possibility of sufferers carrying risk factors into their activities of daily living. Suitable levels or status amongst selected factors may have potent moderating effects on the rate at which symptoms of MN develop and importantly, the extent to which treatments are successful in alleviating symptoms. No single feature has yet been identified which can either lead to confident diagnosis nor prognostic certainty (Sharp et al. 2003; Naraghi et al. 2017). Identification of early prognostic indicators of sub-clinical changes towards MN gives rise to the possibility of bringing about more favourable risk profiles amongst potential sufferers through modification of those factors that can be altered.

While research findings about the relative hierarchy of importance amongst mental and physical health factors are somewhat inconsistent at present in MN, the outcome metrics of this thesis reflect both aspects and offer the opportunity to further explore factors contributing to optimum non-surgical clinical outcomes. The primary aim of this study was to explore selected antecedent psychological and physical health factors contributing to efficacious outcomes associated with the non-surgical treatment of MN.

8.2. **Methods**

The methods employed in this chapter aim to explore whether selected pre-existing health factors can be identified, which may contribute to improved conservative care choices and outcomes in the treatment of MN.

8.2.1. *Participants*

This represented secondary data analyses of data elicited from patients with MN and described in Chapters 4 (General methods), 6 (Responses of outcome metrics VAS and PTT) and 7 (Responses of outcome metrics involving foot and ankle inventories of functionality and general health). As such, participants in this study comprised those contributing to Chapters Six and Seven and described therein (please see Table 6.1). In summary, sixty-four patients with MN gave their informed consent and participated in this single-centre, cohort study.

8.2.2. *Non-surgical intervention strategies for MN and selected outcome metrics*

Patients in this study had participated in a comparative trial of the efficacy of MAN and CSI non-surgical interventions for the treatment of MN. The details of this clinical intervention have been described in general within Chapter 4 (General methods [please see sections 4.2.3 and 4.2.4]) and within Chapter 6 (Methods: MAN versus CSI; VAS and PTT outcome measures [please see sections 6.2.2 and 6.2.3]). In summary, participants were screened against the inclusion and exclusion criteria and a diagnosis of MN was confirmed clinically. Patients gave written informed consent prior to baseline assessment. Allocation was to one of two groups matched for age, gender, severity and duration of symptoms. This was performed using the Minim software from the University of York. The MAN group (n = 29) underwent weekly joint manipulation of the forefoot for six consecutive weeks. The CSI group (n = 32) followed contemporary practice for MN. Primary and secondary outcome measures were recorded at baseline, one and a half months (immediately after

completion of all MAN and in keeping with contemporary initial review following CSI interventions) and then during follow-up at three months, six months, nine months and at one year.

8.2.3. *Selected outcome metrics*

This study focused attention on PROMs deployed within Chapters 6 (VAS; primary outcome; PTT [please see sections 6.2 and 6.3]) and 7 (MOxFQ, FAAM and SF-36 [please see sections 7.2 and 7.3]) and described in detail therein and within Chapter Four (General methods [please see sections 4.9]). In summary, metrics included an exploration of antecedent clinical metrics, including patients' history, and candidate PROMs (VAS; PTT; MOxFQws; MOxFQp; MOxFQsi; FAAMdl; FAAMspt; SF-36 PCS; SF-36 MCS) contributing to subsequent optimum non-surgical clinical outcomes in the treatment of MN. It involved a secondary analysis of data derived from Chapters 6 and 7.

8.2.4. *Experimental design*

In clinical populations several factors, including current levels of perceived pain, duration of pain, age, functional capability and anatomical location of symptoms have been suspected of having the potential to influence clinical outcomes of treatment (Lizano-Díez et al. 2017). However, apart from being important as general determinants of outcome, such factors have not been successful individually in predicting favourable responses of patients to treatment. It is plausible that only when clinical history, physical and anatomical characteristics of an individual have also been considered alongside psychological perspectives and perceptions of functional capabilities and health, will a composite model demonstrate significant prediction of successful clinical outcome, and especially in the context of non-surgical intervention. Prospective modelling of this type in which antecedent subtle sub-clinical and clinical markers of subsequent patterns of favourable susceptibility to treatments, has obvious utility in clinical triage and selection of appropriate treatment interventions. Similarly, successful retrospective modelling of such factors in conjunction with treatment selection and outcome would corroborate the latter's initial and longer-term characteristics of efficacy. With relatively little known about the hierarchy of relative importance of factors influencing the successful non-surgical treatment of MN, such information may help guide effective interventions to improve perceptions of pain, functional capability and the ability to undertake activities of daily living.

As alluded to earlier, the main purpose of this investigation was to provide evidence of selected factors that may facilitate and predict efficacious outcomes in patients undergoing non-surgical treatment for MN. Consequently, a model consisting of variables relating to patients' clinical history, physical and anatomical characteristics, psychological perspectives and perceptions of functional capabilities and health was tested prospectively and retrospectively in relation to patients demonstrating high and low responses (as measured by patient-reported levels of pain [VAS]) to efficacious non-surgical treatments for MN.

8.2.5. *Statistical analyses*

Patients' clinical history, physical and anatomical characteristics, psychological perspectives and perceptions of functional capabilities and health are considered to have multi-dimensional structures, and so a one-way multivariate analysis of variance was employed to provide a simultaneous comparison of the latter multiple variables, in relation to their response to treatment.

In the absence of definitive metrics, it has been assumed that high and low threshold levels of response (VAS) to efficacious non-surgical treatments for MN correspond to upper and lower tertiles, respectively. Consequently, participants were grouped into two categories (high and low responses) on the dependent variable VAS, according to this criterion. Multiple discriminant analysis using a stepwise approach, was used to determine which variables significantly separated high (High-R) and low response (Low-R) groups, where the latter responses to treatments for MN corresponded to low and high post-treatment VAS scores, respectively.

8.3. **Results**

MANOVA and discriminant analysis

MANOVA results using Wilk's Lambda as the test statistic, indicated a rejection of the null hypothesis of no overall difference between High-R and Low-R group means ($W = 0.55$; $F_{[8,112]} = 19.7$; $p < 0.0005$). Summary statistics of mean and standard deviations for each dependent variable are provided in Table 8.1.

8.3.1. *Stepwise multiple discriminant analysis*

A canonical correlation of 0.79 indicated that 62.4% (i.e. R^2) of the variance between High-R and Low-R groups could be explained by linear combination of seven selected variables. However, using a significant ($p < 0.05$) stepwise change in Rao's V as the criterion for selection, further scrutiny revealed that only three out of the seven dependent variables made significant contributions to group separation. These three variables were set apart and subsequently entered into the discriminant function in the order inter-digital Cleft affected, PTT and Treatment allocation (MAN; CSI). None of the variables in each set were substantially related to each other ($r = 0.16$ to 0.28). Table 8.2 provides a summary of these results.

Table 8.1. Absolute group mean (standard deviations in parentheses) for variables associated with patients' clinical history, physical and anatomical characteristics, psychological perspectives and perceptions of functional capabilities and health assessed by response grouping (high [High-R]; $n = 18$]; low [Low-R]; $n = 20$]) to non-surgical treatment for MN.

Variables		High-R	Low-R
Pain duration	(wk)	226 ± 171	261 ± 232
Cleft affected		2.5 ± 0.5	2.8 ± 0.5 [*]
PTT [0 weeks]	(kg)	2.2 ± 0.9	2.7 ± 1.0 [*]
VAS [0 weeks]	(mm)	68 ± 21	67 ± 20
Age	(yr)	52.7 ± 17.7	54.4 ± 12.3
FAAM [dl; 0 weeks]	(units)	67.6 ± 15.5	59.7 ± 17.6
FAAM [spt; 0 weeks]	(units)	51.5 ± 20.3	37.6 ± 24.1
MOXFQ [ws; 0 weeks]	(units)	51.3 ± 25.5	58.3 ± 18.3 *
MOXFQ [p; 0 weeks]	(units)	58.2 ± 14.9	55.0 ± 13.7
MOXFQ [si; 0 weeks]	(units)	37.6 ± 23.4	39.8 ± 23.0
GHQ SF-36 [PCS; 0 weeks]	(units)	43.5 ± 7.6	44.1 ± 8.5
GHQ SF-36 [MCS; 0 weeks]	(units)	50.1 ± 9.6	51.6 ± 9.1
Treatment [MAN; CSI]	(*n*)	17; 1	0; 20 *

Key: MAN = manipulation; CSI = corticosteroid injection; MN = Morton's neuroma; VAS = Visual analogue scale (pain); PTT = Pressure threshold testing for discomfort; MOXFQ = Manchester-Oxford foot questionnaire; FAAM = Foot and ankle ability measures; SF-36 = General Health Questionnaire, Short Form-36;
* $p < 0.05$; [*] p approaching significance at 0.05.

Table 8.2. Stepwise multiple discriminant analysis of selected variables associated with patients' clinical history, physical and anatomical characteristics, psychological perspectives and perceptions of functional capabilities and health for response grouping (high [High-R]; $n = 18$]; low [Low-R]; $n = 20$]) to non-surgical treatment for MN.

Step number	Variables	Wilk's Lambda	Rao's V	Change in Rao's V	Significance of change (p)
[5]	Pain duration	0.68	11.9	0.2	0.81
[3]	Cleft affected	0.79	11.3	1.2	0.01
[2]	PTT [0 weeks]	0.79	10.1	0.8	0.05
[4]	VAS [0 weeks]	0.69	11.7	0.4	0.68
[6]	Age	0.68	12.1	0.3	0.72
[7]	FAAM [spt; 0 weeks]	0.65	12.4	0.3	0.71
[1]	Treatment [MAN; CSI]	0.79	9.3	9.3	0.005

Key: MAN = manipulation; CSI = corticosteroid injection; MN = Morton's neuroma; VAS = Visual analogue scale (pain); PTT = Pressure threshold testing for discomfort; MOXFQ = Manchester-Oxford foot questionnaire; FAAM = Foot and ankle ability measures; SF-36 = General Health Questionnaire, Short Form-36.

8.3.2. *Prediction of High-R and Low-R*

A three-variable model using pre-treatment metrics (0 weeks) was tested using the classification procedure to determine its ability to predict actual group membership. Internal classification results (Table 8.3) indicate that 89.5 % of all cases could be correctly assigned. When viewed in terms of prediction rate gain versus prior probability of group membership, these results suggest gains in predicting High-R and Low-R of 43.8 and 35.1 %, respectively. Internal classification typically provides an inflated estimate of a discriminant

function's true performance in a general population. Except for the modest sample size in this exploratory study, a similar procedure would have been used ideally as an external classification in order to determine the model's ability to assign unknown observations. Under such circumstances, a larger sample would have been divided into two approximately equal subsamples and the appropriate discriminant function applied to raw score observations from the other subsample to facilitate a double cross-validation. A future study would be able to attend to the latter.

Table 8.3. Internal classification results for multiple discriminant analysis associated with patients' clinical history, physical and anatomical characteristics, psychological perspectives and perceptions of functional capabilities and health for response grouping (high [High-R]; $n = 18$]; low [Low-R]; $n = 20$]) to non-surgical treatment for MN.

Actual group	Cases	Predicted group				Correctly assigned	
		High-R		Low-R			
	no.	no.	%	no.	%	no.	%
High-R	20	18	90.0	2	10.0		
Low-R	18	2	11.1	16	88.9		
						34/38	88.9

8.4 **Discussion**

There are a number of variables likely to affect the experiences and outcomes of those with MN. These include aspects of their clinical history, physical and anatomical characteristics, psychological perspectives and perceptions of functional capabilities and health prior to commencing treatment. Nevertheless, the composition of variables within a model that influences the positive outcome of treatment significantly, was relatively parsimonious. The patient who is affected typically by MN is most likely to achieve a high response to treatment displays a more lateral inter-digital cleft, has a lower pressure threshold for discomfort and importantly, will be undertaking manipulation as a non-surgical treatment.

The equality of metrics between High-R and Low-R groups for several indices of clinical history, physical and anatomical characteristics, psychological perspectives and perceptions of functional capabilities and health prior to commencing treatment, indicated that many of

these candidate variables were unable to contribute to discrimination. It was interesting to note that there appeared to be intra-group heterogeneity of responses amongst many of the latter variables. It would seem therefore, that when measured prior to treatment, variables such as VAS, duration of MN related-pain and other PROMs involving inventories of self-perceived functional capability and physical and mental health status, would not be able to contribute meaningfully to predicting successful clinical outcomes following non-surgical treatments for MN. Similarly, it is plausible that other subtle prognostic markers would also be ineffective.

It was notable that with the exception of allocation to treatment (manipulation), univariate comparisons of dependent variables were not always decisive and only contributed to High-R and Low-R group differentiation more holistically within multivariate modelling. In this respect, the dominance of allocation to manipulation treatment within the exploratory discriminant analysis predicting clinical outcome demonstrates this factor as having the highest relative importance within a hierarchy of influence and thus as such, indirectly corroborates much of the evidence within Chapters 6 and 7 (and visualised especially within Figure 6.3 as individual patient responses to MAN and CSI treatments) in which manipulation is favoured as an efficacious treatment.

It was also notable that PTT rather than VAS had contributed to a model discriminating between High-R and Low-R groups. While both metrics were considered as candidate variables, especially as the former outcome had shown acceptable clinimetric characteristics (Chapter Five), it may be that the specific assessment of a MN-affected joint for discomfort under pressure afforded by PTT rather than a more generic appraisal of perceived pain by VAS, contributed most to discrimination. Nevertheless, counter-intuitively perhaps, it was intriguing to note that a lower antecedent perceived threshold of discomfort (i.e. lower PTT) was associated with higher responses to treatment. It is plausible that a lower initial threshold and greater relative scope for change towards higher thresholds of discomfort as treatment progresses.

This multivariate analysis has shown that selected antecedent markers of the patient's physical and anatomical characteristics associated with MN, perceptions of discomfort and selection of treatment, taken together, can provide a significant prediction model for successful non-surgical treatment outcomes and correctly assigning 88.9 % of patients

(notionally exceeding substantially the ~ 50 % likelihood of belonging to either of the treatment options). Nevertheless, the predictive power of this model may not yet be sufficient for reliable practical or clinical use: a proportion of the response to treatment variance (11.1 %) has yet to be accounted for by this method. This points to other, as yet unidentified and untested, factors playing a role in determining successful treatment outcome. Furthermore, the modest sample size associated with the study meant that the model was limited to an internal classification, which as alluded to earlier, typically provides an inflated estimate of a discriminant function's true performance in a general population. Once again, the relative importance of selecting manipulation as the treatment modality within the discriminant model is paramount, as without it, internal classification recedes to 62.3 % prediction accuracy.

Another pragmatic limitation for this model is that other than the choice of best treatment modality for MN, the contributing factors are largely immutable and not amenable to prehabilitative interventions. As such, the model may have limited practical usefulness for directing pre-treatment alterations more effectively, but instead offer a tool for aspects of triage.

8.5 **Conclusions**

In conclusion, this study has offered an exploratory insight in regard to selected antecedent psychological and physical health factors contributing to efficacious outcomes associated with the non-surgical treatment of MN. Multivariate modelling has shown that selected antecedent markers of the patient's physical and anatomical characteristics associated with MN, perceptions of discomfort and selection of treatment provided a significant prediction model for successful non-surgical treatment outcomes, correctly assigning 88.9 % of patients in internal classification analyses. Ultimately, the predictive model is highly reliant on an *a priori* assignment of patients with MN to the efficacious treatment modality of manipulation, and as such, indirectly endorses the evidence favouring the latter treatment shown within Chapters 6 and 7.

CHAPTER NINE

General discussion and conclusions

9.1. **Review of thesis aims and objectives**

This chapter brings context and critical review to the results offered in previous chapters. In it, the advancement of knowledge is discussed, as are the clinical applications of the research findings. The potential for future research is also considered and some recommendations for the direction of such study are offered. Figure 9.1 mirrors the organisation of Figure 1.1 and offers a summary of findings from thesis's chapters, with descriptions of implications for clinical practice.

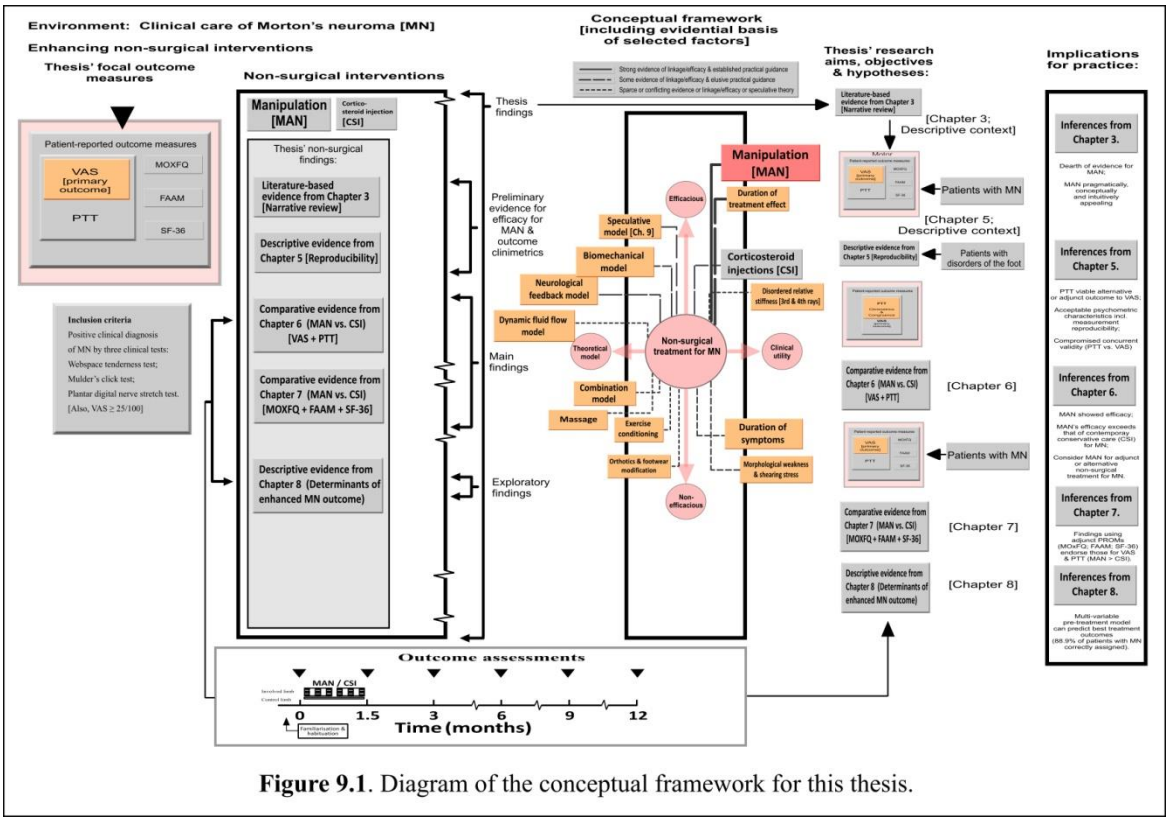

Figure 9.1. Diagram of the conceptual framework for this thesis.

This thesis has presented the rationale, methodological approach, and results of comparing two conservative interventions in the treatment of people with MN. The primary aim of this thesis was to investigate the efficacy of MAN as a conservative treatment for patients with MN. Prior to this study, the literature agreed that conservative interventions for MN demonstrated unsatisfactory results, with a recurrence rate of 47% (Valisena et al. 2018) and almost half of all sufferers progressing to surgery due to unrelenting pain (Jain and Mannan 2013). It has further been noted that surgical interventions are themselves subject to poor outcomes, with failure rates being reported as high as 30% (Bhatia and Thomson 2020). Despite a rigorous and methodical search, very few papers pertaining to MAN as an intervention for MN, could be identified within the current literature base. There were no prospective studies and only one, randomised controlled trial, which had combined MAN with mobilisation (Govender et al. 2007). As the first prospective, randomised study to explore MAN as a stand-alone intervention for the treatment of MN, this thesis' study adds value to the knowledge base by comparing a novel treatment approach to current best practice. Figure 9.2 summarises the aims, main findings and implications for clinical practice associated with Chapter 6 in which the thesis' primary outcome (VAS) and a novel outcome measure in MN research (PTT) had been studied.

PRIMARY QUESTION:	KEY FINDINGS of Chapter 6, including implications for clinical practice
Does MAN compare favourably to current best practice (CSI) for the treatment of MN? **Linear outcome measures.** **(VAS; PTT)**	• There were substantial gains elicited by MAN immediately after intervention (VAS Cohen's *d*, 3·3; 84·4%; PTT: *d*, 2·3; 147·0%;) were prominent and favoured MAN. Treatment improvements were retained substantively at 12 months after MAN's cessation. • Concomitant gains for CSI participants were modest (*d*, 0·4 to 1·0; 16·6% to 45·9%) • Recovery to asymptomatic status (VAS < 10mm/100 mm) in response to MAN and CSI similarly favoured MAN immediately after therapy (62% vs. 7%, respectively) and at each follow-up assessment (57% to 62% vs. 8% to 18%). • immediate gains for all MAN participants exceeded a minimum clinically important difference (MCID) criterion for VAS [20 mm] and also exceeded the performance changes of many control participants. • Retention of improvement in the perception of pain following MAN's cessation (VAS [Cohen's *d*, 3·4; 83·6%, *proportion of gain as a percentage*) was substantial, significantly better than baseline scores and consistently exceeded those for CSI ($p < 0·001$).

Figure 9.2. Summary of aims, findings and implications for clinical practice of Ch. 6.

The results involving VAS and PTT in Chapter 6 showed a superior efficacy for MAN to reduce self-reported pain and thresholds for discomfort when compared to CSI.

Figure 9.3 summarises the aims, main findings and implications for clinical practice associated with Chapter 7 in which focused attention on the thesis' secondary PROMs (MOxFQ, FAAM and SF-36). Similarly to the findings associated with VAS and PTT, MOxFQ, FAAM and SF-36 corroborated MAN's superior capability to improve functionality compared to CSI. Taken together, the latter findings suggest that MAN may demonstrate potential to improve first-line outcomes and reduce the incidence of onward referral to surgical colleagues. Future studies might go beyond this explorative trial to establish manipulative therapy's cost and logistical effectiveness, together with patient tolerance.

PRIMARY QUESTION:	KEY FINDINGS of Chapter 7, including implications for clinical practice
Does MAN compare favourably to current best practice (CSI) for the treatment of MN? **Non-linear outcome measures.** **(MOxFQ; FAAM; SF-36)**	• MOx saw substantial, immediate gains elicited by MAN MOxFQws [52·8%]; MOxFQp [45·5%]; MOxFQsi [39·2%]). Concomitant gains for the CSI group were modest by comparison. • Both treatments elicited significantly improved FAAMdl and FAAMspt ratings. MAN provoked greater improvements than CSI for both aspects of FAAM. • 12 month Retention of treatment-related gains for non-linear metrics largely mimicked the linear metrics of chapter 6, with all PROMs in all dimensions and at all time points favouring MAN over CSI. • SF-36 demonstrated poor sensitivity to all changes detected by other instruments. •

Figure 9.3. Summary of aims, findings and implications for clinical practice of Ch. 7.

The participant cohort in this study broadly matched those reported in the literature relating to MN. The gender bias heavily favoured females and the pain report of interdigital pain with weight-bearing, made worse with shoe gear was universal. Participants also reported paraesthesia or altered sensation of an intermittent nature which became progressively more frequent with time. The distribution of symptoms across the inter-digital clefts was again consistent with the literature with the majority of cases presenting in the third inter-digital cleft. As this study was designed to pragmatically mimic the clinical environment of the UK podiatrist, diagnosis was purely clinical. Whilst many studies opt for a radiological confirmation of diagnosis, robust evidence from within the current literature demonstrates that a clinical diagnosis is at least as sensitive and specific as a radiological one (Claassen et al. 2014), and this serves to give confidence to the diagnostic accuracy within this study.

9.2. **Implications for clinical practice of data studies involving VAS and PTT**

The use of pressure algometry in this trial was a direct attempt to offer a new and innovate method of assessment for MN. The goal was to limit treatment delay caused by referral for radiological tests such as USS. To achieve this, it was first necessary to validate the tool for use in the foot as this had never previously been accomplished. With this first step achieved it was then possible to demonstrate that PTT had the potential to identify joints which were failing to withstand appropriate joint stresses, signifying the potential presence of pathology. Such work has already been undertaken in the hand, where joints exhibiting pathology were shown to produce lower PTT scores than their asymptomatic counterparts (Wajed et al. 2012), but further work is required to establish if, and how this tool could be employed to aide accurate diagnosis of MN specifically.

Figure 9.4 summarises the aims, main findings and implications for clinical practice associated with Chapter 5 in which the psychometric characteristics (reproducibility and single-measurement reliability) of a novel outcome measure in MN research (PTT) had been studied.

SECONDARY QUESTION:	KEY FINDINGS of Chapter 5:
Is there single measurement reliability & reproducibility associated with indices of pressure threshold testing using algometry in adults?	• Systematic or learning effects are likely to intrude within any PTT assessment and as such, the first trial should be excluded from analyses and considered habituation or accommodation to test procedures. • PTT undertaken by inexperienced compared to experienced test administrators of algometry provoked greater measurement variability. • No differences in variability were noted between PTT scores associated with left and right limbs and amongst metatarsophalangeal joints. • Intra-session and inter-day reproducibility indicate a limited capability to discriminate differences in thresholds of discomfort based on a single PTT. • Limiting the number of repeat measurements to just three is associated with error of 13%, which would be an acceptable clinical protocol.

Figure 9.4. Summary of aims, findings and implications for clinical practice of Ch. 5.

In general, comparisons of the modes of delivery for PTT show that algometry offered statistically at least as good if not better equivalent levels of measurement reproducibility and single-measurement reliability compared to other traditional methods of assessment such as VAS and inventories of function including FAAM and MOxFQ, during intra-session and inter-day assessments. As such, the current data lends support to the assessment of MN by means of algometry. Chapter 5 also helped to elucidate the most appropriate measuring protocol, allowing for corresponding levels of error. Importantly, the data established the intrusion of a systematic learning effect which served to render the first PTT score 'unreliable' and subject to errors other than the requisite random error needed for this type of psychometric assessment. In other words, in all situations and at all measurement points, the first measurement should be discarded as a habituation to test procedures and should not be used for comparison. Furthermore, an inexperienced PTT user provoked greater measurement variability, suggesting that experience is an important consideration in regard to this tool. There was also greater variability noted in measurements across days

as opposed to across sessions. When looking for changes in the magnitude of 1.0 kg and more in the clinical setting, this variability is not worrisome but should still be considered.

In Chapter 5, it was identified that an error tolerance of 5% in PTT inter-day testing (95% confidence limits) would require some 15 trial measurements to be taken. Clearly this is impractical in the clinical setting, both from a time constraint point of view and also from a patient compliance standpoint. However, reducing the number of required measurements to just three, increases the error to around 13%. Given that the painful foot in MN tends to record initial PTT scores below the 3 kg mark, this would represent a maximum error of 0.36 kg. The expected PTT of the asymptomatic foot is in excess of 5.5 kg, some 80% above the upper threshold of the symptomatic foot. That being the case, a 13% error may be considered within tolerance in the clinical setting and therefore a three-measurement protocol could be gainfully employed.

9.3. **Factors in enhanced outcomes of non-surgical treatment of Morton's neuroma**

When considering VAS and PTT as predictors of outcomes rather than merely monitors of progress, the weight of evidence leans toward PTT. Chapter 8 highlighted that only three of thirteen candidate variables offered any prognostic value relating to MN. PTT was one such variable, but VAS showed no utility in this regard. This serves to reinforce the concept that VAS and PTT are measuring different physiological changes in response to intervention. The fact that they did not enjoy a significant baseline or treatment-based correlation reinforces this idea somewhat. Figure 9.5 summarises the aims, main findings and implications for clinical practice associated with Chapter 8 in which the hierarchy of relative importance amongst antecedent and baseline metrics was considered in relation to predicting favourable outcomes following treatment.

SECONDARY QUESTION:	KEY FINDINGS of Chapter 8, including implications for clinical practice
What are the key factors in enhanced outcomes of non-surgical treatment of Morton's neuroma?	• Only 3 of 7 variables made significant contributions to group separation. inter-digital Cleft affected, PTT and Treatment allocation. • 89.5 % of all cases could be correctly assigned. • VAS, duration of MN pain and other PROMs were not able to predict clinical outcomes. • PTT rather than VAS contributed to a model discriminating between High and Low responders. • Lower baseline PTT score was associated with higher responses to treatment.

Figure 9.5. Summary of aims, findings and implications for clinical practice of Ch. 8.

Whilst participants were invited to report their foot pain by means of the VAS scale, it is conceivable that some degree of error and/or bias could intrude on this procedure as conceptualising their pain may have a significant global effect. Conversely, the distinctly localised pressure, leading to immediate and local pain, produced by the application of the PA device would likely lead to a focused, localised pain report by means of the subsequent PTT. Furthermore, as MN is widely considered a malady of mechanical origin, the mechanically induced pain which results in the PTT may arguably mimic the symptoms of MN closely and therefore correlate well with the patient's recognition of symptoms. When considering these points, it could be argued that PTT is the tool of choice over VAS for monitoring MN changes, due to its sensitivity, reliability and ability to help predict outcomes. Certainly, the data presented in Chapters 5, 6 and 8 gives weight to the statement that the PROMs such as VAS for pain and PTT, as a clinician-reported outcome, outperform PROMs, involving inventories such as MOxFQ, FAAM and SF-36.

9.4. **Mechanistic insights, development of the MAN approach and implications for clinical practice**

Manipulation has been used as a therapeutic intervention for several centuries, with references found from around 2700 BC in the Chinese manuscripts of Kong-Fou (Leach 1994) through to the detailed recordings of their use by Hippocrates and their continued

employment to the present day (Pettman 2007). For a fuller history of the intervention, the reader is referred to section 8 of Chapter 2. To date however, other than the findings within this thesis that confirm the efficacy of a specific dosage of MAN and its superiority over CSI, the mechanisms at play in lower extremity manipulation remain incompletely understood and the means by which MAN may have an impact on conditions such as MN remains an arena for debate. Extrapolating from research on spinal manipulation though, may offer us some tentative insight into what happens in cases of MN, and how this might influence judgements on the optimal dosing within MAN treatments.

Despite several papers in the MN literature referring to nerve entrapment as an aetiology for the condition, this may prove to be an over-simplification of the pathoneuromechanics of the malady. It may be speculated that it is unlikely that the axon potential transmission of the nerve is dramatically interfered with by means of mechanical compression at the inter-digital cleft. Whilst such compression injuries have been demonstrated as a component of pathologies such as spinal stenosis (Morishita et al. 2006), the same study found that disc herniation was insufficient to reproduce such a degree of compression pathophysiology. There is good research which demonstrates that peripheral nerves are rarely physically crushed by the surrounding structures (Song et al. 2003; Haavik et al. 2021). What has been shown, in animal studies at least, is that considerable forces of compression are required to create neural disintegration, but that far lower magnitudes of compression can be sufficient to allow normal nerve functionality to co-exist with expressions of mechanical hypersensitivity and allodynia (Hubbard and Winkelstein 2008), as is seen in cases of MN. This suggests that the mechanical compression in MN is insufficient to impede neural communication as there is no loss of nerve function reported in the literature. Instead, the experience is more likely to be, one of repeated nerve irritation and subsequent inflammatory processes, and not entrapment. These inflammatory reactions subsequently induce altered feedback from the PNS to the CNS. It therefore appears that the concept of relieving mechanical compression on the nerve by manipulating is extremely unlikely to be a full and accurate summation of the therapeutic process.

A more plausible theory is that MAN reduces frictional and distension stresses on the nerve whilst simultaneously disrupting mechanical adhesions within the joint complex (Evans 2002), which in turn, facilitates a return to a greater articular range and quality of motion,

with a consequential increase in proprioceptive afferent nerve inputs from the manipulated joint to the CNS.

A supplementary hypothesis to be challenged in future research is that high-velocity, low-amplitude thrust (HVLAT) manipulations to joints, have the potential to flood the CNS with "normalised" mechanoreceptive inputs from the PNS and thereby, induce a central pain modulation process that inhibits nociception. Such manoeuvres are commonly associated with an audible, and occasionally a palpable, pop or crack, known as "cavitation", which is generally accepted to signify a successful manipulation that has taken the joint beyond its own paraphysiological barrier and subsequently reduced the internal joint pressure by fracturing the synovial fluid. Evans reports on strong evidence that demonstrates the efficacy of manipulation but concedes that the mechanisms of action remain elusive. However, there are some effects that are unique to HVLAT manipulation and occur in tandem with the incidence of cavitation. The most pertinent of these from a CNS communication point of view, is the release of neuropeptides from the manipulated joint, which initiate communication with the CNS (Evans 2002). This is in keeping with the findings of Chapter 7 that showed an improvement in the pain report and a corresponding improvement in processes that are controlled by the central nervous system – in this case walking and standing, as reported in the MOxFQ.

Such a process has been demonstrated with spinal manipulation in a rat population (Reed et al. 2017). This changes the parameters of manipulative intervention altogether. If the therapeutic benefit is not solely a mechanical one at the point of action, but also a CNS processing response to PNS stimuli at the site of injury, then the response to the manipulation is both a biomechanical reorganisation and a CNS reimagining and remapping of the inner body and external world schemas (Taylor et al. 2010; Holt et al. 2016).

It could be argued that if the improvements demonstrated in this thesis were exclusively of a biomechanical nature, then the social interaction scores of participants should not be expected to improve significantly. Improving the function of a single digit would not in isolation, improve social functioning, but where the said improvement in function is in tandem with corresponding CNS responses, then global changes can be expected to follow. Nevertheless, it was notable that the thesis' findings within Chapter 7 demonstrated a marked improvement in MOxFQsi scores. This 'talks to' the potential for MAN directed

at the lower extremity, having the capability to impart a meaningful impact on the CNS, as well as the PNS and the local tissues.

Every aspect of our daily life depends on appropriate sensorimotor integration; it is this that allows us to seamlessly engage with the world around us. Such integration leads a baby to smile at the sight of its mother, or makes a person retract their hand from a hot surface. This system relies on a two-way feedback loop, with proprioceptive feedback confirming motor activity and motor response reaffirming proprioceptive information (Taylor et al. 2010).

It could be speculated that when insult or trauma creates biomechanical dysfunction at the MTPJ joint, this in turn leads to altered afferent input from the joint proprioceptors and therefore, by default, to a maladaptive alpha motoneuron response, leading to further aberrant motion and restriction of the MTPJ. This self-maintaining cycle will force the CNS to alter its external world schema to "understand" the world through the lens of the injured joint. Haavik and co-workers state the position concisely when they say "Over time, these changes in the awareness of the CNS of what is occurring inside the body and the world around it are thought to lead to maladaptive changes in neural function, as well as maladaptive changes in body structure and function, worsening its ability to adapt and respond to internal and environmental cues, thus leading to the development of less than ideal motor control, a variety of symptoms, diseases and disorders" (Haavik et al. 2021).

Injury, and the resultant pain and inflammatory reactions, all play a part in altering proprioceptive input. One example of this is the suggestion that whiplash injuries induce disturbances of the vestibular and visual systems because the insult alters afferent proprioceptive input from the cervical spine to the CNS, which in turn, alters the CNS response (Solarino et al. 2009). Similarly, it is conceivable that in the case of MN, trauma results in aberrant afferent input from the PNS, which the CNS cannot decipher, forcing the CNS to rely on previous experiences already mapped into the schema to control local motor function. Sensorimotor control is now effectively dependent on an outdated operating system, resulting in sub-optimal outcomes. This in due course, leads to repetitive dysfunction at the MTPJs, with associated increased neural tension and pain. Lund et al. have demonstrated these neural imbalances between the excitatory and inhibitory influences over muscle activation around painful tendons that result in, or from, an apparently

protective adaptation (Lund et al. 1991). Rio et al. have expanded on this theory relating to recurrent musculoskeletal pain (Rio et al. 2016).

As has been confirmed by the findings of efficacy favouring MAN over CSI substantively within Chapter 6 in particular, one can envisage that manipulation may yield improved efficacy and effectiveness by challenging internal imbalances, whilst also being well-tolerated by patients. Because of these self-reported improvements (see MOxFQ and FAAM in Chapter 7), a re-envisioning towards contemporary practices for treatment might consider a retreat from the current prescribing of CSI towards MAN, with the intention of increasing the density of neural stimuli for the purpose of beneficial neuromuscular adaptation. Further research might usefully consider the latter approach in conjunction with its optimal dose.

It is not contentious that the CNS relies heavily on proprioceptive feedback from the PNS to coordinate movement and posture (Hellström et al. 2005). Furthermore, a relationship has been established between increased sympathetic excitation and decreased proprioceptive input, with a resultant decrease in motor activity (Grassi et al. 1993; Roatta et al. 2005). One should then consider the possibility that circumstances which lead to an increase in sympathetic activity, will also result in a proprioceptive deficit and a dampening of motor specificity, leading in turn, to inappropriate muscle tone and activity. It has been postulated that this may be, at least in part, responsible for chronic pain (Passatore and Roatta 2006). Passatore and Roatta embolden their hypothesis with the reminder that epidemiological studies frequently explore the relationship between chronic pain and a stressful working environment. Additionally, the literature reports chronic pain sufferers experience disturbances in control and coordination of movement, associated with a deterioration in proprioceptive information. It was notable therefore, that the formulation of MAN treatment used in this thesis appeared to be successful in surmounting heterogeneity in the duration of pain experienced by patients, since the extent of gains for VAS and PTT were independent of the antecedent pain's duration (Chapter 6).

A 2005 study was able to demonstrate that an increase in sympathetic nervous activity had a direct effect on muscle spindle activity, reducing proprioceptive and motor function (Hellström et al. 2005). They conclude that such interactions will likely impair any body function in which muscle spindles are involved. Because the spindle controls real-time muscle tension, a loss of stability in movement would likely ensue and a suboptimal, time

delayed re-stabilisation would be required. Such deficits are hinted at in this thesis by the poor MOxFQws baseline scores and the diminished baseline PTT scores relative to the contralateral limb.

The recruitment of additional agonistic and antagonistic muscles would inevitably create increased joint stiffness in an attempt to produce the required joint stability. Therefore, proprioceptors are implicated in establishing and maintaining MTPJ function and dysfunction. If the CNS fails to accurately pinpoint the exact spatial location and movement pattern of a given MTPJ, it cannot appropriately control the movement patterns that are desired for the joint. If an injured articulation does not heal fully and the CNS mapping continues to be inaccurate, then integration of the subsequent aberrant sensory feedback, generated by the joint's new movement pattern, is destined to lead to an increased maladaptation. If proprioceptive input remains aberrant, as a result of prolonged joint dysfunction, it will, in turn, contribute to the maintenance of the abnormal movement pattern of that part of the foot.

It is recognised that, with time, this compromised strategy is a precursor to pain (Hellström et al. 2005). Whether such patterns exist in MN could be usefully explored in a future study by using computerised gait analysis software, or by establishing a reliable measurement of digital plantarflexion. No such tools were available to this research team, but the predictive nature of PTT, identified and discussed in Chapter 8, does potentially shed some early light on this area. Since the lowest PTT scores were associated with the greatest gains, and lower PTT scores have been shown to reliably detect dysfunction (Fischer 1987; Fischer 1990), one can postulate that the localised maladaptation detected at baseline (Chapter 6) has a greater potential for improvement, if starting from a lower baseline. Additionally, improving MOxFQsw scores (Chapter 7) may relate to improved movement pathways, although this too, remains untested.

Pacinian corpuscles are mechanoreceptors which play an integral role in proprioceptive feedback. They exhibit a strong bias for congregating in tight clusters around the MTPJs (Germann et al. 2021), with almost half of all plantar Pacinian corpuscles being grouped in this area, whilst the midfoot and rearfoot saw only sporadic, solitary corpuscles spread throughout (Sugai et al. 2021). Given that the forefoot is a dense source of proprioceptive feedback, heavily relied upon by the CNS to communicate information about our ever-

changing contact with the ground, it is conceivable that a forefoot proprioceptive deficit would have a profound impact on foot stability and function. Deficits in proprioceptive function affect the body's ability to predict, correct and learn from errors of movement, which leads to marked defects in fine motor control, whilst still permitting gross movement. This is perfectly demonstrated in the gait of those suffering from sensory neuropathies. It is becoming increasingly clear that deficits in proprioceptive activity have deleterious effects that go much deeper than just position, posture and mobility. Bornstein et al. have shown that the proprioceptive system plays a crucial role in the maintenance of musculoskeletal biology and is intimately involved in such processes as fracture repair. They state that its failed regulation can be seen in conditions such as scoliosis and hip dysplasia. They also expand on how proprioceptive deficits alter muscle activation patterns, leading to abnormal mechanical signals to cells and affecting the integrity of the joint itself (Bornstein et al. 2021).

This interdependence, between the CNS and the PNS, has been demonstrated in a study by Holt et al. They showed that a short course of spinal manipulation, with no extremity manipulation, improved ankle proprioception (Holt et al. 2016). Since there was no intervention at the ankle, one is led to conclude that this may be more related to the global impact of the CNS redrawing its schematic maps in response to proprioceptive stimuli at the lumbosacral plexus, than to any local effect. It would be logical to propose that a dysfunctional foot may have a similar effect on low back proprioception, because the proprioceptive pool for the lower body includes both areas. Thus, future research might usefully incorporate metrics of proprioceptive capability and status to better challenge this speculative conceptual model.

The research into the intricacies of these complex neural mechanisms is still in its infancy, but such complexities might help to explain why manipulation may have the analgesic effect that has been shown in this study (Chapters 6 and 7). Given that there was no alteration of participant's footwear, activity or weight-bearing, the observed effect can be explained by the manipulation in the following way: The introduction of a wave, or series of waves of normative neural input by way of a HVLAT thrust of the joint beyond its paraphysiological border and the subsequent increase in joint motion, will revolutionise proprioceptive input and once again, evoke a change in post-insult CNS schematic processing. In other words, the foot in its injured state, is likely to experience altered neural inputs and subsequent

responses as compared to its functioning in the pre-injury state. This culminates in a decrease of the nociceptive threshold and a corresponding increase in muscle tone and joint tension. In the clinical environment, this manifests as a painful response to normally non-painful stimuli (such as is seen when the clinical tests for MN are positive) and a loss of "play" in passive joint motion, coupled with a loss of range in active motion. Pickar and Wheeler (2001) state that this decreased motion is due to an increase in Gamma motoneuron activity that creates an abnormal hypersensitivity to stretch stimuli, thereby impeding joint mobility. If there is no challenge to this altered functional paradigm, then this becomes the status quo for the structures involved. During a manipulation moment, the joint is forced beyond its current functional parameters; new neural information is sent from the PNS, informing the CNS of a rapid increase in joint function and range of motion. This comes from the proprioceptors of the joint surfaces, the Golgi tendon apparatus and also the neural components of the muscle spindle, which report on posture and movement. Such a rapid and full range stretch will stimulate an increased Alpha motoneuron response and dampen the Gamma motor neuron activity, thereby resetting the Gamma motor bias somewhere closer to pre-injury levels. Such input will create a new schema within the CNS and once again, alter how the local joint and associated structures are controlled by, and interact with, the CNS and PNS. This new schema should, by virtue of the 'normal motion' mimicking of the manipulation, closely resemble the pre-injury schema.

Because manipulation is primarily a mechanical act, the mechanoreceptors are most likely responsible for the initial and subsequent transmission of stimuli. The primary response to the latter process is a motor one, starting with the local musculature. Nevertheless, an autonomic effect is also inevitable, with enhanced proprioceptive signalling. This in turn, should improve the motor response and begin to normalise function and feedback. Again, future studies should identify dosing for optimal responses in this context.

The central processing of neurological interactions is not the only neural activity worthy of consideration when exploring extremity manipulation in future studies that could follow the findings in this thesis. In evolutionary terms, physical pain has been intrinsically and powerfully linked to our survival, motivating the individual to actively avoid dangerous or threatening behaviours. The historical benefit of this trait has largely been lost as the direct threats to human life from the external environment have greatly decreased in number and severity. In modern society, many episodes of pain no longer serve to confer a survival

advantage. This is especially true with chronic pain (Mouraux and Iannetti 2018). In the case of MN, Mulder described this phenomenon succinctly in his seminal paper when he stated that "…those sudden sharp pains which make Morton's metatarsalgia such a crippling – though innocent – disease" (Mulder 1951). According to Scholz et al., neuropathic pain after peripheral nerve injury such as in the case of MN, can be considered chronic beyond the three-month duration point (Scholz et al. 2019). Using this definition, all participants in this study can be classified as having had chronic neuropathic pain prior to, and at the point of, enrolment.

In 1965, two neurophysiologists published a seminal paper on pain thresholds and pain control which revolutionised the thinking regarding mechanisms of pain (Melzack and Wall 1965). Their work, with some minor modifications, is largely how we understand the function of pain to this day. Their gate control theory of pain states that non-painful stimuli being transmitted at the same time as nociceptive stimuli through the PNS, will effectively "close the gate" on the nociceptive stimuli and subsequently, no pain will be registered at the CNS level. The reason for this is that non-noxious stimuli activate interneurons, which in turn, inhibit the progress of nociceptive signals. However, we now know that in the periphery, this can be complicated further by the ability of damaged peripheral neural structures to independently produce pain, without recourse to the sensory receptors at all (Millan 1999).

The gate theory predicts that movement, rubbing, massaging and even kissing will lead to a neurological response that causes presynaptic inhibition of dorsal root nociceptor fibres and so serves to inhibit the progress of afferent nociceptive information to the CNS. In this way, the sensory fibres create a hypothetical "gate" that can open or close the system to pain stimulation. The gate can be forced open by a sufficiently large number of nociceptive action potentials, or forced closed by sufficient sensory feedback. In other words, the greater the nociceptive stimulation, the less secure the gate becomes. One can see that this is a balance between the level of sensory information and the level of nociceptive information. The greater the sensory stimulus, the greater the noxious stimuli will have to be in order to force the gate open and register pain. Following this through helps us to understand why many patients are often in more pain over-night or first thing in the morning, when little sensory or motor stimulus has occurred, leaving the gate easily opened by a small amount of nociceptive feedback. Additionally, it is clear how manipulation can have an analgesic

effect by increasing the range of motion at the site of pain, and by increasing the sensory stimulus due to touch, pressure, thermal alteration, stretch and release. Increasing the sensory feedback in this way will in turn, serve to dampen the body's response to nociceptive stimuli, effectively closing the gate. Furthermore, it has been posited that higher cortical functions contribute to this gating mechanism. This allows for psychological phenomena to directly affect the subjective experience of pain.

Having considered what may be happening at the CNS level during extremity manipulation, we should also consider what responses are evoked at the site local to the manipulative intervention. What intra-articular responses occur that may impact the local neurological and biomechanical processing?

The joints of the human skeletal system are structured to withstand long-term cyclical loading. The synovial joints of the forefoot cope well with thousands of repetitive loads and rotations on a daily basis, as well as the shock impact of ground contact. Their success is in part due to the relationship between articulating cartilage and synovial fluid. Inside each joint of the forefoot, the cartilage is coated by, and immersed in, synovial fluid. The cartilage forms a mesh which traps synovial fluid within its pores, leading to stress-related lubrication akin to stepping on a fluid-filled sponge. This ensures that the joint surfaces enjoy remarkably low levels of friction and shearing stress. De Boer et al. explains that under load, the cartilage deforms and causes synovial secretion which, in turn, reduces friction and enhances the capacity of the joint to bear load (De Boer et al. 2020). The cartilage is hyperelastic and its deformation under load serves to inhibit the free-flow of synovial fluid, preventing it from immediately escaping the loaded environment and thereby, increasing interstitial pressure within the joint capsule and creation of the optimum load-bearing environment. Because fluid movement is impeded rather than arrested by the cartilage, and because the high viscosity of the fluid itself creates resistance to movement, synovial fluid will, given time, drain from this high-pressure environment (Popov et al. 2021). This stress-relaxation function ensures that initial joint loading is met with immediate high pressure, which steadily dissipates (De Boer et al. 2020). In other words, every time a step loads the MTPJs, there is an instantaneous increase in intra-joint hydrostatic pressure, which serves to lubricate and protect the joint surfaces, whilst simultaneously promoting locomotor efficiency.

When one considers that during ambulation, the load visited upon the joints of the forefoot is several magnitudes of body weight, it is evident that the miniscule lining of cartilage alone is insufficient to ensure prolonged protection. Brandt et al. state that although cartilage enjoys excellent shock-absorbing qualities, it is too thin at these sites to be the primary joint protector (Brandt et al. 2008). This role is shared with the periarticular muscles and the synovial fluid. Passive muscle stretch through the contact phase of gait, will result in the absorption of considerable energy and affords excellent protection to the local structures. Brandt et al. note that "The energy produced by normal walking is sufficient to tear all the ligaments of the knee; that this tearing does not occur routinely attests to the importance and effectiveness of the active energy absorption by the muscles that surround the joints and cushion them from mechanical stress" (Brandt et al. 2008).

Conversely, an unanticipated alteration of load, even of insignificant magnitude, could potentially damage joint integrity, as the protective muscles have insufficient opportunity to activate. Recent research has shown that, with age, the protective startle reflex is delayed and exaggerated, resulting in greater landing impact when one is unprepared for an event (Sanders et al. 2019). If this is related to MN, it may explain why onset tends to be in the fifth decade of life and beyond. Interestingly, it is smaller trips and stumbles that are likely at play here, as falls from greater heights afford the musculature more time to respond, whilst a trip from a kerb, though seemingly innocent, deprives the joint of muscle protection and demands increased shock absorption from the internal joint structures (Brandt et al. 2008). Additionally, the presence of muscle weakness may present a similar risk even in the absence of sudden loading. An inability of the muscle to perform its protective duties will undoubtedly put greater strain on the other associated structures. Brandt et al. demonstrate this well in their paper, discussing the impact of quadricep's weakness on knee integrity.

Muscle function is not limited to producing movement or to the aforementioned protection remit. Muscles are also sensory units, which report position and motion to the CNS by way of proprioceptive inputs. If there is weakness and/or dysfunction in that unit, then it is conceivable that it contributes to poor function of the startle reflex, by way of offering inaccurate proprioceptive feedback to the CNS and effectively blurring the vision of the body's whereabouts. Muscle weakness has long been associated with osteoarthritis, the assumption being that poor joint use leads to muscle atrophy. It may in fact be the other way around (Slemenda et al. 1998). Bone, like cartilage, is viscoelastic; that is, the fluid in

the tissue acts to dampen the effects of loading. With rapidly applied impulsive loads, however, the viscoelasticity of the tissue becomes problematic. Viscoelastic damping requires time to have an effect: fluid must flow. About one third of normal adults are afflicted with micro-incoordination, and in these persons, the important muscle-based protective mechanisms needed to dampen the forces of joint loading, are not fully coordinated. These individuals therefore subject their knees to impulsive loading during walking. Future studies might usefully explore the possibility that micro-incoordination would increase the cascade of effects involving neural stress within the third cleft particularly, where there is increased tethering of neural tissue.

When a manipulative force is applied to a joint, the distention of the joint surfaces is resisted in part by the tensile integrity and cohesive qualities of synovial fluid. As the fluid is stretched under strain and the joint space enlarged, the hydrostatic pressure falls and particles of carbon dioxide that have invaded the fluid, begin to coalesce. As this bubble of gas rapidly increases in diameter, its surface tension decreases making its perimeter increasingly unstable (Bang et al. 2015). If the hydrostatic pressure drops to a negative value rapidly enough, the synovial fluid will fracture (Huang et al. 2016), the violence of which alters the surface tension and ruptures the gaseous bubble (Oratis et al. 2020). Synovial fluid will now rush into this void created by the escaping gas (Evans 2022).

Furthermore, Watt et al. demonstrated that joint distraction produced long-lasting molecular changes in synovial fluid consistent with a clinically meaningful improvement in knee pain for sufferers of osteoarthritis (Watt et al. 2020). Their distraction was mechanically induced and sustained for a period of several weeks, but it may be that such changes, or similar, can also be induced by short, repeated distractions, such as are performed during joint manipulation, and the subsequent increased joint play under weight-bearing. Only further study will illuminate these issues.

Whilst the results of this study show promise for the therapeutic benefits of manipulative interventions for MN, further multi-centre and multi-clinician studies are now required in order to establish whether these results hold under the burden of deeper scrutiny. Additional studies should also explore the learning curve associated with the manipulating physician.

To facilitate such endeavours, the healthcare community should develop manipulation as a treatment pathway. Encouragement for this direction is offered by the significant improvement offered over the current conservative treatment of choice, CSI in this study.

There is now a need for research which furthers observation and review of MAN of the foot. Increasingly, there is a demand for healthcare research to deliver realistic healthcare options, which operate not only in the research realm, but in the clinical world, where decisions are needs and resource based. If MAN is to become a mainstream first-line intervention, then cost analysis research should demonstrate MAN's relative value, together with a clear understanding of the actual costs incurred in its function. Research should also focus on creating and defining resource-efficient means of delivery, which serve to enhance the patient experience.

9.5. **Further achievements of the data-driven studies**

The secondary aims of this thesis included assessment of the psychometric qualities of selected PROMs and assessing the relative importance of factors contributing to the successful treatment of MN. The data explored in chapter seven showed that MOxFQ and FAAM demonstrated modest interrelationships with both the VAS and PTT PROMs which were also employed in this thesis. MOxFQ, FAAM and SF-36 PROMs further disclosed significant differences in all categories when comparing MAN to CSI. Perhaps the most profound difference was evident in the measures within MOxsi, where the MAN group enjoyed a significant and sustained improvement over the twelve-month period, whilst the CSI group journeyed to a modest improvement at the three-month follow-up period, before enduring a steady regression backward to around baseline scores by the twelve-month point. A similar dominance of MAN over CSI was demonstrated in the FAAM outcomes where peak gains in both domains disproportionately favoured MAN (40.8% versus 19.8% for FAAMdl and 66.1% versus 23.1% for FAAMspt). Both the MOxFQ and the FAAM consistently portray an immediate and sustained beneficial change in the MAN group, which sharply contrasts with the responses of the CSI group, in which the modest improvement was of a considerably lesser magnitude and much shorter duration.

9.6. **Implications for clinical practice of the achievements of data-driven studies (MOxFQ, FAAM and SF-36)**

The MAN protocol employed in this thesis of 6, weekly episodes of treatment provoked immediate responses in MOxFQ, FAAM and SF-36, which surpassed statistical, precision and reliability criteria (~ 4% - 10%). These results suggest that MAN may be a useful addition to the clinician's range of options for conservative care of MN. As a first line intervention, MAN may prove to be robust enough to stand-alone but could certainly be recruited as an adjunct to contemporary treatments.

One implication from the data study reported in chapter seven is the need for greater scrutiny of the SF-36 for use in conjunction with MN. As mentioned in previous chapters, it has frequently been utilised to assess the effectiveness of various therapeutic interventions for MN. During the main trial of this thesis, the SF-36 appeared relatively unresponsive, despite moderate to large changes being detected by other instruments. Other recent studies have also reported that either seven, or all eight of the subscales of SF-36 detect no changes in response to MN related interventions (Habashy et al. 2016; de Oliveira et al. 2019; Pabinger et al. 2020). This calls into question the value that SF-36 brings to such studies. Given that there are a large number of PROMs readily available to the researcher and the clinician alike, one is tempted to conclude that the SF-36 is not the best suited for studying MN.

In a wider context, the value of such PROMs in the evaluation of MN would appear to be limited to the research setting. Whilst they were able to shed some light on the participants changing ability to walk/stand, partake in sport, complete tasks of daily living and socially interact which could not be achieved using VAS and PTT metrics, it is not clear that having such measured data on these aspects of life would make any meaningful impact on treatment choices and protocols or on outcomes. Indeed, the data of Chapter 8 clearly indicates that the MOxFQ, FAAM and SF-36 were particularly poor predictors of outcomes. Given that the individuals' motivation for seeking treatment is almost always driven by perceptions of pain, it is prudent to ensure that the primary outcome measure is a reporter of such pain. This indeed has been the default position for many years, with VAS being the instrument of choice by many. Add to this the predictive prognostic value of PTT and it becomes difficult to argue a case for PROMs such as MOxFQ, FAAM and SF-36, in the clinical realm. Beyond the pain report, it is commonplace for sufferers to report restrictions in activity and social interaction and there can be no doubt that improving these variables can add meaningfully to the individual's experience. However, given the limited time and

financial resources available in the clinical setting, it is perhaps impractical and unnecessary to burden both the patient and the clinician with such data gathering, when it offers little in return and it may be argued that PROMs, such as MOxFQ, FAAM and SF-36, have their natural home in the research setting.

9.7. **Further insights into the clinical benefits of MAN**

In terms of MN, this is the first randomised study to explore MAN as a stand-alone intervention. It builds on a previously weak evidence base of case studies and retrospective audit. The body of evidence exploring the benefits of MAN as a treatment option in musculoskeletal medicine is growing steadily, but still there remains a paucity of evidence relating to maladies of the foot. Whilst the results within this thesis are certainly encouraging, many areas require ongoing exploration to establish how and when MAN creates clinical benefit. For example, the dosage of MAN employed has received little or no investigation and it may be that the six, weekly dosage regime described in Chapter four is in fact, an over-treatment of some degree. A cost benefit analysis would help to identify optimal dosing, going forward.

There was however a distinct clinical benefit identified within this thesis, insomuch as MAN was shown to produce an immediate, significant and lasting nociceptive effect (Chapters 6 and 7). Given that pain is the primary symptom reported for MN, this is a welcome step forward. This suggests that clinicians may finally be able to offer a long-term conservative intervention, which enjoys relatively high success rates and may prove to reduce the number of sufferers progressing to surgery, with its associated increased costs, risks, and rehabilitation. Add to this the MOxFQsw and MOxFQsi reported improvements within Chapter 7, and a picture emerges of MAN positively impacting the more subtle aspects of MN, which in turn, impact on the life of its victims.

9.8. **Benchmarking of MAN with concurrent treatment methods**

The findings of this thesis serve to push MAN to the forefront of conservative care as, along with CSI, this exploratory study (Chapters 6 and 7) shows that it might have the capability to now enjoy stronger favourable evidence than any other conservative intervention. If the outcomes here can be replicated in multi-centre, multi practitioner studies in future, then an argument could be made for MAN as the gold standard intervention. Of additional value, is that MAN can be employed alongside any of the other conservative treatments,

potentially increasing the effectiveness of any single treatment episode. That being the case, there is a sound rationale for proposing that MAN should now be considered as a first-line intervention in every suitable case, whether as a stand-alone intervention, or as a combination therapy.

9.9. **Achievements of the literature review comparing the efficacy of MAN treatment properties using levels of pain and discomfort threshold outcomes**

The literature review served to highlight the fact that there is a dearth of research pertaining to extremity manipulation. Even in the wider gamut of maladies of the lower limb, MAN does not figure significantly as a treatment option. This may be due in part to researcher bias as the vast majority of manual therapists target their MAN on the spinal column and it follows that most of the research effort would be directed likewise. It is hoped that works such as this one, will begin to create some momentum and interest into extremity manipulation and serve to set an upward trajectory from the current barren landscape.

9.10. **Implications of the thesis' findings for clinics and research**

Emanating from this thesis is the need to establish by further research and clinical discourse, where exactly MAN sits in the gamut of treatment options for MN. On face value, this study would suggest that MAN is superior to CSI (see again Fig. 6.1), which in turn is generally considered the conservative intervention of choice. Therefore, MAN may be worthy of consideration as a front-line intervention. However, further study may challenge that stance, or perhaps identify that a MAN and CSI combined approach is better still than either stand-alone intervention. This would be unsurprising as both interventions seek to impact the condition via differing mechanisms. In MN, despite the nerve structure itself being degenerate, CSI is not thought to target the fibrosis within the nerve tissue, but rather the inflammatory reactions local to the digital nerve and thereby reduce local neural pressure (Bhatia and Thomson 2020). This study suggests MAN acts by reducing the local mechanical stresses and normalising the neural stimuli. In light of the findings of this thesis, consideration should be given to the mode of action of MAN in order to better understand why MAN should have such an impact on MN. Deeper understanding of the PNS and CNS interplay may help us to predict which sufferers may enjoy better outcomes and also whether MAN of the spine may serve to further enhance therapeutic outcomes for MN. While the work of Haavik et al. and others serves to demonstrate a CNS adaptation and reconfigured processing in response to spinal manipulation (Haavik et al. 2021), it is as yet

a matter of speculation, whether this also holds true for extremity manipulation. Schueren and Hunger et al. argue that, despite the joint-specific intervention, changes seen in response to extremity manipulation, such as alterations in the body's centre of pressure, cannot readily be reconciled as merely localised phenomena (Schueren et al. 2022). There is though currently, no model or evidence that offers insight into the various benefactions of the CNS and PNS in response to extremity manipulation. This thesis does serve to equip the research community with insight into the improved load-bearing capabilities of the MTPJs post MAN (see again Fig. 6.1) and it also speaks to the currently under-reported analgesic potential of extremity manipulation. Similarly, Figure 6.2 offers clear visual representation of the numbers of participants in each group attaining asymptomatic status. Such graphical data is valuable and helps the reader grasp the context of between-group difference. Compared to the direct visual representation of the statistically significant patterns of group-related differences between MAN and CSI over time for the study's primary outcome (VAS) offered within Figure 1(a), Figure 6.2 presents instead an important alternative perspective for clinicians as to the comparative extent and rapidity with which recipients of MAN and CSI treatments achieve a status of being asymptomatic based on the responses to VAS assessments.

By inspecting group mean z-score responses instead of the equivalent raw data and thus mitigating the extent of heterogeneity amongst participants within the MAN grouping in particular, Figure 6.4 also offers important insights for the reader to assess the relative merits of deploying either VAS or PTT within this clinical context. This figure importantly captures and standardises patterns of VAS responses relative to each participant's fluctuations and variability (using standard deviation as a proxy) over time. Controlling statistically for inter-participant variability in this way revealed some statistical incongruence (and thus concerns for their inter-changeable use) between VAS and PTT patterns of response over time, which was not obvious within the group mean raw score data shown in Figures 6.1(a) and 6.1(b), respectively. Congruence amongst PTT and VAS responses was the subject of interest within Chapter 5 in its evaluation of concurrent validity of PTT, but the graphical representation of these characteristics was logically presented within Chapter 6, in which longitudinal patterns of PTT and VAS have been evaluated.

In this way, the thesis begins the process of equipping the researcher with a new tool for measurement of pain and dysfunction in the foot. It also adds to the body of work regarding

the efficacy of CSI for MN and expands on the debate regarding USS versus anatomically guided injections for MN. The data provided within this thesis will equip future researchers for a deeper dive into the mechanisms of action of MAN as well as the exploration of new combinations of treatment for MN.

From a clinical perspective, the benefits of this thesis are the development of a new way to measure foot pain and its progress, by means of PTT, and the introduction of a rapid and cost-effective intervention for MN. If the results obtained here can be broadly replicated in the clinical environment, then this would represent a number of substantial gains for the MN sufferer. Most obviously, any improvement in conservative treatment outcomes would serve to reduce the likelihood of an individual progressing to surgery. This means both financial and time cost savings for the treatment provider as well as for the patient. For the individual who avoids surgery, there is a corresponding reduction in health risks. Surgical intervention brings with it the risks of deformity; incision scarring; infection; loss of neural function; complications of anaesthesia; complications of wound healing and the need for revision surgery. All of these risks are entirely absent when the patient is successfully treated with extremity manipulation. Given that the training required to competently manipulate the lower extremity is significantly less than that required of a surgeon, there is scope to train a large body of clinicians in these methods. That means more timely interventions, which further leads to additional cost efficiencies. Whilst the cost savings against injection therapy may be less obvious, the reduced clinical risk remains clear. The risk of anaphylaxis, injection flare, tissue necrosis and injection-induced infection are all absent for MAN, which comes only with a risk of joint sprain to the relevant MTPJ.

Since it is currently commonplace to offer orthoses as the first line of treatment, this thesis also offers potential for efficiencies to be derived by reducing the volume of orthotic provision. A recent systematic review concluded that there is no evidence in favour of orthotic intervention for MN and recommended that they should not be employed for this condition (Thomson et al. 2020). Despite this, the same research team noted that orthoses are the commonest form of treatment (Bhatia and Thomson 2020). It is possible that the fear of doing nothing for the patient, drives the clinician to provide orthoses despite the dearth of evidence. For some, it may be about ameliorating the patient until onward referral can be arranged. Other clinicians may also argue that their own clinical experience recommends orthoses to them. However, Smitham et al. note that between 28-50% of

patients are dissatisfied with their devices (Smitham et al. 2012). Eddison et al. noted that the *per* orthotic cost in the UK ranges from £58 - £106, depending on the NHS trust. This is the cost of the device only and in the case of MN, some man-hours will likely be required in addition to this, as most orthoses will require some form of bespoke modification. The cost of staffing on a *per* appointment basis was estimated to fall between £48 - £239 (Eddison et al. 2022). In other words, the cost to the NHS for the provision of an orthotic device to a patient cannot fall below £106, assuming said provision occurs at the initial appointment, requires no subsequent modification and is provided by the lowest grade clinician. The results of this thesis offer the clinician a rapid and effective alternative to orthotic therapy and increase their treatment options at the initial consultation. Cost savings would be incurred by the resultant reduction in both initial and repeat orthotic provision, although this would have to be balanced against the slightly increased frequency of the patient's clinical attendance.

In summary, the implications of this thesis on future research are such that PTT can gainfully be employed as an objective outcome measure for studies investigating the human forefoot. Additionally, MAN should be considered for further exploration as it relates to MSK dysfunction in the lower limb. The mode of action and optimal dosage of MAN are also worthy of future research efforts. From a clinical perspective, podiatrists who work in MSK should consider additional training in extremity manipulation and should also consider adopting PTT as an objective outcome measure for MN. Clinicians should also re-evaluate their use of PROMs, especially the SF-36. It may be argued that, even with this limited evidence from an exploratory trial, that MAN may supplant orthotic therapy in the hierarchy of treatment options, and this should be further explored in future research.

9.11. **Strengths and limitations of the thesis' studies**

There were a number of strengths within this study. The fact that potential participants were initially identified and then screened against the inclusion and exclusion criteria by podiatrists who were wholly independent from the study reduced the chance of researcher induced selection bias during recruitment. Additionally, the potential participants demonstrated a significant range of pain severity and symptom duration, meaning that those experiencing only mild pain (VAS < 20/100) or those who had been suffering for only a short time could be excluded. This may inadvertently lead to prevalence incidence bias (otherwise known as Neyman bias) (Wang and Cheng 2020), but given that MN is a

progressive disorder and severity is thought to be linked to duration, the potential for such bias should be minimal, but cannot be discounted. However, the inverse could equally be argued that the inclusion of mild cases would potentially lead to overly optimistic study outcomes. Sample size was sufficient to guard against type II error in particular, even with some loss-to-follow-up, and the extent of superiority of MAN over CSI minimised any intrusion from type I errors. Both of the treatment interventions were delivered by an experienced clinician with over twenty-five years of experience in MAN and injection therapies for the foot. This helped mitigate the effect that poor technique or lack of experience might have had on the results. The impact of recall bias was limited but not excluded as participants were asked to score their pain as it currently felt, and PTT measurements were taken in real time. The potential remains for some degree of physiological or psychological carry over effects, but this can reasonably be expected to be minimal. The questionnaires of PROMs such as MOxFQ, FAAM and SF-36 asked participants to recall information pertaining to their health status over the previous three months and it is possible that recall bias was a factor in these reports. However, Rasmussen et al. have demonstrated that pain recall over a three-month time-period is stable at the group level (Rasmussen et al. 2018). Physiological and/or psychological carry-over effects may have unavoidably intruded into some aspects of measurement and intervention, despite all of the above, and some caution should therefore be exercised in the extrapolation of findings from this thesis.

Whilst the use of only one clinician to provide all diagnostic tests, clinical interventions and measurements offers the aforementioned protections, it also serves to introduce potential bias. There is a possibility that the clinician's own favoured treatment will prevail because of the clinician's subconscious bias toward it. Additionally, there is a risk of unconscious incompetence as the clinician employs a technique which they use less frequently than his or her favoured options. Given that the MAN group achieved excellent outcomes and the CSI group enjoyed outcomes that matched those already published in the literature, such bias would appear to represent only a minimal risk in this thesis.

The decision to use a single clinician was made, because of the need for any manipulator to demonstrate good forefoot manipulation skills (Kurtzman et al. 2016) and also partly due to financial constraints. An inexperienced manipulator would likely produce less than optimal outcomes, and experienced manipulators in the podiatric field are currently few and

far between. Considering the pragmatic design intention together with the potential strengths and weaknesses of different approaches it was determined that a single clinician was the optimal protocol in this instance.

Being a single centre, single clinician trial was recognised as building some frailty into the study design at the expense of pragmatically adhering to usual clinical practice. The option to pursue a multi-centred and multi-clinician approach was considered and approaches were made to additional podiatry departments in both Fife and Dundee. Ultimately, it became clear that the scarcity of podiatric manipulators would render such a study impractical at this stage. With the steady development of lower extremity manipulation, it is hoped that this approach to a more expansive investigation could be revisited in the near future.

Further limitations include methods of symptom measurement. Part of this thesis investigated intra and inter-rater agreement in PTT measurement. This investigation compared an experienced male rater to an inexperienced female rater and found that intra-rater scores were consistent but inter-rater measurement was not. This potentially limits the value of PTT scores obtained in the MAN versus CSI study for any inter-rater reflection, as they were all collected by a single clinician. Future studies should help to identify acceptable ranges for normal PTT scores.

In summary, limitations to this study were related to its delivery and design. Logistical and ethical constraints had precluded routine assessment by means of medical imaging. Similarly, experimental controls in this trial were focused on an extended period of longitudinal evaluation of the performance capabilities of the ipsilateral foot and differential inter-group responses, rather than on those of the contralateral foot. Other limitations included that group allocation could not be concealed from participants or from those overseeing the participants testing administration and treatment as it was evident to all whether one was receiving an injection or not.

Similarly, physical activity behaviors associated with travel to and from the MAN's venue for its delivery and assessments were not monitored directly and varied physical activity might have elicited heterogeneous carry-over effects amongst the patients' responses to MAN. Participants' self-perceived pain assessments within the MAN protocol had been monitored, but not reported here. Furthermore, while the patient's compliance with the

MAN's treatment prescription was monitored directly, this approach that may not be facilitated in all environments, such as within self-managed care. Nevertheless, future studies could aim to identify optimised MAN dosing and approaches for its scalability and delivery amongst varied care environments. This study's findings were derived from a modestly sized sample of participants (n = 61), aged ~53 years, with a female gender bias (77%; Table 6.1), which might preclude generalisation. Observed Type II error rates were modest (≤ 0.12) and appeared to offer suitable experimental design sensitivity and statistical power amongst the selected indices of participants' perceptions about functional capacity amongst concomitant pain and discomfort.

Further research will be required in a number of key areas to progress this body of work further. Optimum dose-response characteristics for MAN should be explored in order to ensure maximum treatment potency and most efficacious resource employment. Additionally, given that VAS and PTM appear to be measuring related but separate physiological responses, some effort to establish which is more pertinent for MN sufferers may be rewarded with better symptom tracking and ultimately potentially more accurate outcome prediction. In conclusion, both VAS and PTT outcome measures employed here agreed that MAN offers more immediate and more robust outcomes than CSI as an intervention for MN.

9.12. **Scope of application of MAN**

As further studies develop a more robust argument for the application of MAN, it is feasible that it becomes a first line intervention for many musculoskeletal conditions of the lower extremity. The results presented in chapters six and seven serve to highlight the potential for MAN to play a leading role not just in the treatment of MN but also potentially other nerve entrapments of the foot and ankle such as Baxter's neuritis and Tarsal tunnel syndrome. Whilst they were not directly studied here, they pathophysiology is not dissimilar to MN and it is a pragmatically appealing concept that similar interventions could yield similar outcomes.

9.13. **Revisiting the aetiology and treatment of MN**

Given that MAN is an intervention which targets the joints in the locality of the digital nerve, rather than the nerve itself, the effectiveness of this approach serves to open an array of questions challenging previously held beliefs regarding MN. The most commonly held view of the aetiology of MN is that it is a compression of the digital nerve under the DTML.

This proposed theory is extremely difficult to reconcile with the success of joint manipulation as a treatment. The nature of the MAN procedure offers no direct impact on the DTML. Furthermore, since the neighbouring metatarsal is not immobilised when delivering the therapeutic thrust, it is unlikely that any meaningful stretch or elongation of the DTML occurs. In the absence of such stimuli to either the nerve or the DTML, it is difficult to perceive how changes in the nerve/DTML relationship might come about in response to MAN. Additionally, the finding in this thesis that the neighbouring MTPJ consistently registers a lower PTT score than its counterparts also serves to throw a shadow over the theory of DTML involvement. If the cause of the pathology is exclusively DTML compression, then the MTPJ should remain unaffected. If the argument is driven that dysfunction of the neural tissue and/or the DTML lead to joint dysfunction, then it follows that the MTPJ on either side of the affected cleft, should suffer. Neither of these scenarios proves to be the case and therefore, this thesis serves to strongly caution the reader against the DTML compression theory.

Intuitively, the less popular joint trauma theory sits more neatly alongside the results of this study. This aetiology is given more weight by the findings of Kim et al. who demonstrate that the MN lesion consistently sits some way distal to the DTML and adjacent to the MTPJs of the neighbouring digits (Kim et al. 2016). Since MAN targets maximal rotational movement of the MTPJ, with an associated distraction of the joint, it is compatible with the concept of releasing nerve tissue trapped within, or irritated by, a previously immobile MTPJ and of reducing nerve irritation caused by its dynamic collision into an immobile joint during gait. Furthermore, since none of the other etiological theories involve the MTPJs in any fashion, it is difficult to rationalise how manipulating specifically, and only the MTPJs, would result in such meaningful benefit. For these reasons, this thesis leans toward the joint trauma theory as the most likely explanation for the onset of MN.

It is not beyond the realms of possibility that none of the currently offered aetiological theories are substantively accurate. Given that asymptomatic neuromas have been detected in some 30% of the population (Zanetti et al. 1997; Bencardino et al. 2000), and that the neural tissue degeneration seen on post-surgical histological examination is consistent with age-related degeneration seen in the asymptomatic population (Morscher et al. 2000), it is possible that the apparent neural lesion is in fact, incidental and the pathology is purely joint related. Certainly, based on the significant response seen to the predominantly joint-focused

intervention of this thesis, there must be a degree of joint involvement, which has to date, gone completely unacknowledged since Morton first postulated the possibility (Morton 1876).

9.14. **Suggestions for practice and future research work**

According to the American college of surgeons *"participation in clinical trials requires that surgeons have proven capability and knowledge in the conduct of the research-related operations. Failure to do so may expose patients to risk and compromise the ability of the researcher team to test the study's hypothesis"* (Kurtzman et al. 2016). It is probable that this same issue exists in the field of manipulation, which also being a manual skill relies on clinicians to be adept at a given procedure. No clinical trial of manipulation, that was reviewed, has described such a vetting procedure or indeed tried to highlight the learning curve for a manipulative technique. A review study into keyhole surgery for the gallbladder suggests that lack of this basic information may well be why there are such great differences in outcomes in this common surgical procedure. They found only five articles provided a precise cut-off value to see proficiency in the learning curve, but that these five ranged from 13 to 200 laparoscopic cholecystectomies (Reitano et al. 2021).

There is a dearth of quality epidemiological studies pertaining to MN. Such studies would help to target training and resource allocation according to community needs. It would be beneficial to perform detailed cost/benefit analyses exploring the employment of MAN versus other conservative care for MN. This would allow an objective valuation of the treatment possibilities and therefore guide patient and clinician choices.

MAN should be explored as a combination therapy with CSI, orthoses, exercise therapy and other conservative interventions. Given these results and the known impact MAN has on the neurologic system, it would seem logical to develop studies comparing manipulation to other conservative treatments for other nerve entrapment pathologies of the lower limb such a Baxter's neuritis and tarsal tunnel syndrome (Gyer et al. 2019).

The results demonstrated here suggest a significant change in neurological foot function. If that is so, it is plausible that manipulation also changes mechanical foot function and studies to establish if that is the case, would be enlightening. In a clinical context, treatment pathways for MN should be expanded to include MAN and training in MAN should be

encouraged within the podiatric profession. There may be scope to develop an exercise protocol for MN, that would mirror the effects of manipulation and thereby, possibly reduce the burden of care and the impact of the pathology. Because the data explored here does not relate directly to exercise, further research would be required to establish the feasibility and effectiveness of an exercise protocol. However, exercises which target increasing the range of motion available within the forefoot and especially the MTP joints, may achieve similar outcomes to the MAN protocol here. In other words, if exercises can target a mechanical increase in MTP joint plantarflexion, or even the delivery of plantarflexion-led neural stimulation, then this may also lead to changes in the individual's pain report. One would certainly expect differences in mechanical and neurological response to exercise as compared to MAN, but it is not beyond the imagination to conceptualise a degree of overlap. If MAN is introduced into podiatry clinics there should be an ongoing audit of effectiveness similar to that in surgery so that we can understand the exact shape and length of the learning curve.

9.15. **Possible future development pathways**

A case can be made for podiatry departments to invest in pressure threshold meters to better collect and collate outcome data and therefore, improve our understanding of pain thresholds and sensitivity. For example, we are not currently aware if pain sensitivity is directly related to patient's weight or not. Since current diagnostic tools for MN are limited by cost restraints, future research could explore the role of PTT as a specific diagnostic instrument. The early indications from the results of Chapter eight are that PTT may offer some value in this regard. This would allow an in-house diagnosis to be confirmed at relatively low cost.

9.16. **Final conclusions**

From the findings of this thesis which represents a first to market exploration of MAN for MN, manipulation would appear to be an efficacious first line treatment protocol. It compares favourably to contemporary practice and has the potential to reduce the suffering of those afflicted with MN. Despite the limited evidence, as a result of this thesis and previous efforts, MAN now enjoys a stronger evidence base than the commonly employed orthotic intervention for MN and should, where conditions permit, be preferred in the hierarchy of treatment options. Further logistical studies should be performed to evaluate its effectiveness when compared to CSI, additional conservative interventions and surgical

outcomes. Depending on the outcomes of these subsequent studies, the podiatry profession should look to include manipulation in its post graduate continual professional development courses with the aim of improving patient's access to this safe and efficient treatment protocol. Furthermore, deeper inter-professional collaboration with our colleagues who manipulate should be encouraged for the betterment of clinical outcomes. Additionally, a review of aetiological theories in light of the findings of this thesis, may be warranted should subsequent studies align with current findings. To that end, this thesis marks the start of the exploration of MAN in the podiatric field and equips the profession with the initial data and insight upon which to build. Further, it identifies future areas of study to challenge the place of MAN. Finally, it also serves to develop the author's ability to pursue deeper independent research with a more critical understanding of the process.

In summary, the programme of research within this thesis identifies the following conclusions: (i) Manipulation elicited significant and clinically relevant improvements and retention in self-reported levels of pain, discomfort and functionality for patients electing treatment for Morton's neuroma; (ii) Exploratory multivariate modelling provided a significant prediction model for successful non-surgical treatment outcomes; (iii) Single measurements showed compromised precision amongst serial assessments of PTT.

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Appendix I

Ethical approval

Lothian NHS Board

Mr David Cashley
Podiatrist
School of Health Sciences
Queen Margaret University
Musselburgh EH21 6UU

Dear Mr Cashley

South East Scotland Research Ethics Committee 01

Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG

Telephone 0131 536 9000

www.nhslothian.scot.nhs.uk

Date 15 June 2015
Your Ref Our Ref

Enquiries to: Sandra Wyllie
Extension: 35473
Direct Line: 0131 465 5473
Email: Sandra.Wyllie@nhslothian.scot.nhs.uk

A randomised controlled trial to compare the clinical effectiveness of lower extremity manipulation to that of steroid injection in the treatment of Morton's Neuroma:

A pragmatic study 15/SS/0099 129586

The Research Ethics Committee reviewed the above application at the meeting held on 10 June 2015. Thank you for attending to discuss the application.

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 Mrs Sandra Wyllie, sandra.wyllie@nhslothian.scot.nhs.uk. 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.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

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

The Participant Information Sheets – (and protocol as applicable) should be revised as follows:-

1. It should be detailed where the sites that will be used for recruitment will be.

2. Detail how long each study visit will take.

3. Ensure that the contact details for the NHS complaint procedure are included rather than QMU.

4. Detail that the manipulation process may be a bit painful.

5. Amend the wording regarding informing the GP from "..we will automatically inform your GP.." to "…with your consent we will inform your GP.."

The Consent Form – (and protocol as applicable) should be revised as follow:-

1. Please insert the following additional point for the monitor clause : "I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Sponsor [NHS Lothian], from the NHS organisation or other authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records."

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

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

NHS Sites

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

Non NHS sites

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

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee queried whether the second set of pre-intervention questionnaires on the same day was necessary?

The research team advised the Committee that there are different QoL questionnaires and that they were keen to see which was most suitable.

Recruitment arrangements and access to health information, and fair participant selection

The Committee were unclear as to where the clinic for recruitment actually is.

The Committee were informed that there are several clinics through out Edinburgh that will be used for recruitment, and agreed to detail this information in the PIS.

The Committee queried how will the clinicians be made aware of the inclusion/exclusion criteria.

The research team explained that they would liaise with the clinicians to make ensure that they were advised.

The Committee sought clarification as to how the initial contact will be made.

The Committee were advised that the patient will contact the research team.

The Committee queried whether patients who did not meet the exclusion criteria and had to go back onto the NHS waiting list would have a delay in their treatment.

The research team reassured the Committee that the patients would not be disadvantaged if this was the case.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee noted that the PIS does not detail how long each appointment visit is expected to take.

The research team clarified to the Committee that the first appointment should take about 1hr and subsequent visits about 15 mins.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee noted that no travel expenses had been mentioned and queried whether there would be anything made available.

The Committee were advised that there was no funding available for travel expenses.

Informed consent process and the adequacy and completeness of participant information

The Committee requested that information for the NHS complaint procedure is included rather than the QMU.

This was agreed to.

The Committee noted that the manipulation may be painful and requested that this information is detailed in the PIS.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		14 August 2014
GP/consultant information sheets or letters	Version 1	27 May 2015
Letters of invitation to participant	Version 1	27 May 2015
Other [Manchester-Oxford Foot Questionnaire (MOxFQ)]		
Other [SF-36 QUESTIONNAIRE]		
Participant consent form		
Participant information sheet (PIS)		
REC Application Form [REC_Form_22052015]		22 May 2015
Research protocol or project proposal		
Summary CV for Chief Investigator (CI)		
Summary CV for supervisor (student research) [D Santos]		
Summary CV for supervisor (student research) [J Veto]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language		
Validated questionnaire		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

D Santos had a declaration of interest and left the room during discussions of this application.

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

After ethical review

Reporting requirements

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

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

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

User Feedback

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

HRA Training

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

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

Yours sincerely

Dr Chee Wee Tan Vice Chair

E-mail: sandra.wyllie@nhslothian.scot.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Dr Fiona Coutts*
Elizabeth Brownsell, NHS Lothian

South East Scotland REC 01

Attendance at Committee meeting on 10 June 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Janet Andrews	Retired Associate Specialist	No	
Mrs Christine Beadle	Research Nurse	Yes	
Dr Gail Corbett	GP Partner	No	
Dr Kyle Gibson	CT2 Doctor (ACCS Anaesthetics)	Yes	
Dr George Howat	Retired - Computing Services	Yes	
Dr Calum MacKellar	Director of Research	No	
Mrs Linda Morrow	Director of Community Stroke Services	Yes	

Mrs Patricia Perry	Lecturer - Faculty of Health and Life Sciences.	Yes	
Dr Derek Santos	Senior Lecturer - Faculty Of Health Sciences	Yes	
Dr Lillian Schweizer	Retired Molecular Geneticist	Yes	
Dr Sandy Small	Clinical Physicist / Head of Nuclear Medicine Physics	Yes	
Dr Sara Smith	Senior Lecturer- Dietetics	No	
Dr Chee-Wee Tan	Lecturer in Physiotherapy	Yes	(Chair for this meeting)

Also in attendance:

Name	*Position (or reason for attending)*
Dr Alex Bailey	Scientific Officer
Mrs Sandra Wyllie	REC Manager

South East Scotland REC 01
Waverley Gate
2 - 4 Waterloo Place
Edinburgh
EH1 3EG

Telephone:
0131 465 5473 12 November 2015

Mr David Cashley
Podiatrist
School of Health Sciences
Queen Margaret University
Musselburgh
EH21 6UU

Dear Mr Cashley

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		August 2014
GP/consultant information sheets or letters	Version 1	May 2015

Letters of invitation to participant	Version 1	May 2015
Other [Manchester-Oxford Foot Questionnaire (MOxFQ)]		

Study title: **A randomised controlled trial to compare the clinical effectiveness of lower extremity manipulation to that of steroid injection in the treatment of Morton's Neuroma: A pragmatic study REC reference: 15/SS/0099 IRAS project ID: 129586**

Thank you for your letter of 11 November 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 15 June 2015

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Other [Referral Clinics]		
Participant consent form	Version 3.2	15 June 2015
Participant information sheet (PIS)	Version 5	15 June 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

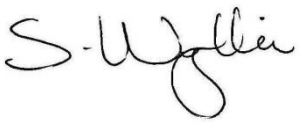
Other [SF-36 QUESTIONNAIRE]		
Other [Referral Clinics]		
Participant consent form	Version 3.2	15 June 2015
Participant information sheet (PIS)	Version 5	15 June 2015
REC Application Form [REC_Form_22052015]		22 May 2015
Research protocol or project proposal		
Summary CV for Chief Investigator (CI)		
Summary CV for supervisor (student research) [D Santos]		
Summary CV for supervisor (student research) [J Veto]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language		

Validated questionnaire		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/SS/0099	**Please quote this number on all correspondence**

Yours sincerely



Sandra Wyllie REC Manager

E-mail: sandra.wyllie@nhslothian.scot.nhs.uk

Copy to: *Dr Fiona Coutts*
Elizabeth Brownsell, NHS Lothian

Appendix II

Participant information sheet

Queen Margaret University
EDINBURGH

Participant Information Sheet

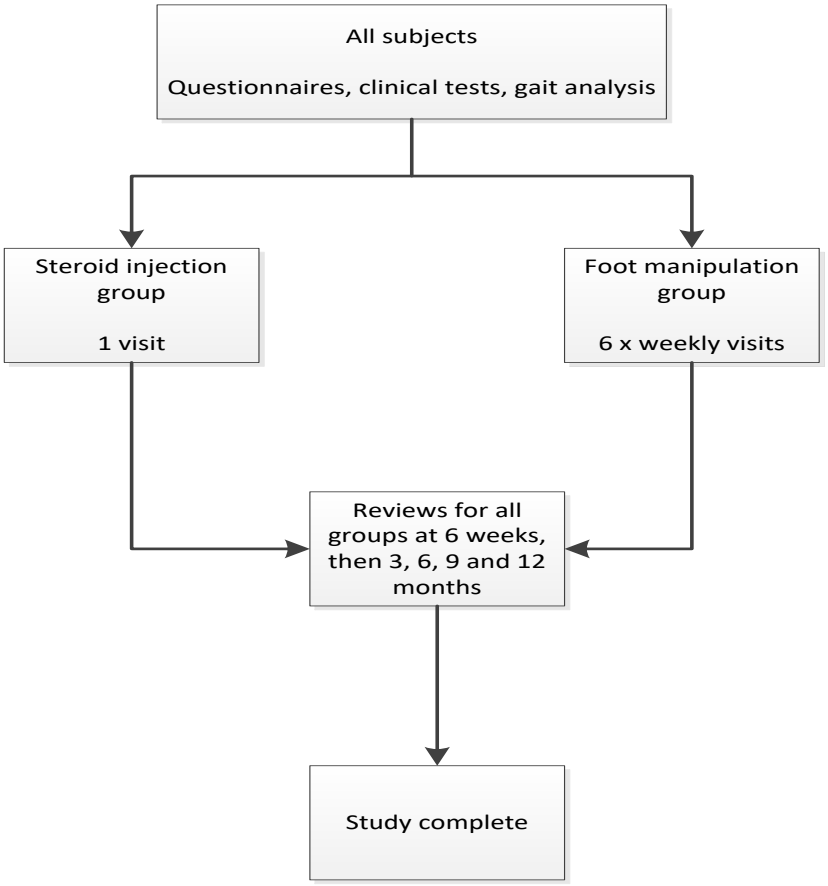
"A randomised controlled trial to compare the clinical effectiveness of lower extremity manipulation to that of steroid injection in the treatment of Morton's Neuroma."

Lay title: *"What is the most effective treatment for Morton's Neuroma; steroid injection or manipulation."*

You are being invited to take part in a trial to compare two different conservative treatments for Morton's Neuroma. Before you decide whether or not to take part, it is important to know why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Contact us if anything is unclear or you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
Morton's Neuroma is a common condition that causes pain in the ball of your foot but treatments other than steroid injection and surgery have not been extensively researched. We want to find out which non-surgical treatments work best for this condition. This study will compare two different conservative treatments – steroid injection and foot manipulation.

Why have I been asked to take part?
We need volunteers who have been diagnosed with Morton's Neuroma so that we can compare the outcomes of their treatment.



Do I have to take part?
No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. You do not have to take part and you will always be free to withdraw from the study without consequence. Even if you withdraw from the study, we will make sure that you receive the treatment you need for your foot pain.

What will happen if I take part?

When you first attend the university you will be asked to complete three questionnaires. You will also be asked to rate your pain on a sliding scale. A small pressure meter will be pressed onto the sole of your foot to give the researcher a reading of how much pressure elicits discomfort in the ball of your foot. After this you will undergo a series of short clinical tests in order to confirm the diagnosis of Morton's Neuroma. You will then be asked to walk over a computerised walkway which will give the researcher information about how your foot is functioning. After this you will be assigned to one of the treatment groups. Your first visit will last approximately 90 minutes. Depending on which group you are in you will either receive a steroid injection or foot manipulation as a treatment for your foot pain. If you are in the manipulation group, you will be treated every week for six weeks. Each of these visits will last about 20 minutes. The steroid group only need to be seen once in the first six weeks. All participants will then be reviewed after six weeks, then 3,6,9 and 12 months from the start of their treatment. These review appointments will last no more than an hour.

What are the possible benefits of taking part?

Because there are two different treatment arms to this study, you can quickly and easily access further treatment for your condition if you are not responding to your initial treatment. Once the study has been able to establish which treatment works best for Morton's Neuroma you will be able to have that treatment, even if you were not in that treatment group to start with.

What are the possible disadvantages and risks of taking part?
It is not thought that there are many disadvantages; however, it may be that your recovery is slower than it would have been normally if you are assigned to a treatment group that does not work for you. If you are assigned to the manipulation group then you may find the treatment momentarily uncomfortable. If this is the case, it will subside quickly. If you are in the steroid injection group, there is a small risk of side-effects from the injection, including facial flushing, anaphylaxis and changes in skin colour at the injection site.

What happens when the study is finished?
Once the study is finished the two different treatments will be evaluated and reported in the health care literature. You will be offered the most effective treatment and further intervention if you require it.

Will my taking part in the study be kept confidential?
All the information we collect will be kept confidential and there are strict laws which safeguard your privacy at every stage. Your name will be removed from the data so that you cannot be recognised from it. All consent forms and any other identifying material will be destroyed within three months of completion of the study. We will request your permission to inform your GP that you have agreed to take part in the study. Please let us know if you do not want us to contact your GP.

What will happen to the results of the study?
We will publish the results in a peer reviewed journal so that other clinicians can assess the value of these treatments for their patients. You will also be given a lay report of the findings.

Who is organising the research and why?
This study is organised by David Cashley in the QMU podiatry department, in part fulfilment of a PhD.

Who has reviewed the study?
The study proposal has been reviewed by Dr Derek Santos of Queen Margaret University and by William McMurrich of Lothian NHS Trust. A favourable ethical opinion has been obtained from QMU Divisional Ethics Committee and from South East Scotland Research Ethics Committee.

If you have any further questions about the study please contact David Cashley on: (0131 6100790) or email: Dcashley@qmu.ac.uk. If you would like to discuss this study with someone independent of the study please contact: Dr Kavi Jagadamma email: KJagadamma@qmu.ac.uk

If you wish to make a complaint about the study please contact:

NHS Lothian Customer Relations and Feedback Team

Waverley Gate
2 – 4 Waterloo Place
Edinburgh
EH1 3EG

Thank you for taking the time reading this information sheet.

Appendix III

Participant consent form

Queen Margaret University
EDINBURGH

CONSENT FORM Title of Project: *"A randomised controlled trial to compare the clinical effectiveness of lower extremity manipulation to that of steroid injection in the treatment of Morton's Neuroma."*

Lay title: *"What is the most effective treatment for Morton's Neuroma; steroid injection or manipulation."*

Name of Researcher: DAVID CASHLEY

Please initial box

1. I confirm that I have read and understand the information sheet dated 15/06/2015 (Versio 5) for the above study. I have had the opportunity to consider the information, ask question and have had these answered satisfactorily.

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

3. I agree to take part in the above study

4. I understand that if I am assigned to the steroid injection group of the study I shall receive a
injection of local anaesthetic and steroid.

5. I understand that if I am assigned to the manipulation group then I will need to attend once
week for six weekly treatment sessions.

6. I give permission for my G.P. to be informed of my participation in this study.

7. I understand that relevant sections of my medical notes and data collected during the stud
may be looked at by individuals from the Sponsor [NHS Lothian], from the NHS organisation c
other authorities, where it is relevant to my taking part in the research. I give these individual
permission to have access to my records.

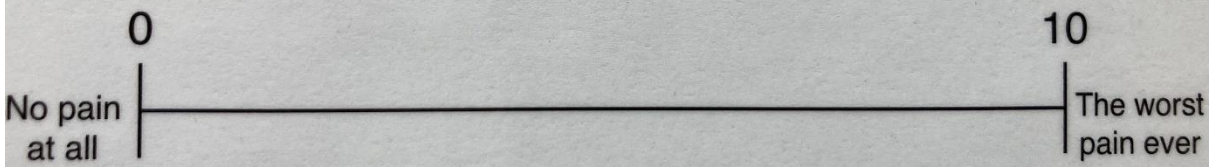
Name of Patient	Date	Signature
David Cashley		
Name of Person taking consent	Date	Signature

Appendix IV

Visual analogue scale for pain

VISUAL ANALOGUE PAIN SCALE

0 is no pain. 10 is the worst pain you have ever experienced. Draw a vertical line through the printed line to show where your foot pain is this week.
(Your previous score is shown in red)



School of Health Sciences
Queen Margaret University

Appendix V

Manchester-Oxford foot questionnaire

Manchester-Oxford Foot Questionnaire (MOxFQ)

English version for the United Kingdom

Prior to completing the Questionnaire please complete the following:-

Today's Date:

					2	0		
D	D		M	M	Y	Y	Y	Y

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

Left ❑

Right ❑

Both ❑

If you said 'both', please complete the <u>first</u> questionnaire thinking about the <u>right side</u>. A second questionnaire, for the left side, will follow.

Circle as appropriate **Right / Left** Please tick (✓) one box for each statement.

1. During the past 4 weeks this has applied to me:

I have pain in my foot/ankle

None of the times	Some	Most of the time	Rarely	All of the time
☐	☐	☐	☐	☐

2. During the past 4 weeks this has applied to me:

I avoid walking long distances because of pain in my foot/ankle

None of the time	Some times	Rarely	Most of the time	All the time
☐	☐	☐	☐	☐

3. During the past 4 weeks this has applied to me:

I change the way I walk due to pain in my foot/ankle

None of the the time	Rarely	Some times	Most of time	All the time
☐	☐	☐	☐	☐

4. During the past 4 weeks this has applied to me:

I walk slowly because of pain in my foot/ankle

None of the time	Some times	Most of the time	Rarely	All the time
☐	☐	☐	☐	☐

5. During the past 4 weeks this has applied to me:

I have to stop and rest my foot/ankle because of pain

None of the time	Some times	Most of the time	Rarely	All the time
☐	☐	☐	☐	☐

6. During the past 4 weeks this has applied to me:

I avoid some hard or rough surfaces because of pain in my foot/ankle

None of the time	Rarely	Some times	Most of the time	All the time
☐	☐	☐	☐	☐

7. During the past 4 weeks this has applied to me:

I avoid standing for a long time because of pain in my foot/ankle

None of time	Some times	Most of the time	Rarely	All the time
☐	☐	☐	☐	☐

8. During the past 4 weeks this has applied to me:

I catch the bus or use the car instead of walking, because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

9. During the past 4 weeks this has applied to me:

I feel self-conscious about my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

10. During the past 4 weeks this has applied to me:

I feel self-conscious about the shoes I have to wear

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

11. During the past 4 weeks this has applied to me:

The pain in my foot/ankle is more painful in the evening

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

12. During the past 4 weeks this has applied to me:

I get shooting pains in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

13. During the past 4 weeks this has applied to me:

The pain in my foot/ankle prevents me from carrying out my work/everyday activities

None of the time	Some times	Most times	Rarely	All of the time
☐	☐	☐	☐	☐

14. During the past 4 weeks this has applied to me:

I am <u>un</u>able to do all my social or recreational activities because of pain in my foot/ankle

None of the time	Some times	Most of the time	Rarely	All times
☐	☐	☐	☐	☐

15. During the past 4 weeks…

How would you describe the pain you <u>usually</u> have in your foot/ankle?

None	Very mild	Mild	Moderate	Severe
☐	☐	☐	☐	☐

16. During the past 4 weeks…

Have you been troubled by pain from your foot/ankle in bed at night?

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

Finally, please check that you have answered every question.

Thank you very much.

Appendix VI

Foot and ankle ability measure

Foot and Ankle Ability Measure (FAAM)
Activities of Daily Living Subscale

Please Answer **every question** with **one response** that most closely describes your condition within the past week.
If the activity in question is limited by something other than your foot or ankle mark "Not Applicable" (N/A).

	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Standing	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking on even Ground	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking on even ground without shoes	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking up hills	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking down hills	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Going up stairs	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Going down stairs	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking on uneven ground	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Stepping up and down curbs	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Squatting	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Coming up on your toes	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking initially	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking 5 minutes or less	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking approximately 10 minutes	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Walking 15 minutes or greater	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ

Foot and Ankle Ability Measure (FAAM)
Activities of Daily Living Subscale
Page 2

Because of your foot and ankle how much difficulty do you have with:

	No Difficulty at all	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Home responsibilities	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Activities of daily living	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Personal care	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Light to moderate work (standing, walking)	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Heavy work (push/pulling, climbing, carrying)	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Recreational activities	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ

How would you rate your current level of function during you usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities.

__ __ __ . 0 %

Martin, R; Irrgang, J; Burdett, R; Conti, S; VanSwearingen, J: Evidence of Validity for the Foot and Ankle Ability Measure. Foot and Ankle International. Vol.26, No.11: 968-983, 2005.

Foot and Ankle Ability Measure (FAAM)
Sports Subscale

Because of your foot and ankle how much difficulty do you have with:

	No Difficulty at all	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Running	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Jumping	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Landing	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Starting and stopping quickly	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Cutting/lateral Movements	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Ability to perform Activity with your Normal technique	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ
Ability to participate In your desired sport As long as you like	ϒ	ϒ	ϒ	ϒ	ϒ	ϒ

How would you rate your current level of function during your sports related activities from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

__ __ __ . 0%

Overall, how would you rate your current level of function?

ϒ Normal ϒ Nearly Normal ϒ Abnormal ϒ Severely Abnormal

Martin, R; Irrgang, J; Burdett, R; Conti, S; VanSwearingen, J: Evidence of Validity for the Foot and Ankle Ability Measure. Foot and Ankle International. Vol.26, No.11: 968-983, 2005.

Appendix VII

GHQ SF-36

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:_____** **Date: _____**

ID#: _____ **Age: _____** **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

Excellent Very Good Good Fair Poor

Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago

Somewhat better now than one year ago

About the same

Somewhat worse now than one year ago

Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

Yes, Limited a lot Yes, Limited a Little No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Lifting or carrying groceries

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing several flights of stairs

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing one flight of stairs

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bending, kneeling, or stooping

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking more than a mile

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking several blocks

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking one block

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bathing or dressing yourself

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Were limited in the kind of work or other activities

Yes No

Had difficulty performing the work or other activities (for example, it took extra effort)

Yes No

EMOTIONAL HEALTH PROBLEMS:

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

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Didn't do work or other activities as carefully as usual

Yes No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all Slightly Moderately Severe Very Severe

PAIN:

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

None Very Mild Mild Moderate Severe Very Severe

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

Not at all A little bit Moderately Quite a bit Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

All of the time

Most of the time

A good Bit of the Time

Some of the time

A little bit of the time

None of the Time

Have you been a very nervous person?

All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time

Have you felt calm and peaceful?

All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time

Did you have a lot of energy?

All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time

Have you felt downhearted and blue?

All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time

Did you feel worn out?

All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:

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

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

Definitely true Mostly true Don't know Mostly false Definitely false

I am as healthy as anybody I know

Definitely true Mostly true Don't know Mostly false Definitely false

I expect my health to get worse

Definitely true Mostly true Don't know Mostly false Definitely false

My health is excellent

Definitely true Mostly true Don't know Mostly false Definitely false