Exploring the use of manual therapy as an adjunctive therapy to 'care as usual' on outcomes in chronic migraine

James Odell

January 2021

A thesis submitted in partial fulfilment of the requirements of Bournemouth University for the Degree of Doctor of Philosophy (PhD)

Faculty of Health and Social Sciences
Bournemouth University

Abstract

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Although chronic migraine (CM) has an estimated of worldwide annual prevalence of between1.4% and 2.2%, with the greatest impact on females, the understanding of its pathophysiology is still largely unknown. This has led to a lack of effective treatments and at the time of this study Onabotulinumtoxin A (Botox) was the only medication licensed specifically for CM. However, whilst there are other treatment options, including psychological and physical therapies, their effectiveness in CM is uncertain. A rationale for the use of MT in CM was developed from a narrative review, with a systematic literature review of peer reviewed publications confirming limited research into the role of MT in the treatment of CM. The aim of this study was therefore to explore the effectiveness of manual therapy (MT) as an adjunctive treatment to 'care as usual' in females with CM, using a pragmatic, randomised controlled trial (RCT) in a tertiary headache clinic. Sixty-four female participants with severe CM were randomised into two groups: 'care as usual' and 'care as usual' with MT. The primary outcome was the between group difference in change scores using the Headache Impact Test (HIT6). Secondary outcomes included Patient Global Impression of Change (PGIC) and responder rates. The primary outcome favoured the use of adjunctive treatment with a significant difference in between-group HIT6 change scores. The MT group also had significantly higher responder rates in the HIT6 and PGIC outcomes. The presence of higher baseline levels of cutaneous allodynia, negative coping and emotional distress indicated a greater benefit from the combined MT/ 'care as usual' intervention than 'care as usual' alone. This was the first MT-CM RCT to take place in a UK tertiary NHS headache clinic and contributed new knowledge in several areas: (1) the first use of PGIC outcomes to be reported in an adjunctive CM study which suggested it provides a broader and potentially more patient centred measure of treatment effectiveness, compared to the HIT6 alone. (2) the potential to use movement between allodynia symptom checklist (ASC) categories as a better indication of reduction in allodynia brought about by MT rather than the normal dichotomous cut off score. (3) the first MT-CM study to examine psychological factors and propose that 'care as usual' treatment may be reinforcing negative coping behaviours and maintaining disability in treatment of CM. This study contributes to a body of knowledge on MT for CM, and concluded that MT plus 'care as usual' produced better outcomes versus 'care as usual' alone in females severely affected by CM.

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Abbreviations	
≤	Less than or Equal to
≥	Greater than or Equal to
ADL	Activities of Daily Living
ASC	Allodynia Score Checklist
AE	Adverse Event
ANOVA/ANCOVA	Analysis of variance/covariance
BOTOX	Onabotulinum A
BMI	Body Mass Index measured in kg/m2
BC	Brief Cope
CA	Cutaneous Allodynia
CI	Confidence Interval
CM	Chronic Migraine
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CGRP	Calcitonin Gene-Related Peptide
H (0) H (1)	Null Hypothesis Alternative Hypothesis
HIT 6	Headache Impact Test 6
ICHD	International Classification Headache Disorders
IHS	International Headache Society
IMPACCT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MCID	Minimal clinical important difference
MI	Multiple Imputation
MIDAS	Migraine disability assessment score
MMS	Manipulation, Mobilisation, Soft Tissue
MO/H	Medication Overuse /Headache
MT	Manual Therapy
MSQ2.1	Migraine Specific Quality of Life 2.1
n	Number of Participants
NRS	Numerical Ratings Scale
NDI	Neck Disability Index

NHS	National Health Service (UK)
OCEBM	Oxford Centre for Evidence-Based Medicine.
p	Probability
PGIC	Patient Global Impression of Change
PI	Principle Investigator
PNS	Peripheral Nervous System
PSS10	Perceived Stress Scale 10
r	rho (correlation coefficients)
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RI	Regional Interdependency
SD	Standard Deviation
SMT	Spinal Manipulative Therapy
STAI6	State Trait Anxiety Inventory
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analogue Scale
YLD	Years Lived Disabled

Acknowledgments

This PhD has been an interesting and thought-provoking piece of work and I have benefitted from the help, knowledge and understanding of many people.

However, I am particularly indebted to my mentors; Dr Andrew Dowson, for sharing his knowledge and giving encouragement over many years, and Professor Adrian Hunnisett, for his calm guidance throughout the study.

My thanks must also go to my supervisors Professor Carol Clark, Dr Jonny Branney and Dr Osman Ahmed for their support, with each providing their own unique steer. Sadly, there are too many people to mention in the NHS and at Bournemouth University who had no need to help me but found the time. Although special thanks go to neurologist Dr Adam Zermansky, head nurse Siobhan, and the participants for making the study possible in their clinic.

I am also grateful for the funding from the Royal College of Chiropractors, the McTimoney College of Chiropractors and Bournemouth University, without which this PhD would not have been possible.

Finally, thanks go to Sabra for her proof reading, the task nobody wants, Sara for her reassurances and to my Wif (sic) Helen who fed and watered me as I sat at the desk typing, and listened patiently as I went on and on about chronic migraine and manual therapy.

CHAPTER 1 INTRODUCTION

This chapter starts with a brief overview of the author's journey with this study, based on professional experience of treating patients with headaches and migraines and involvement with a range of headache specialists. It then introduces the global impact of chronic migraine (CM) and its epidemiology, before examining current theories on the pathophysiology and chronification process, and how these theories form a basis for the connection between other pain conditions and migraine. A narrative review of the role of manual therapy (MT) in these pain conditions and other headaches then develops the rationale for manual therapy in the context of migraine treatment. It concludes with an overview of existing CM treatments and the need for additional approaches (Figure 1.1).

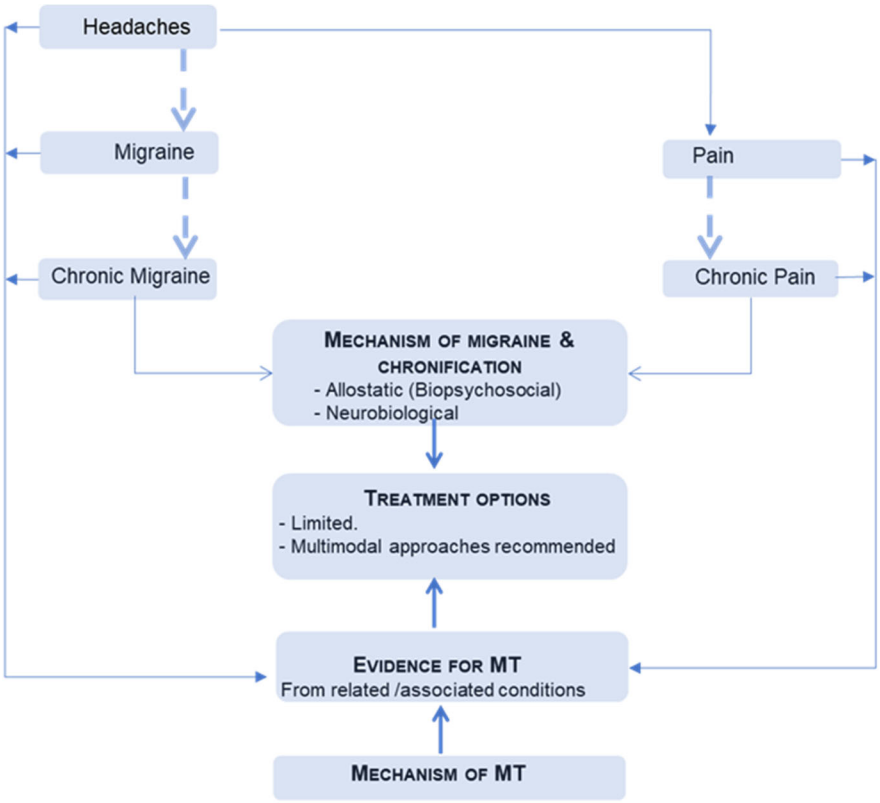

Figure 1-1. Developing a rationale for manual therapy in chronic migraine

The overall reason for this research was to explore the issue of migraine, as a multifactorial condition that most likely required more than a mono-therapy treatment approach (Gaul et al. 2011; Gaul et al. 2016; Grazzi and D'Amico, 2019). This is an important area of research as migraine ranks second behind low back pain in terms

of disability (Leonardi and Raggi. 2019) with approximately three percent of those with migraine transforming to CM annually (Lipton and Silberstein. 2015). CM is the most disabling and refractory type of migraine, disproportionately affecting females, in their most productive years (Weatherall, 2015; Aurora & Brin, 2016) with the current, limited number of, mono-therapies failing to offer relief to a substantial proportion of sufferers (Lipton and Silberstein. 2015; Su and Yu. 2018; Velasco-Juanes et al. 2018).

As such, the overall aim of the study was to examine the effectiveness of MT, with female CM patients, as part of a multi-modal approach rather than to compare MT against existing treatments.

1.1. The author's research journey

The idea for this study had been germinating over 10 years of working with headache and particularly migraine patients as a chiropractor and discussing the role of MT with neurologists. Many neurologists did not view MT as a useful approach, despite the improvements I saw in many of my migraine/headache patients. However, after meeting one particular headache neurologist, the lack of professional consensus became evident. Subsequent collaboration with this neurologist began to examine how MT may be useful particularly in those most affected - those with CM. At the time licensed medications specifically for CM did not exist and the success of those in use was limited, often with significant side effects. The introduction of Botox to the NHS in 2012 signalled a change, as this was the first drug targeted specifically at chronic migraine. However, the efficacy and effectiveness of Botox were still under debate, with a high proportion of patients not gaining substantive benefit. At the same time evidence was mounting to suggest the pathophysiology of migraine was a multi-factorial condition amenable to a multi-modal approach, including MT (Gaul et al. 2011; Wallasch et al. 2012; Grazzi 2013; Burstein et al 2015; Gaul et al. 2016; Grazzi & D'Amico. 2019). As a chiropractor, I always considered it unlikely that MT alone would work for everyone with CM and therefore sought to understand how MT might help some with CM and work with, not replace current approaches. Thus, my personal rationale for this study, with a focus on females, resulted from the evidence that they were disproportionately affected by CM and represented the bulk of my patients and those attending tertiary headache clinics.

1.2. Classification and epidemiology of migraine

The World Health Organisation (WHO) estimates that between 50% and 75% of adults aged 18–65 years worldwide have headaches in a year. Of these, more than 10% report migraine, with between 1.4% and 2.2% estimated to have chronic migraine (WHO, 2016). With an annual prevalence of 14.7%, migraine is classed as the third most prevalent neurological condition worldwide (Stovner, 2014). While the annual prevalence of migraine in the UK is estimated to be between 5% and 25% in women and 2% to 10% in men, the prevalence of chronic migraine in the UK is unknown, although the National Institute for Clinical Excellence (NICE) estimates that 1 in 1000 people are affected (NICE, 2011).

However, there are still no biological markers for migraine, with the diagnosis based on clinical history and exclusion of alternative headache disorders. Its definition is classified by the International Headache Society (IHS) in its International Classification of Headache Disorders (IHS. 2018) and based on the symptoms presented (Table 1.1 and Table 1.2).

In the most recent study into the global burden of health, migraine is recognised as the third largest cause of disability in people under fifty years of age, and the second-largest overall just behind low back pain, based on years lived with disability (YLDs) and early mortality in years of life lost (Steiner et al. 2016; Leonardi and Raggi. 2019).

Table 1-1. Migraine classification (ICHD Beta -3)

Migraine without Aura - episodic migraine (EM)	**Migraine with Aura - episodic migraine**
Previously used terms: Common migraine; hemicrania simplex.	**Previously used terms:** Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; complicated migraine.
Description:	**Description:**
Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.	Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.
Diagnostic criteria:	**Diagnostic criteria:**
A. At least five attacks1 fulfilling criteria B to D	A. At least two attacks fulfilling criteria B and C
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)	B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal
C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)	C. At least two of the following four characteristics 1. at least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession: 2. each individual aura symptom lasts 5-60 min 3. at least one aura symptom is unilateral 4. the aura is accompanied, or followed within 60 mins, by headache
D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia	D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded
E. Not better accounted for by another ICHD-3 diagnosis	

Table 1-2. Classification chronic migraine (ICHD Beta-3)
Chronic Migraine (CM)
Description:
Headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of migraine headache.
Diagnostic criteria:
A. Headache (tension-type-like and/or migraine-like) on =15 days per month for >3 months2 and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura
C. On =8 days per month for >3 months, fulfilling any of the following 3:
1. Criteria C and D for 1.1 Migraine without aura 2. Criteria B and C for 1.2 Migraine with aura 3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

Headaches in primary care (when extrapolated to the whole of the UK) cost approximately €1.2 billion in service costs and €5.8 billion of lost productivity (McCrone et al. 2011). An EU study calculated migraine costs at between €18 and €27 billion per annum, with an average annual cost per headache patient of €370 (Stovner, 2008; Oleson, 2011). Studies comparing episodic and chronic migraine consistently show annual CM costs far exceeding those of EM (Table 1.3).

Table 1-3. Comparison chronic and episodic migraine costs

Chronic	Episodic	Country
€3700	€866	UK
€2250	€526	Italy
$8243	$2649	USA
$471	$172	Canada

(Bloudek et al. 2011; Stokes et al. 2011; Lanteri-Minet et al. 2013; Messali et al. 2016)

In addition to the financial impact on migraineurs, the impact of migraines may be measured in social, economic, and inter-personal terms with the effects greatest for those with CM (Serrano et al. 2013). Individuals with chronic migraine are 20% less likely to be employed compared to those with episodic migraine, with losses through the cost of lost productive time much greater in chronic than episodic migraine at all ages and for both men and women (Lanteri-Minet. 2011). One study highlighted that, whilst chronic migraineurs comprised 8% of employed migraineurs they accounted for 35% of lost work time (Katsarava et al. 2012), with the highest loss in males and females aged 45 -54 years (Serrano et al. 2013).

Chronic migraine is also associated with higher levels of personal disability than in episodic migraine (Katsarava et al. 2012). A clinical study with over 331 subjects found that most standard measures of migraine disability, including health related quality of life (HQoL), Migraine Disability Index (MIDAS), and Migraine Specific Quality of Life v2.1 (MSQoL) were statistically higher in chronic migraineurs than episodic migraineurs (Wang et al. 2012).

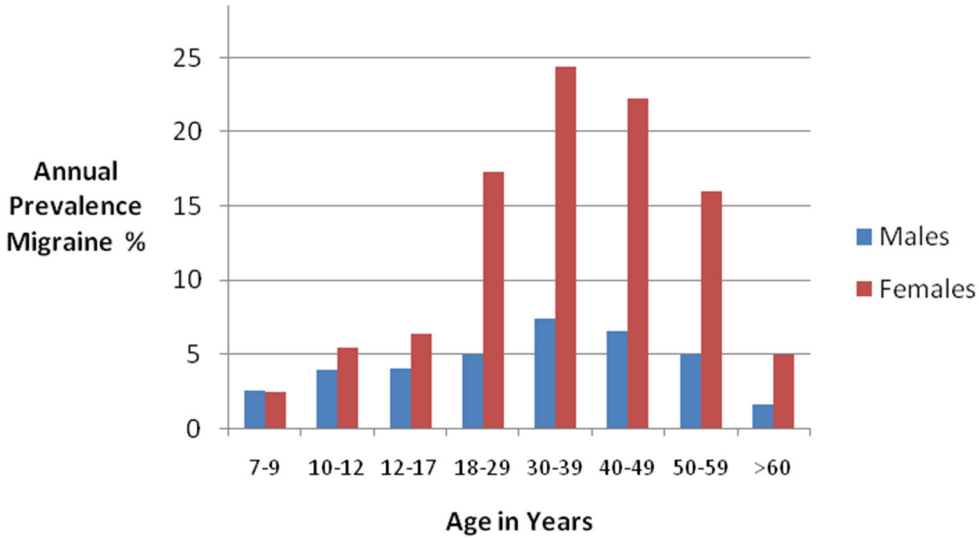

Figure 1-2. One-year prevalence of migraine by age and gender (Finochi & Strada 201)

The annual prevalence figure of chronic migraine worldwide is estimated to be up to 5.1%, with a typical range of 1.4% to 2.2% (Natoli et al. 2010; Buse et al. 2012; Chiang & Starling. 2018). Slightly higher figures were seen in a comparison study in the USA of two large scale longitudinal studies (Lipton et al. 2016), which concluded that annual prevalence for chronic migraine is between 6.6% and 8.8%. Further analysis of these figures reveals that females are most likely to have migraine, and even more likely to have chronic migraine. Burch et al. (2015) estimated the 3-month prevalence of migraine or severe headache to average 20.2% in females, with 9.4% of them having had constant chronic migraine over the last 10 years. Finochi & Strada (2014) presented figures from a number of studies that demonstrated the gender difference in the annual prevalence of migraine (Figure 1.2), and Natoli et al. (2010) indicated that the annual prevalence of chronic migraine was higher in females (1.7%–4.0%) than in males (0.6%–0.7%). This was further supported by Buse et al. (2012), who concluded that the group most affected by chronic migraine was women aged 18-49 years (Figure 1.3).

Despite years of investigation, the reason females seem to be more affected by migraine than males remain unclear, although most theories focus on hormonal involvement. Large USA-based and Swedish studies have noted that boys and girls have the same annual prevalence until puberty. Prevalence increases in both sexes during puberty although the gap between males and females widens. This continues until around 50 years of age when the gap closes again with migraine becoming less prevalent in both sexes (Allais et al. 2020). Likewise, the difference between males and females in chronification to CM is equally not understood, although if headaches were seen on a continuum then the greater prevalence of migraine in females would, at a minimum, lead to a greater prevalence in CM. However, although the percentage of those transitioning from EM to CM (chronification), is thought to differ between males and females, figures are sparse and conflicting (Munakata et al. 2009; Finnochi & Strada. 2014; Allais et al. 2018). Some reports have highlighted large differences between the transition from EM to CM women compared to men; with one suggesting it was 5 times greater in females (Vetvik and MacGregor.2017) whilst others (Scher et al. 2018) found similar transition rates between sexes.

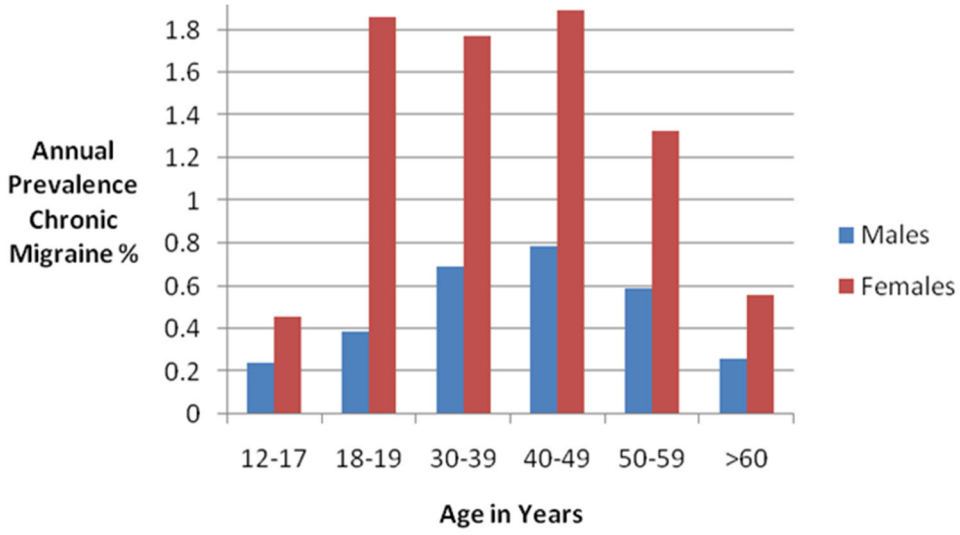

Figure 1-3. Prevalence figures for chronic migraine by age and gender. (Buse et al. 2012)

Despite the substantial economic and personal impact on both society and migraineurs (and in particular females), the understanding of the pathophysiology of migraine is still largely unknown (Asina et al. 2013; Burstein et al 2015; May & Schulte. 2016; Andreou and Edvinsson. 2019).

This lack of understanding has led to a paucity of specific treatment approaches to migraine and fewer yet for chronic migraine (Su & Yu 2018).

1.3. Pathophysiology of migraine and chronification

Different models exist to explain both migraine and the process of chronification, with no single model of pathophysiology dominating. The current consensus is that migraine is a neurobiological pain condition involving vascular, neurological, and psychological components. The most widely accepted theories of migraine pathophysiology suggest an inherited level of brain excitability, intracranial vessel dilatation, and activation and sensitisation of the trigeminovascular system with permanent structural and functional alterations in genetically-susceptible individuals (Chakravarty & Sen, 2010; Ashina et al. 2013; Burstein. 2015; Brennan & Pietrobon. 2018). This section outlines some key strands in the theories of migraine and the chronification to CM that informed the study rationale.

1.3.1. Central sensitisation

Despite early theories of a discrete migraine generator in the brain that stimulates migraines (May & Schulte. 2016), one of the most commonly held current views is that migraine develops as an interaction between both the central and peripheral nervous systems (CNS and PNS) involving a number of components in a complex, multi-faceted response to initiating triggers (Striessnig. 2005; Oleson. 2009; Kojic & Stojanvic. 2013; Schwedt. 2014; May& Schulte. 2016; Bonivita et al. 2018).

Dodick and Silberstein (2006) describe migraine as a consequence of sensitised nociceptors starting to load the spinal cord with increasingly large stimuli, known as peripheral sensitisation. This leads to the phenomenon known as central sensitisation, which increases pain via a dysfunctional processing pathway when sensitised in susceptible individuals. They concluded that peripheral sensitisation is associated with throbbing pain and poor response to movement, whilst central sensitisation results in allodynia, or the perception of pain induced by non-painful stimuli. Oleson et al. (2009) suggested nociceptive input is a necessity for localised headache with the central nervous system and central sensitisation modulating pain. Exactly how the peripheral sensitisation is initiated is not clear although sources of the initial nociceptive input are thought to include the trigeminal perivascular and periarterial nociceptors, extra cranial, or dural sources (Schueler et al. 2013; Bonivita et al. 2018).

In contrast, Panerai (2013) contested that migraine is a CNS-driven process with normal external inputs being affected by abnormal CNS processing and concluded that the answer is probably a combination of both. Migraine patients are unlikely to have a single dysfunction within the excitatory or inhibitory system, but rather an inability to maintain a cortical excitatory/inhibitory balance. Burstein et al. (2015) investigated cutaneous allodynia in 60 migraineurs. These authors hypothesised that the migraine process, from initialisation through to cutaneous allodynia, is a progression of the sensitisation of first-order neurones to second and finally third-order neurones in the brainstem and spinal cord (Figure 1.4).

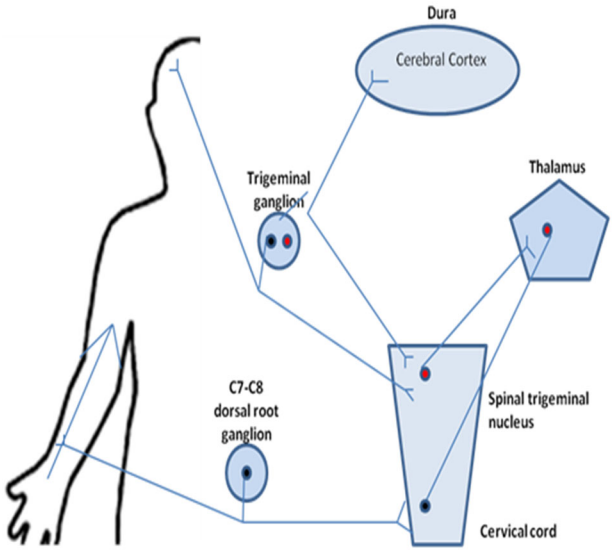

Figure 1-4. Process of central sensitization.

1.3.2. Migraine, pain and allostatic model

The relationship between pain and emotions has been shown to exist in many conditions that, like migraine, have little readily observable cause (Lumley et al. 2011; Bussone et al. 2012; Bussone & Grazzi. 2013; Adams et al. 2018) e.g. chronic pain and fibromyalgia (Phillips & Clauw. 2011; Pak et al. 2018). Buse et al. (2012) proposed that emotional response is a factor in the chronic pain of headache as a result of dysfunctional modulation in neurological system. This was consistent with the findings of Panerai (2013), albeit this process was specifically the integration of nociceptive input with the emotional network. In part this is thought to contribute to the increased prevalence and impact of migraine on females compared to males. Females with migraine have been found to have more comorbidities compared to

males, with a higher incidence of anxiety, depression and pain conditions (Lantéri-Minet et al. 2005; Vetvik & MacGregor 2017; Allais et al.2020). This is consistent with findings of greater activation in areas of those brain involved with emotional processing compared with male migraineurs and may partly explain why males reported less pain than females despite similar levels of pain intensity (Bartley & Fillingim. 2013; Guo et al. 2019).

Borsook et al. (2012) theorised that an allostatic model of migraine addressed many of the findings in migraine research including the variety of triggers and responses; pain experienced; central sensitisation; changes in brain structure; dysfunctional modulation of the neurological system, and the role of common psychological comorbidities such as anxiety and depression. The factors in this model also align with the biopsychosocial model of pain espoused by Engel (1977) which was later developed to explain the complexity of headaches and migraine (Andrasik et al. 2005; Gil-Martinez et al. 2016; Meints et al. 2018). Based on the work of McEwen and Wingfield (2003), the allostatic model focussed on the brain being the major organ of stress. It decides what stress is and how to respond, with the “fight or flight” response being one such mechanism. Some responses are positive adaptations, whilst others are considered maladaptive.

Allostasis is not in itself an entity but rather a mechanism by which the body protects itself from stresses through adaptive processes, or as McEwan (2003) stated, *"maintaining stability through change, as a fundamental process through which organisms actively adjust to both predictable and unpredictable events"*. Allostatic load is the cumulative impact on the body of allostasis, as individuals adjust their body, physiology, and behaviour to changes in the environment, socio-economic state, etc. Borsook et al. (2012) proposed that as the stressors in life ebb and flow (Figure 1.5) the adaptive capability of the brain in susceptible people (i.e. the migraine brain) was less able to cope with this allostatic loading. The contribution of individual ‘effectors’ to the overall allostatic load is not known, although they may be additive or cumulative. Some effectors may be continuous (e.g., genetic) or episodic (e.g. musculoskeletal pain), or developmental over time (e.g. white matter lesions).

Image redacted. Fig 4 page 223. Borsook, D., Maleki, N., Becerra, L. and McEwen, B., 2012. Understanding Migraine through the Lens of Maladaptive Stress Responses: A Model Disease of Allostatic Load. Neuron, 73 (2), 219-234.

Figure 1-5. Effectors of allostatic loading. (Borsook et al. 2012)

1.3.3. Chronification in migraine

Although approximately 2.5% of people with EM transform to CM, the precise mechanism of chronification is unknown (Bigal et al. 2008; Aguggia & Saracco. 2010; Su & Yu. 2018). In the allostatic model of migraine, the failure of the brain to adapt to effectors (stressors) may be seen initially as EM, but with higher allostatic loading, this inability to adapt leads to more migraines. The increase in migraines is an additional neurological load, thus creating a vicious cycle (Figure 1.6).

Image redacted. Fig 1 page 220. Borsook, D., Maleki, N., Becerra, L. and McEwen, B., 2012. Understanding Migraine through the Lens of Maladaptive Stress Responses: A Model Disease of Allostatic Load. Neuron, 73 (2), 219-234.

Figure 1-6. Migraine frequency and allostatic load. (Borsook et al. 2012).

Image redacted Fig 1 page 8. Bigal, M. and Lipton, R., 2007. Concepts and Mechanisms of Migraine Chronification. Headache: The Journal of Head and Face Pain, 48 (1), 7-15.

Figure 1-7. Natural history of migraine. (adapted from Bigal, 2007)

The allostatic model may also offer an explanation of the gender differences in the transition to CM. Recent functional magnetic resonance imaging (fMRI) studies have indicated structural differences in parts of the brain associated with stress and anxiety in women with migraine compared with men with migraine and healthy women. Maleki et al. (2012) suggest that these alterations could be due to differences in response to intermittent stress (migraine attacks) and the effects of hormones. Gupta et al. (2007) proposed that female sex steroids enhance neuronal excitability by triggering mechanisms in migraine and involves calcitonin gene-related peptide (CGRP) which itself impacts the trigeminovascular system and stimulation of pain centres. Recent studies of the new CGRP medications for CM support a view that trigeminal neurones may be sensitive to variations in levels of sex hormone, particularly oestrogens and progesterone These fluctuations may add directly and indirectly to the cumulative allostatic load as a recurring stressor (Boorsook et al. 2012; Tedeschi et al. 2015; Labastida-Ramırez et al. 2017; Allais et al. 2020).

Another feature of chronification in migraine is the increased presence of central sensitisation and concomitant cutaneous allodynia. Over half of migraineurs have allodynia during, and over a quarter between, episodes of migraine (Lovati. 2008; Tietjen et al 2009; Benatto et al. 2016; Dodick et al. 2019). Bigal et al. (2007) proposed a model in which migraine was seen as a progressive, chronic condition with episodic periods (Figure 1.7). This suggested that repeated central sensitisation

is linked to permanent neuronal damage at or around the periaquialgrey (PAG), leading to poor pain modulation and resistance to treatment and thus making disease progression more likely. The idea of reduced pain inhibition in descending pathways in migraine has also been identified in studies of other chronic pain conditions where central sensitisation is found (Meus & Nijs, 2007; Nijs, 2009; Chen et al. 2015; Pak et al. 2018).

Nijs et al. (2010) provided a detailed explanation of the potential relationship between musculoskeletal issues and central sensitisation in chronic pain (Figure 1-8) which is consistent with mechanisms expressed in migraine pathogenesis in the allostatic model.

Image redacted Fig 1. Page 136. Nijs, J., Van Houdenhove, B. and Oostendorp, R., 2010. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. Manual Therapy, 15 (2), 135-141

Figure 1-8. Simplified display of nociceptive processing in the nervous system. (adapted from: Nijs et al. 2010)

1.3.4. Risk factors for chronification

Despite the mechanisms of chronification being uncertain, multiple studies have identified risk and remission factors for migraine progression. These include medication over-use; elevated frequency of migraine at baseline; psychological comorbidities, particularly depression and anxiety; obesity, and being female (Bonavita & Simone. 2010; Schwedt. 2014; May & Schulte. 2016; Pak et al. 2018).

Although depression and anxiety have both been associated with chronic migraine for many years, the exact balance and prevalence vary between study authors, populations, and measurement tools. Smitherman et al. (2009) estimated that anxiety and depression are found in 25% and 66% respectively of chronic migraineurs, compared to 14% and 48% in episodic migraineurs. Overall, there is evidence to suggest that chronicity of symptoms is associated with higher levels of both anxiety and depression (Rossi et al. 2005; Chen et al. 2012; Oh et al. 2014; Tome-Piris et al. 2017; Seng et al. 2017). Schwedt et al (2014) provided a more comprehensive list of these risk factors (Table 1.4), with the potential neurobiological balancing mechanism of all of these factors illustrated in Figure 1.9.

Table 1-4. Risk factors associated with migraine chronification and reversion

- *Table redacted. Table 1 page 3 Schwedt, T., 2014. Chronic migraine. BMJ, 348 (mar24 5), g1416-g1416..*
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(Adapted from Schwedt. 2014)

Image redacted Fig 1 page 459. May, A. and Schulte, L., 2016. Chronic migraine: risk factors, mechanisms and treatment. Nature Reviews Neurology, 12 (8), 455-464.

Figure 1-9. Multiple factors contributing to chronification. (May & Schulte, 2016)

The neurobiological and the allostatic models outlined above present an argument for migraine and its chronification being a complex and not fully understood process. Blumenfeld et al. (2012) highlighted that migraine is a syndrome, with probable multiple pathogenic mechanisms involved in its presentation, logically lending itself to the possibility that there may be multiple therapeutic options besides pharmacological treatments (Gaul et al. 2011; Wallasch et al. 2012; Diener et al 2015; Gaul et al 2016; Cho et al. 2017; Grazzi & D'amico.2019).

1.4. Role of manual therapy in pain conditions

As part of this narrative review, this section outlines a theoretical basis for the treatment of headaches with MT based on models and evidence for the benefit of MT in conditions with similar symptoms and pathophysiology.

1.4.1. Overview of manual therapy

For the purposes of this PhD study the definition of manual therapy is defined as a hands-on approach utilising mobilisation, manipulation and soft tissue work singly or in combination (Farrell & Jensen.1992; Bronfort et al. 2010; Moore et al. 2017). This is distinct from physical therapy which can include MT but also extends to include exercise; the use of equipment and, acupuncture. However, the definition of MT differentiates the three modalities. Manipulation used by manual therapists is often called "high-velocity, low amplitude (HVLA) thrust joint manipulation". This is often referred to as "spinal manipulative therapy (SMT)", or "manipulation". It involves a fast thrust into a joint to establish normal motion and may be accompanied by an audible release. Mobilisation is rhythmic motion aimed at improving the motion of joints and or soft tissue. It can be done actively or passively (Hengeveld et al. 2014).

Soft tissue work can involve a number of different techniques, including trigger point work, soft tissue release, muscle energy techniques and myofascial release

Bialosky et al. (2009; 2018) proposed that MT has two fundamental effects; biomechanical and neurophysiological. The mechanical force from the MT intervention results in neurophysiological responses that affect pain inhibition via both the peripheral and central nervous systems. This theory has been supported by studies and systematic reviews, each of which shows MT to produce central hypoanalgesia and activation of the descending anti-nociceptive pathways, which are thought to be involved in central sensitisation and migraine pathogenesis (Wright. 1995; Taylor & Murphy. 2010; Voogt, et al. 2015; Muhsen et al. 2019).

However, although the effects of each method of MT may be similar, including improved range of motion, decreased muscle tension and reduction in localised pain, the mechanism of each method and the clinical relevance of the changes in pain inhibition remain unclear. It has been suggested that each modality may or may not work through the same neurophysiological pathways (Bialosky et al. 2009; Clark et al.2012; Bishop et al.2015; Vigotsky & Bruhns. 2015; Bialosky et al. 2018).

The main neurophysiological pathway for the development of migraine and headaches is thought to be via localised nociception and the trigeminocervical complex, linked to structures in the cervical spine (Bartsch & Goadsby, 2003), suggesting that MT at this level should be the primary target. However, the concept of regional interdependency (RI) proposes that dysfunction in a remote anatomical area can contribute to or affect the patient's primary condition and, as a result, MT aimed at dysfunction in this remote area may affect the primary condition (Wainner et al. 2007; Sueki et al. 2013; McDevitt et al. 2015) Thus, to gain maximum benefit from MT in a clinical setting, dysfunction in areas outside of the cervical spine should be considered as part of the MT intervention. Studies have demonstrated the RI between the cervical thoracic regions that result from the many muscular and ligamentous structures extrinsic to the cervical spine. These exert direct and indirect forces on the joints, soft tissue and other potentially pain generating structures. This may be seen, for example in the connections from the thoracic spine to the cervical via the trapezius, longissimus and splenius muscles and the spinal ligaments. As such, it has been shown that neck pain and mobility can be improved via thoracic MT (Sueki et al. 2013; McGregor et al. 2014; Karas et al. 2016; Engell et al. 2019)

Whilst all of the above are theories that require further work to establish mechanisms and clinical relevance, they do offer a working rationale for the use of MT in migraine and in areas away from the cervical spine (details of the MT used in this study are provided in Appendix 11).

1.4.2. Chronic pain and chronic migraine

The theories of migraine pathophysiology and the allostatic model highlight many commonalities between chronic migraine and other chronic pain conditions, in terms of potential mechanisms, risk factors and the refractory nature towards similar treatment approaches.

Whilst there are differences between CM and those conditions typically classed as chronic pain (low back pain, neck pain, fibromyalgia, osteoarthritis) these differences are often related to the specifics of location and type of autonomic disturbances (Cortelli & Pierangeli. 2003; Crofford. 2015). However, like CM, the majority of chronic pain conditions are associated with reductions in activity, sleep disturbances, fatigue and mood changes, and many involve severe disability. All are characterised by continuing pain/symptoms that no longer reflect measurable damage to tissue, combined with central sensitisation and, in many cases, allodynia (Bonavita et al. 2018; Pak et al. 2018; Manion et al. 2019).

More recently there have been attempts to group chronic pain conditions based on their underlying similarities, indeed to re-code chronic pain conditions under a label of Chronic Primary Pain. ICD 11 (Nicholas et al. 2019): defined as pain in one or more anatomical regions that (1) persists or recurs for longer than 3 months (2) is associated with significant emotional distress (eg, anxiety, anger, frustration, or depressed mood) and/or significant functional disability (interference in activities of daily life and participation in social roles) and (3) the symptoms are not better accounted for by another diagnosis.

Beneath this general definition lay primary chronic pain conditions, including chronic widespread pain (e.g. fibromyalgia), chronic headache (e.g. CM and CTTH) and chronic musculoskeletal pain (e.g. chronic cervical, thoracic and lumbar pain as well as chronic limb pain).

All of these conditions are considered multi-faceted syndromes, often with significant overlapping or co-occurances, known as chronic overlapping pain conditions (COPCs). One hypothesis is that COPCs often co-occur because of common neurobiological vulnerabilities. These views, particularly combining physical with psychological components including the impact of stress, are also consistent with earlier models of migraine being a pain condition. Bussone et al. (2012) considered that Melzack's neuromatrix model (Melzack, 2001) was an effective model for chronic migraine (Figure 1-10). CM was viewed as chronic pain in which the output from the body's self neuromatrix produced changes in perception, homeostasis and behaviours after an injury, pathology or chronic stress; in a manner similar to those proposed in biopsychosocial and allostatic models. The neuromatrix theory considers that pain involves the distributed brain neural network rather than simply being a direct response to sensory input from injury, inflammation, and other pathologies (Melzack, 2001).

Image redacted Figure 1 page 1382 Melzack, R., 2001. Pain and the Neuromatrix in the Brain. Journal of Dental Education, 65 (12), 1378-1382.

Figure 1-10. Melzack's neuromatrix (Melzack. 2001)

The common underlying neurobiological and psychological processes proposed in the COPCs suggests a potential for the use of similar multi-modal treatment approaches, as outlined below.

Despite NICE (2020) in the UK stating that a 'number of commonly used drug treatments for chronic primary pain have little or no evidence that they work and shouldn't be prescribed' for all of the chronic pain disorders, in the UK the mainstay of treatment has been pharmacological. Analgesics are used to manage chronic

pain with the NICE guideline on pharmacological management of neuropathic pain in adults recommending amitriptyline, gabapentin or pregabalin as initial treatment for neuropathic pain. These are some of the same choices provided for CM and for which the evidence is weak or non-existent e.g. gabapentin was removed from NICE guidelines for CM in 2015. However, the most recent medications developed and licensed for CM (post this doctoral research study) are CGRP medications which were earlier examined for widespread chronic pain (Iyengar et al. 2017; Schou et al. 2017).

A recent evidence assessment by NICE as part of the guidelines for chronic pain (NICE, 2020) involved a systematic review of 46 studies of psychological therapy of which fibromyalgia studies represented 74%, with cognitive behavioural therapy (CBT) as the treatment for fibromyalgia representing 41% (19). It also produced a similar systematic review of 16 studies for MT and chronic pain which included 45% chronic neck pain and 30% fibromyalgia studies. The reviews concluded that psychological modalities (CBT and acceptance and commitment therapy [ACT]) and manual therapy (manipulation, mobilisation and soft tissue) modalities all offered potential for the treatment of chronic pain despite almost all of the studies being considered low quality. A suggestion for more research into the use of MT was also made. However, a similar review by NICE (2012; 2016) for CM concluded that whilst psychological interventions (CBT) and MT (mobilisation, manipulation, soft tissue/stretching techniques) are used and recommended for people living with chronic painful disorders, more evidence is required for CM.

The above UK summary suggests that many of the approaches for chronic pain treatment are beset by the limitations found in treatments for CM but also that those treatments developed for either condition may also offer benefit for the other.

The intervention chosen for this study was manual therapy as opposed to the psychological or pharmaceutical options despite more research needed in all fields. The rationale was built partly on the use of MT in in treatment of similar chronic conditions including musculoskeletal pain, chronic widespread pain (e.g. fibromyalgia) and the requirement for more research into MT and CM and the professional background of the author. The next section in this narrative review explores support for the range of MT interventions used in pain studies.

1.4.3 Overview of manual therapy modalities in pain conditions

Bronfort (2010) and the Warwick review (2014) both concluded that there was positive evidence for SMT in acute and chronic low back, migraine and various forms of neck pain. SMT for back pain gained more positive support in a recent systematic review (Paige et al. 2017) whilst Coronado et al. (2017) concluded that SMT seems to modulate the pain of pressure point threshold (PPT) through the CNS and PNS pathways. SMT had a positive effect compared with other interventions on increasing PPT with some subgroups experiencing a reduction in pain sensitivity at sites distant to the application of SMT.This indicates a possible influence on the CNS at higher levels. Whether SMT was better than other types of MT in the treatment of pain could not be elucidated from reviews of SMT and pain (Schmidt et al. 2008; Voigt et al. 2014).

Soft tissue massage has been used for many years with a range of different musculoskeletal conditions. A recent systematic review of 26 studies concluded that massage improves function and reduces pain in the shoulder, pain from osteoarthritis of the knee and low back pain (Bervoet et al. 2015). Trigger point therapy has been used for headaches for many years and was first clinically elucidated by Travell in the 1950's (Shah et al. 2015) when it was observed that head pain was noted to be linked to certain muscular trigger points. An earlier study of 98 participants found trigger points in 94% of migraineurs compared with only 29% in a control group (Calandre et al. 2006). In the study of Calendre et al. (2006) the number of individual migraine trigger points correlated with the frequency of migraine attacks and the duration of the disease, indicating that pain and migraine chronicity are potentially linked (Stuginski-Barbosa et al. 2012). Systematic reviews (Li et al. 2013; Yuan et al. 2015) concluded that there was moderate evidence from consistent findings among multiple low-quality randomised trials; controlled clinical trials and, one high-quality randomised trial with small but positive, clinically relevant effect sizes (Cohens 0.1-0.3) for myofascial release on fibromyalgia symptoms. Castro-Sanchez (2011) compared a placebo group with massage in 60 FMS patients in an RCT with similar outcomes. Consequently, approaches to the treatment of fibromyalgia (FMS) suggest more rationale for manual therapy and chronic migraine.

Support for MT (specifically trigger points) also comes from the use of Botox in the treatment of CM. Injection sites are determined according to a standard called the PRE-EMPT protocol: **P**hase 3 **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy (Ranoux et al. 2017). These sites are typically in the same place as common active trigger points associated with headaches (Figure 1.11). In their analysis of Botox PRE-EMPT studies Silberstein et al. (2017) suggested Botox works by reducing peripheral sensitisation, which in turn reduces central sensitisation; requiring repeated doses for best effect, in a process similar to that proposed for MT. It is proposed that this inhibition of nociception in the peripheral trigeminovascular system reduces mechanical pain signals to the spinal trigeminal nucleus, which leads to a cascade of other neurophysiological effects (Burstein et al. 2014; Do et al. 2018). Jakubowski et al. (2006) also concluded the success of Botox with migraine pain involves extracranial sensory fibres near the injection sites and speculated the involvement of activation of extracranial nociceptors of scalp tissues, bone and periosteum. A further mechanism of action has been proposed for Botox whereby it relaxes muscles by inhibiting acetylcholine (Ach) release resulting from the muscle trigger points. The reduction in peripheral nociception via both MT and Botox has been explained by a reduction of sensitisation in the mechanoreceptors with inhibition of C fibres, decreasing activation of muscle spindles along with the reduction in, and mediation of, inflammatory neurotransmitter actions. Whilst the neurotransmitters involved in Botox and MT are not the same, there is considerable overlap, including substance P, dopamine, serotonin and acetylcholine (Vigotsky & Bruhns. 2015; Do et al. 2018). It has also been proposed that the actions of both Botox and MT are not just at the neuromuscular junction but also the spinal and supraspinal levels. This provokes an (indirect) effect on the CNS via plastic changes resulting, in part, from modulation of the peripheral sensitisation. These mechanisms of action for Botox and MT have commonality and suggest potential neurophysiological effects of MT in migraine and pain.

Images redacted. Fig 3 page 46, Robertson, C., Robertson, C. and Garza, I., 2012. Critical analysis of the use of onabotulinumtoxinA (botulinum toxin type A) in migraine. Neuropsychiatric Disease and Treatment, 35. Figure 1 page 245 Calandre, E., Hidalgo, J., Garcia-Leiva, J. and Rico-Villademoros, F., 2006. Trigger point evaluation in migraine patients: an indication of peripheral sensitization linked to migraine predisposition?. European Journal of Neurology, 13 (3), 244-249.

Figure 1-11. Botox injection sites (left) soft tissue MT trigger points (right). (Calandre et al. 2006, Roberson et al 2012)

1.4.4. Overview of manual therapy interventions in neck pain

One of the most common areas of musculoskeletal pain associated with headaches and migraine is neck pain. The one-year prevalence of neck pain in those with primary headache has been estimated at 85% compared to 57% without headache (Calhoun et al. 2010; Ashina et al. 2014). This is even more so with chronic migraine in which people with CM are four to five times more likely to have moderate or severe neck disability compared to those with episodic migraine (Florencio et al. 2014; Ranoux, et al. 2017). Limitations to both of these studies highlighted that neither had a control group or placebo and Florencio et al (2014) used the neck disability index (NDI) which captures a range of factors that are common to both neck pain and migraine headaches making it difficult to disentangle effects. Ranoux et al (2017) also had a relatively small sample size (n=57) in comparison with similar studies.

Although varying levels of evidence exist for MT and improvements in chronic neck pain, the involvement of the upper cervical joints specifically has long been held as a source of nociceptive input in the pathogenesis of headache. Some authors have proposed that a reduction in the input via MT may help reduce headaches and migraine (Figure 1.12) Bartsch, 2003; Wanderely et al 2015; Lin et al. 2018; Castien & De Hertogh. 2019).

Image redacted Figure 1 page 373. Bartsch, T. and Goadsby, P., 2003. The trigeminocervical complex and migraine: Current concepts and synthesis. Current Pain and Headache Reports, 7 (5), 371-376.

Figure 1-12. Cervical spine in head pain (Bartsch & Goadsby. 2003)

One study of 55 females found a positive relationship between both episodic and chronic migraine and dysfunction in the upper cervical spine, with 83%-93% having pain compared to 23% in healthy controls (Ferracini et al. 2017). Various forms of

manipulation and mobilisation (including chiropractic and osteopathic) have been shown to help with chronic neck pain, although the evidence from good quality studies is still limited. Vernon et al. (2007) found moderate to high-quality evidence that in randomised groups receiving a course of spinal manipulation or mobilisation for chronic neck pain there were effect sizes of between 1.2 and 3.2 at 6 weeks and clinically relevant benefits up to 104 weeks post-treatment. Gross et al. (2010) examined 27 RCTs and suggested that there was moderate quality evidence for improvements in pain relief and function for cervical manipulation and mobilisation in people with neck pain. However, none of the trials analysed in Vernon et al. (2007) had a placebo group and the less than half of all studies had a sample size of greater than 50, which although typical of MT studies impacted on the overall quality of evidence. In Gross et al (2010) there was also considerable variation between the MT approaches used with only 25% of the manipulation trials considered low in bias using the Cochrane methodology.

Soft tissue therapy of different forms has been shown to help with neck pain. An RCT with 64 chronic neck pain patients found that therapeutic massage produced a 40% reduction in the Neck Disability Index (NDI) after 4 weeks compared to the use of an educational booklet at 14% (Sherman et al. 2009). However, these outcomes were weakened by the fact that one in five of the booklet group visited a chiropractor during the study and few had chronic or severe neck pain and, as with many MT studies, there was no placebo group. In a randomised controlled trial (RCT) of 122 women, Häkkinen (2007) found that both manual soft tissue intervention and self-stretching reduced chronic neck pain by between 50% and 60% after 4 weeks. Although a large study by MT standards the findings were limited by the volunteer self-selection process used for inclusion and a lack of medium to long term follow up. Two systematic reviews also found favourable evidence for both spinal manipulation and mobilisation with and without soft tissue work for chronic neck pain (Bronfort et al. 2010; Clar et al. 2014). Bronfort et al. (2010) concluded that the evidence was of moderate quality for most of the studies that combined manipulation, mobilisation and some soft tissue work. Clar et al (2014) added new information to the above study and came to similar conclusions with the combination of manipulation and mobilisations favourable and those for cervical manipulation alone inconclusive.

In summary, the allostatic and neurobiological models both offer a mechanism of migraine and its chronification that has commonality with the mechanism of pain and its chronification in other disorders. Since MT has been shown to help to varying degrees in the management of a of other chronic pain conditions, including neck pain it is suggested there may be a role for the use of MT the management of headaches and in particular CM. The basis for this is discussed in the next section.

1.5. Overview of manual therapy in headaches

1.5.1. Tension-type headaches

A number of studies have examined MT and tension-type headaches. One of the earliest, Boline et al. (1998), was an RCT of 150 participants. This compared the efficacy of MT to that of prophylactic medication, amitriptyline, in the management of chronic tension-type headache. The primary outcomes, headache pain intensity, headache frequency and over-the-counter medication usage were collected using a diary. During the treatment phase both groups showed similar reductions in all factors. However, 4 weeks after the treatment phase the SMT group had reductions of 32% in headache intensity, 42% in headache frequency, 30% in medication usage and 16% improvement in functional health compared to baseline figures. In contrast, the amitriptyline therapy group showed no improvements, or were slightly worse compared with baseline figures, with 80% of the medication group having side effects compared to 4% in SMT.

Chaibi and Russell (2014) completed the first systematic review of the efficacy of manual therapy RCTs for primary chronic headache. They identified six studies, all of which were chronic tension-type headache. Only one (Toro-Velasco et al. 2009) was a purely MT intervention (head and neck massage) versus a sham (detuned ultrasound). Whilst the outcomes favoured the MT with a 24% reduction in headache intensity compared to 3% in the sham, the study was a pilot with only 11 participants and its primary focus was not on headache disability but immediate heart rate variation. All of the other studies involved varying physical therapy (PT) interventions including exercises. However, at the time, Chaibi and Russell (2014) noted that no studies investigating chronic migraine and MT existed and suggested this should be a focus for future work.

Espi-Lopez et al. (2016) conducted an RCT focussed on the benefits of SMT and massage versus massage alone. It used the headache disability index (HDI) as the

primary outcome and was powered at 90% p<0.05 (n=105, 70% female). The results showed a substantial improvement in the HDI scores for both groups but the combined group had a greater reduction in headache frequency across all data points compared to the control group. A similar study by Ferragut-Garcias (2017) used a three- arm RCT with 97 participants of whom 80% were female. The primary outcome (HIT6 score) was clinically and statistically significantly reduced using a combination of neural mobilisation and soft tissue work. Those receiving neural mobilisation or soft tissue techniques each had an 8-point reduction on the HIT6 score, which is considered a clinically significant change in tension-type headaches, with the combined treatment producing a reduction of 9.8 points.

Lozano-Lopez et al. (2016) evaluated MT (not physical therapy) in tension-type headache in a systematic review of 14 headache RCTs. The Jadad measure of RCT quality was used, with 12 of the 14 considered of acceptable quality (Jadad>3). All of the studies showed positive results, particularly in the reduction in headache intensity frequency, reduction of medication usage and improvements in the quality of life. Mobilisation and manipulation techniques were used in four of the studies, soft tissue therapy in five and a combination of approaches in five. Twelve studies used headache diaries to record data although only three used the validated HIT6 measure to record disability. Some of the studies also included mixed groups of headache type and only three had sample sizes greater than 50 with power calculations being absent in most. The conclusion was positive for MT with respect to improvements in headache frequency, intensity, and quality of life compared to placebo or standard care. However, Lozano-Lopez et al. (2016) highlighted issues around the lack of homogeneity in design, the use of different outcome measures and approaches to interventions. More high-quality studies were recommended that focused on specific headache types as they all have different pathophysiological mechanisms, and are likely to respond differently to manual approaches. Wandereley et al. (2015), in a systematic review of six papers on headache relief from MT, came to a similar conclusion, highlighting the absence of clarity in terms of techniques used and the lack of power calculations as reasons for ambiguity in the evidence for MT and headaches. In summary, despite an increased number of favourable RCTs utilising manual therapies for tension-type headache there are still only a limited number of high-quality studies.

1.5.2. Migraineous headaches

Chaibi et al. (2011) evaluated six RCTs that included massage therapy and chiropractic manipulative therapy. Only five were manual therapy (excluding exercise) and only three studies had migraine diagnosed by a neurologist in line with current ICHD guidelines (Tassorelli et al. 2018). The remaining three studies were diagnosed by questionnaire and one by a chiropractor. The analyses led Chaibi et al. (2011) to comment that the included RCTs suggest MT might be equally efficient as propranolol and topiramate in the prophylactic management of migraine. Nelson et al. (1998) included a measure of the adjunctive benefit of chiropractic spinal manipulative therapy (CSMT) by comparing three groups: CSMT; Amitriptyline; Amitriptyline and CSMT combined. The reduction in headache index scores compared with baseline was 49% for amitriptyline, 41% for the combined group and 40% for CSMT alone. Thus, the combination did not show any benefit over medication alone. However, in the post-treatment period (one month) the reduction was 42% for CSMT alone and 25% for amitriptyline.

The study of Chaibi et al. (2011) has been analysed in several systematic reviews and each concluded something different depending on the process of analysis used. Bronfort et al. (2001) highlighted the decreases in medication use and longer-term maintenance of effect for SMT, although the primary outcome measure (headache index) showed no difference between groups. The methodology scored 87% but concluded the trial's design was not for equivalence and was underpowered. Bryans et al. (2011) had similar conclusions and gave it a quality rating of 5/10. However, Pozadzki & Ernst (2011) concluded there was no difference between groups, although these authors failed to discuss any findings other than the primary one (headache index).

The other four studies in evaluated in Chaibi et al. (2011) used different interventions: massage therapy (Hernadez-Reif et al. 1998; Lawler & Cameron. 2006), cervical manipulation (Parker et al. 1978), and chiropractic SMT (Tuchin et al. 2000). Hernandez-Reif et al. (1998) demonstrated a mean reduction of 71% in pain intensity post massage intervention and unchanged in the control group, Parker et al. (1978) compared SMT delivered by a medical professional, physiotherapist and chiropractor, with mean reductions in attack frequency of 13%, 34% and 40% and in intensity of 12%, 15% and 43% in each of the three groups respectively. The outcomes in Tuchin et al. (2000) were statistically better in the SMT than the control group for migraine frequency, disability and medication use. The frequency of

headache from baseline to the two-month follow-up was reduced by 35% in the SMT group and 17% in the control. Lawler and Cameron (2006) conducted a two-arm randomised study with 48 participants of massage versus diary control in migraine (in which 80% were females). The overall outcomes were in favour of massage, which had a reduction in frequency of migraine but not intensity, with the control group having neither. Although this study's primary outcome was the stress response, with migraine frequency and intensity as secondary measures, the results were marred by a lack of valid measurement instruments, such as HIT 6, and of power calculations.

Apart from Lawler and Cameron (2006) there are few other recorded studies of massage and migraine. Jahangiri Noudeh et al. (2012) used massage and spinal manipulation of the upper back and cervical spine in 10 migraineurs. Pain was assessed using a verbal analogue scale with post-treatment pain reduced by 50% in eight of the ten patients. However, this was a poorly designed study with no control, no validated outcome instruments, and all of the patients were male i.e. not a representative sample of migraine patients. The measurements were also taken after one hour with patients still in the clinic, which is most likely to have raised the placebo response. Voight et al. (2011) conducted the first recorded RCT of osteopathy and migraine in females. The study design had several weaknesses including a lack of both power calculation, for sample size, and primary outcome measures. The participants were also diagnosed with migraine via a telephone discussion. There was no blinding and the control group received no active intervention. However, the validated HRQoL and MIDAS instruments were used to measure outcomes with the osteopathic group observing a reduction of four days per month in their headache days compared to no change in the 'care as usual' group.

Chaibi et al. (2016) conducted a three-arm migraine-chiropractic RCT: sham manipulation (placebo); chiropractic manipulation; and treatment as usual (medication, control), involving 105 migraineurs. The location was a tertiary clinic and 80% of participants were female. Although the primary outcome (reduction in headache days/month) was similar for each group, the placebo and manipulation groups maintained the improvements at the follow-up times of 3, 6 and 12 months, whereas the control group returned to base line. Medication usage was statistically reduced in the chiropractic group compared to the placebo and control. Despite this,

Chaibi et al. (2016) concluded that the effect in the manipulation group was most likely placebo. However, Chaibi limited the MT to Gonstead chiropractic which is not as well used as the analysis suggested (Cooperstein 2003) as it is a technique that requires radiographic intervention prior to treatment (placebo and manipulation groups had a full spinal x-ray prior to the study). No mobilisation or soft tissue work was performed which may have limited the results as previous research suggests that a combination of manipulation, mobilisation and soft tissue technique is more beneficial than a single intervention.

Two recent systematic reviews of primary headaches, including both tension-type and migraine were completed by Falsiroli Maistrello et al. (2018; 2019). The first considered the effectiveness of trigger point therapy in reducing the frequency, intensity, and duration of attacks in primary headaches (Falsiroli Maistrello et al. 2018). The conclusion from the review, comprising five TTH and two migraine studies, was that trigger point therapy when compared to minimal active intervention was favourable, but the evidence was of low to very low quality. Particular issues were highlighted with the heterogeneity of study design, including small sample sizes and high risk of bias. The second systematic review (Falsiroli Maistrello et al. 2019) was specifically of MT in primary headaches, including migraine and tension-type headaches. The conclusion was that MT when compared to placebo or ‘care as usual’ should be seen as an effective approach to improving the quality of life in these conditions. However, it also reflected many of the criticisms of previous studies highlighting the low quality of evidence and the need for suitable control groups and the use of headache specific outcome measures.

Only one recent systematic review was found that specifically examined the effect of MT (spinal manipulation) on migraine pain and disability (Rist et al. 2019). In total seven studies were included: six migraine and one CM, however due to anomalies in the CM study (Cerritelli et al. 2015), it was excluded from the final analysis. The results from the remaining studies were favourable for MT, although the effect size for reduction in both disability and pain were small (Hedges’ g = - 0.35 [95% CI -0.5, -0.16]). The final conclusion was tempered and considered preliminary due to the variation in study quality.

Few studies have compared MT as an adjunctive to medication. Bevilaqua-Grossi et al. (2016) studied the adjunctive effect of manual therapy (soft tissue, mobilisation

and traction plus medication) to normal pharmacological treatment in 50 female migraineurs. A significant improvement was seen in both groups for headache frequency post-treatment but no significant difference was observed between groups. At post-treatment there was an 18% greater reduction in mean frequency of headaches in physiotherapy plus medication patients compared to control patients. Although the active group had a 12% greater reduction than the control during the follow-up period, this difference was not statistically significant. However, the global perception of change was statistically significantly higher in the combined intervention group than in the control. Ghanbari et al. (2015) examined the use of trigger point therapy as an adjunctive to medication in a smaller study of 44 migraineurs. The main outcomes of headache frequency; intensity; duration and, medication usage were all reduced in both groups, but with a statistically significant difference in favour of the combined MT and medication group. Although improvements were found in the frequency and intensity of migraines, with better perceived change and greater satisfaction than in the 'care as usual' arm, both studies either failed to use, or report, standard measures of migraine impact such as MIDAS or HIT6. The balance of males to females (54% female) in Ghanbari et al. (2015) was also not typical of migraine studies or clinic attendees and may have affected the outcomes.

1.6. Current treatment approaches for chronic migraine

The evidence for current approaches to treating chronic migraine is mixed, with the mainstay treatment being medication. A comparison of European and North American/Canadian guidelines highlights considerable differences in the approaches and the underlying validity of each (European Headache Foundation. 2020; Charles & Rapoport. 2019). The majority of guidelines suggest the use of Sodium Valproate, Gabapentin, Amitriptyline, Propranolol or Topiramate as first line prophylactic treatments. However, whilst these have been shown to help to varying degrees in episodic migraine, only Topiramate has been subject to randomised control trials in chronic migraine. In recent years OnabotulinumtoxinA (Botox) has been the subject of a number of clinical trials in CM and is currently (at time of writing, the only product licensed for CM prophylaxis (Diener et al. 2010; Silberstein et al. 2013; Aurora et al 2014; Ahmed & Gooriah. 2015; Lipton et al. 2016; Young et al. 2019). The current UK NICE guidelines for headaches (NICE.org. 2016) recommend the use of Topiramate, Propranolol, or Amitriptyline, and if these treatments are not successful then a course of acupuncture. If this fails, then Botox

is the recommended option and is the most common treatment in tertiary clinics. International guidelines for the use of non-pharmacological approaches in migraine; including psychological therapy (CBT, ACT), massage, spinal manipulation (chiropractic, osteopathy), acupuncture and exercise are mixed. Some guidelines mention psychological approaches e.g. biofeedback and CBT, while others recommend physiotherapy as a generalised statement for MT. In the main however, specific guidance for multi-modal approaches is sparse (Jensen et al. 2012; Gaul et al. 2016). Despite the use and promotion of medications, their limitations were also highlighted. Most of the above medications have been developed and licensed for other conditions e.g. epilepsy, with use in migraine being “off label”, i.e. without license and often with little supporting evidence (Antonaci et al. 2009; Schwedt. 2014; Schaefer et al. 2015; Al-Quliti and Assaedi. 2016). They are also all known for side effects and/or limitations in usage, particularly in women of child bearing age (most female migraineurs) sodium valproate is known to cause birth defects, and a 2014 Cochrane review of gabapentin for the prophylaxis of episodic migraine advocated that it “should not be used in routine clinical practice” (Linde et al. 2013); Amitriptyline is not recommended for women who are pregnant, trying to become pregnant, or breastfeeding or for those with diabetes, heart conditions or serious psychological issues (UK NHS. 2021). A systematic review of 58 propranolol studies in migraine prophylaxis noted a high dropout rate due to side effects with little

benefit over placebo (Jackson et al. 2018). Some early studies of Botox showed only marginal benefit in terms of the reduction in absolute headache days, and reductions in HIT6, with high placebo rates and a high cost mentioned (Aurora et al. 2011; Aurora et al. 2014; Diener et al.2010; Dodick et al.2010; Frampton & Silberstein.2018). Although Topiramate produces similar reductions, Botox has fewer side effects and a better adherence profile. A major factor in the use of medications for CM is the impact of side effects and when used for CM, Topiramate has been shown to have a drop-out rate of 24% in some studies as a result (Mathew et al. 2009, Rothrock et al. 2019). For women, Topiramate is not recommended if pregnant or trying to conceive, and evidence for the use of acute migraine medications is uncertain (Cady & Schreiber, 2008, Khalil et al. 2014; Ahmed & Gooriah, 2015). Conversely, the side effects of MT are reported as minor in studies, normally short-term aches and headaches (Chaibi et al. 2017; Tabelli et al. 2019). Diener (2012) concluded that medication alone is not always an effective treatment for chronic migraine, and that a multi-modal approach involving neurologists, psychologists, and physical therapists is required (Jensen et al 2008; Gaul et al. 2016; Cho et al. 2017).

1.7. Summary and next steps

This section outlined the rationale for examining the use of MT in chronic migraine by reviewing the pathophysiology of migraine, chronic migraine and the commonalities with other chronic pain (and often comorbid) conditions. It proposed two models on which the basis for the use of MT could be argued, the neurophysiological model and the allostatic model, with environmental and biopsychosocial effectors. To further build the rationale for a study into the use of MT in CM, a summary of findings from studies on the efficacy of MT for non-migraine headaches and migraine was presented. One of findings from the narrative review was the consistently greater impact, in all domains, of migraine on females compared to males and the increased rate of chronification seen in females. There was also a greater prevalence of comorbidities including anxiety, depression and pain conditions in female migraineurs compared to males, which are thought to be affected, in part, by female hormones and play a part in treatment response. This level of impact and associated conditions also fitted with my own clinical experience.

However, despite the review providing an overall positive basis for further study it also highlighted criticisms of the low quality of research. Weaknesses included lack of homogeneity in study design, interventions, measurement tools and a lack of power calculations. The importance was also noted of focusing studies on specific types of headaches. These findings suggested that focusing on one gender and a specific headache, in this case CM and females, would provide a more robust study design.

Having established a rationale for the study, a systematic literature review was undertaken to evaluate the current situation regarding the effect of MT on CM, to identify any gaps in research and to provide guidance on the study design.

CHAPTER 2 SYSTEMATIC LITERATURE REVIEW

2.1. Introduction

The background to this study was outlined in Section 1. This discussed the theoretical and experimental basis for the use of MT in the treatment of CM using studies from pain management, neurology and headache management. Although the findings for its use are generally positive, the majority of the studies fail to provide high-quality evidence for the use of MT as a standalone therapy (Lozano-Lopez et al. 2016; Falsiroli Maistrello et al. 2019).

However, this is also the case with existing pharmacological approaches, under which some people do not benefit, fail to benefit to the extent expected, or experience side effects that reduce adherence (Aurora et al. 2014; Diener et al.2010; Dodick et al.2010; Frampton & Silberstein.2018). This is unsurprising since the consensus is that migraine in all of its variants is a syndrome, with multiple mechanisms involved in its pathophysiology. This situation lent itself to the possibility that the use of concomitant multiple therapeutic options rather than a mono-pharmacological treatment may be a better approach (Gaul et al. 2011; Wallasch et al. 2012; Grazzi 2013; Burstein et al 2015; Gaul et al. 2016; Grazzi & D'Amico, 2019). Thus, rather than treating MT as a replacement to the usual pharmacological care of chronic migraine, it was considered more beneficial to examine it as an adjunctive intervention.

A systematic review of the literature was undertaken to explore the current situation with regard to evidence for the use and effectiveness of MT in the treatment of chronic migraine and to provide support for the proposed RCT. Systematic reviews provide valid and reliable evidence, enabling rigorous conclusions to be drawn from a range of study designs (Bettany-Saltikov, 2010). Although designed to synthesise findings from a multitude of primary research sources, one of the strengths of the process is its rigour in finding relevant papers and enabling analysis utilising quality tools. Systematic literature reviews can also highlight gaps in research despite sometimes finding relatively few studies (Glasziou et al. 2010; Yaffe et al. 2012).

Therefore, this systematic literature review aims to summarise what is known about the effectiveness of MT as a treatment in conjunction with, or separate to, 'care as usual' in chronic migraine.

2.1.1. Review objective

Specifically, the review sought to answer the question:

What is the effect of manual therapy on people (females) with chronic migraine when added to 'care as usual'?

2.1.2. Participants

The participants for studies included in this review were drawn from studies of either gender over 18 years of age who were diagnosed with chronic migraine. However, when reviewing mixed-gender studies an attempt was made to delineate the outcomes by gender since the focus of the proposed study is exclusively females. This was an important decision as there have been shown to be significant differences between males and females in terms of disability from migraine. Males are also thought to respond differently to pain than females and, in migraine, pain has been identified as the main determinant of disability in males compared to a broader range of factors in females (MacGregor et al. 2011; Scher et al. 2018; Sorge & Strath 2018). Moreover, the proposed primary outcome measurement instrument is the HIT6, for which Coeytaux et al. (2006) found that males had a significantly lower reduction in HIT6 change than females. In a mixed gender study these factors potentially skew the results and negatively impact transferability of findings in a clinical setting (Peterlin et at. 2011; Buse et al. 2013; Vetvik & MacGregor. 2017).

2.1.3. Interventions and comparisons

Data were extracted from studies that used MT alone or as an adjunct to other 'care as usual' treatments in headaches and migraine to identify its use in chronic migraine. MT was defined as any variation of the terms mobilisation, manipulation and massage as applied by hands to the musculoskeletal system (Farrell & Jensen.1992; Bronfort et al. 2010; Moore et al. 2017). The variations are set out in the search strategy below. 'care as usual' was defined as the ongoing/normal pharmacological treatment in place and chronic migraine was defined according to the diagnosis by the International Classification of Headache Disorders (International Headache Society. 2018).

2.1.4. Outcomes

The primary outcome evaluated was the difference in change scores in headache impact test 6 (HIT6), which is the most common outcome measure and the only instrument validated for all types of headaches. Other validated instrument of headache disability e.g. the Migraine disability assessment (MIDAS) and MSQ 2.1 were also included. The secondary outcomes include impact of migraine-related symptoms as measured with validated questionnaires, including patient related outcome measures (PROM), reduction in the number of headache and migraine days, and changes in medication usage.

2.1.5. Study design

The review included randomised controlled clinical trials (RCTs), non/quasi-randomised controlled trials (NRCTs) and cohort studies that together represent the highest levels of evidence (Burns 2011). The study selection was limited to literature written in English and those for which full text versions could be obtained. The inclusion and exclusion criteria are listed in Table 2.1.

Table 2-1. Literature search inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Adults aged 18 years or older with chronic migraine as diagnosed by a consultant according to ICHD classification	Age of participants under 18 years Self-diagnosed chronic migraine Not chronic migraine
Studies assessing manual therapy and headaches, migraine, chronic migraine with definitions as outlined above	Studies using exercise therapy, acupuncture, needling and other non 'hands-on therapy' as the primary intervention

2.2. Methods

2.2.1. Data sources and search strategy

The following electronic databases were searched: Web of Science; Medline; PsychInfo; Cinahl complete; EMBASE; AMED; Scopus, and the Cochrane database of systematic reviews. In addition, platforms including Google Scholar, Open Grey, Science Direct and publishers, and Wiley were used to broaden the search. The search had date restrictions from 1988 to 2018 on the basis that this period covers current studies back to the introduction of modern migraine interventions such as the triptans. The search was updated during the writing process to include any new studies until January 2020. The first edition of the IHS Classification of Headache Disorders was followed in the 1990s with the introduction of the first migraine specific medications (Triptans). The general search terms and strategy is shown in Table 2.2; the specific search used for Web of Science, Table 2.3, was repeated, modified for the other electronic database formats, using MeSH terms whenever relevant, e.g. 'headache disorders' and 'musculoskeletal manipulations.'

Table 2-2. Generalised search strategy terms (headings adapted for individual database format)

Number	Search Terms
1.	Migraine*
2.	Headache*
3.	Manual therap*
4.	Chiropract*
5.	Osteopath*
6.	Physiotherap*
7.	Massage
8.	Spinal Manipulati*
9.	Mobilis*
10.	Mobiliz*
11.	Myofascial
12.	Trigger point*
13.	Acupressure
14.	Physical Therap*
15.	Kinesiology
16.	1 OR 2
17.	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
18.	16 AND 17

Table 2-3. Web of science search strategy	
#1	(TS = (migraine or headache)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article) Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=1988-2018
#2	TS=(("manual therap*") OR chiropract* OR osteopath* OR physiotherap* OR massage OR("spinal manipulat*") OR ("physical therap*") OR mobilis* OR mobiliz* OR myofascial OR ("trigger points") OR kinesiology OR acupressure) Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=1988-2018
#3	#2 AND #1 Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=1988-2018

2.2.2. Study records

The initial screening search results were exported to Endnote referencing software and duplicates removed manually based on the titles and abstracts. Studies from other sources (e.g. dissertations) were managed manually. This was performed by the lead investigator (JO). Those studies likely to be of interest from the title and abstract were examined in more detail for the relevant terms including chronic headache, chronic migraine and migraine, when linked to a MT intervention. Those studies requiring clarification were extracted for a full text search. Systematic reviews were assessed to identify additional relevant studies and avoid duplication (Appendix 1). The studies selected as relevant to the systematic review were then moved onto the data extraction phase. The study screening and selection process is documented and summarised in the PRISMA flow chart (Figure 2.1) and a summary of the overall number of studies considered is provided in Appendix 2.

2.2.3. Data extraction

The lead investigator (JO) performed data extraction on included studies using a Microsoft Word template in order to complete the inclusion and quality assessment. Data extracted included study design; migraine diagnosis; method; sample size; follow up duration; population characteristics; MT intervention(s), 'care as usual' intervention; outcome measures, and statistical analysis. In the case of missing or unclear details the lead investigator contacted authors for this information.

2.2.4. Quality assessment

Previous headache studies have been criticised for the low quality of methodology (Podaski & Ernst 2011; Wanderely et al. 2015; Falsiroli Maistrello et al. 2019). For this reason, each included study was assessed using a scoring mechanism specifically developed by Fernandez-de las Penas et al. (2006) for headache studies (Appendix 3) as well as the “Risk of Bias” tool (Table 2.4) from the Cochrane Handbook V.5.1.0.(Higgens & Green, 2011). This uses factors to classify risk of bias as either uncertain, low or high (Table 2-5). This process was cross-checked by a professorial collaborator. Any disagreement was resolved by discussion. Level of evidence and recommendation are based on the OCEMB (Oxford Centre for Evidence-Based Medicine, 2011) criteria.

Table 2-4. Cochrane risk of bias factors

1. Random sequence generation	2. Allocation concealment	3. Blinding of participants and personnel	4. Blinding of the outcome assessments	5. Incomplete outcome data	6. Selective reporting	7. Other sources of bias

2.3 Results

A total of 982 studies were identified with their titles and abstracts screened against the inclusion and exclusion criteria. In total, 27 studies were included in the full-text paper review. Of these 21 were excluded at the outset and four required further clarification with requests sent to the original authors for more detail (Appendix 4). This left two chronic migraine papers included in the review (Figure 2.1).

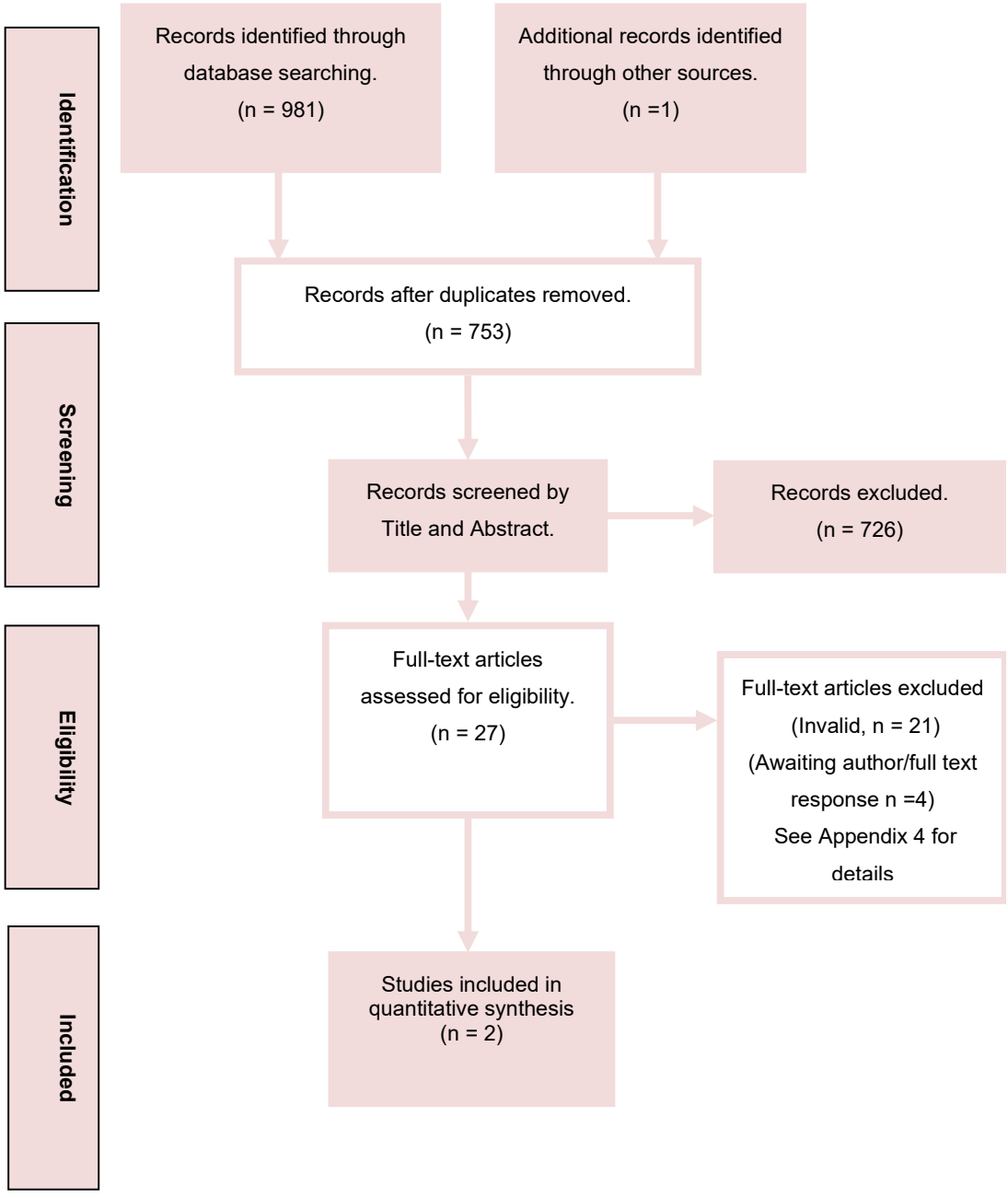

Figure 2-1. PRISMA literature screening process

2.4. Quality of evidence

Previous research into headache and its management with MT has been criticised both for its paucity and low quality (Fernández-de-las-Peñas et al. 2006; Bronfort et al. 2010; Podaski & Ernst 2011; Wanderely et al. 2015). There are various indicators of quality for RCTs including the Jadad (Jadad et al 1996), PEDro (Sherrington et al. 2000 and CONSORT (Consolidated Standards of Reporting Trials) (Moher et al. 2010; Boutron et al.2017). The Jadad is easy to use but limited in scope with scores based on the answers to three questions: was the study (1) randomised (2) described as double blind and (3) description inclusive of withdrawals and dropouts? The PEDro Scale is more comprehensive with 11 questions covering allocation, randomisation, blinding, etc (Figure 2.2) but designed for physiotherapy and rarely used in headache studies and the most recent option was the CONSORT guidelines (including a version for Non-Pharmacological treatments) which is the commonly used, and most comprehensive with 25 items on the checklist, to report quality of RCTs. However, none of the above were developed for headache studies utilising manual therapy. As such, two eligible chronic migraine studies were checked for methodological quality using an approach developed by Fernández-de-las-Peñas et al. (2006) specifically for headaches and MT interventions, with which a score of above 50/100 is considered good quality. Both studies were considered good to high-quality, with Cerritelli et al. (2015) scoring 69/100 and Gandolfi et al. (2017) scoring 51/100 (Appendices 5, 5a). In addition, both studies were also assessed as low in bias, using the Cochrane Risk of Bias, (Table 2.5), although the small sample size in Gandolfi et al (2017) raised 'other bias' to uncertain.

1. Eligibility criteria were specified
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).
3. Allocation was concealed.
4. The groups were similar at baseline regarding the most important prognostic indicators
5. There was blinding of all subjects.
6. There was blinding of all therapists who administered the therapy.
7. There was blinding of all assessors who measured at least one key outcome
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat".
10. The results of between-group statistical comparisons are reported for at least one key outcome.
11. The study provides both point measures and measures of variability for at least one key outcome

Figure 2-2. PEDro scale

Table 2-5. Cochrane risk of bias – identified studies

	Studies	
	Cerritelli et al et al. 2015	Gandolfi et al. 2017
SELECTION BIAS		
Random sequence generation	+	+
Allocation concealment	+	+
PERFORMANCE BIAS		
Blinding of participants and personnel.	+	?
DETECTION BIAS		
Blinding of outcome assessment.	+	+
ATTRITION BIAS		
Incomplete outcome data.	+	+
REPORTING BIAS		
Reporting bias	+	+
OTHER BIAS		
Other sources of bias	+	?

+ Low bias − High bias ? Uncertain bias

2.4.1. Level of evidence

The overall level of the evidence for MT and chronic migraine in this review was established using the OECBM guidelines which provide clinicians with a simple, pragmatic measure of evidence for interventions, suitable for use when few RCTs exist. They do not give definitive recommendations on use but provide a guide as to whether the findings make credible clinical sense (OCEBM, 2011. Appendix 6).

Using the OECBM method in which Level 1 is the highest quality (systematic review with homogeneity of RCTs) the level of evidence for this review is considered Level 2 or 3; single RCTs without narrow confidence intervals; downgraded due to inconsistencies, including the lack of homogeneity in studies as a result of differences in; patient characteristics, the balance of males to females, intervention characteristics e.g. dose and timing, outcome measures e.g. factors and measurement instruments and study design.

2.4.2. Data synthesis

Both of the studies included focussed on chronic migraine with MT interventions, defined as ‘hands on’ techniques which aim to mobilise and manipulate soft tissue and joints. The study of Cerritelli et al. (2015) was a 3-arm RCT and that of Gandolfi et al. (2017) was a 2-arm pilot RCT. Sample sizes were 105 and 22 respectively, making a total sample size of 127 participants. The participants ranged from 18 to 66 years of age, with a pooled mean of 40.25 years. The studies included males and females with 31% being male. The percentage of females in Gandolfi et al. (2017) was higher and more representative of migraine studies (87% female versus 64% female in the study of Cerritelli et al.). Both studies took place in Italy and used the change in Headache Impact Test (HIT 6) as a disability outcome measure. However only Cerritelli et al. (2015) used it as the primary outcome measure. The secondary outcome measures included a variety of those recommended by the IHS; change in medication usage, headache days and headache intensity (Tassorelli et al. 2018). Gandolfi et al. (2017) also used the MIDAS assessment for disability as a secondary outcome measure and both studies used diaries to collect this information. Tables 2.6 and 2.7 summarises the characteristics and outcomes. Gandolfi et al. (2017) also collected pain pressure threshold data on the trapezius, temporalis, occipitalis and frontalis muscles and data on coffee consumption and dietary restrictions.

The duration of each study was 12 weeks (Gandolfi et al. 2017) and 24 weeks (Cerritelli et al. 2015) respectively. Gandolfi (2017) had a post-treatment phase and made a final clinical assessment at 12 weeks with an active treatment phase lasting four weeks from week four to week eight. Cerritelli et al. (2015) did not have a post-treatment phase.

Conventional pharmacological care was used in both studies, with Gandolfi et al (2017) using Botox in both arms in conjunction with the adjunctive MT treatment, whilst Cerritelli et al. (2015) used an unspecified medication regime (‘care as usual’) in 2-arms.

Both studies used manipulative techniques designed to improve joint and soft tissue mobility. Cerritelli et al. (2015) used osteopathic techniques in an unspecified manner based on an initial assessment in the MT arm, whereas Gandolfi et al. (2017) specified the cervical spine C0, C1 and the thoracic spine, T3-T7. These

were treated with low velocity high amplitude manipulation and the cervical spine underwent articulatory mobilisations. The study of Cerritelli et al. (2015) had three groups: MT plus ‘care as usual’ medication; sham MT plus ‘care as usual’ medication: medication ‘care as usual’ only. Gandolfi et al (2017) used transcutaneous electrical nerve stimulation (TENS) as a comparative to the MT with both groups receiving Botox as ‘care as usual’.

The interventions were applied by six osteopaths in the study of Cerritelli et al (2015) and by two experienced physiotherapists, one for each arm, in Gandolfi et al (2017). The MT regime was different in each of the two studies, with Gandolfi et al (2017) having four sessions of 30 minutes for four weeks (one per week) from week four to week eight, following an initial injection of Botox at week one. Cerritelli et al (2015) used 8 sessions lasting 30 minutes, scheduled one per week in weeks one and two, then biweekly for two sessions and monthly for the final four.

2.4.3. Study characteristics and outcomes

Table 2-6. Characteristics of included studies

Author	Population	Age (mean)	Diagnosis	Diagnosis criteria	Comparative Interventions	Type of Manual Therapy	Intervention Protocol	Outcomes
Cerritelli et al (2015) Italy	F:27, M:8 F:22, M:13 F:20, M:15	MT: 36.9(9.3) Sham:40.7 (8.7) Control: 38.4 (9.9)	CM	ICHD by neuro	Sham MT + medicinal 'care as usual' SMT + medicinal 'care as usual' Medicinal 'care as usual'	Myofascial release Osteopathic mobilisation cervical spine	Weekly trt 1 & 2 Bi weekly trt 3 ,4 Monthly Trt 5-8	Primary Change HIT 6 score
Gandolfi et al (2017) Italy	F:10 M:2 F:9 M:1	Manipulation:45.8 (14.1) TENS :50.2 (6.2)	CM	ICHD neuro	TENS + Botox MT +Botox	LVHA Manipulation of cervical and thoracic T3-T7 spine Myofascial release	Weekly trt 1,2,3,4	Primary Change in Pain Secondary - HIT6

Table 2-7. Study outcomes

	Primary Outcome Measure	Secondary Outcome Measures			
Study Time to Outcome Assessment/ follow up (FU)	**Change in Headache Impact Test (HIT6)**	**Days of migraine/month**	**Severity of headache pain**	**Medication usage Number of patients taking medication**	**Functional ability**
Cerritelli et al. 2015 6m FU N/A	Decrease of HIT-6 score for MT vs controls (p<0.001) MT—conventional care: −8.74; 95% (CI) −12.96 to −4.52; p < 0.001 MT—sham: −6.62; 95% (CI) −10.85 to −2.41; p < 0.001 Sham group: No significant difference compared to control (−3.12; −6.61, 0.32; p = 0.08).	MT Sham Control Baseline (mean, SD) 22.5(5.2) 22.3(5.0) 22.5(5.2) 6 Months 1.2(1.9) 18.6(4.6) 22.3(4.2) Diff MT-sham: -17.4; 95% CI -19.57 to -15.3; p<0.001), Diff MT-control: -21.06; 95% CI -23.2 to -18.9; <0.001	MT Sham Control Baseline (median, IQR) 3(2—4) 3(1—4) 3(1—4) 6 Months 0(0—1) 2(0—3) 3(1—4) MT-sham: RR=0.42, 95% CI 0.24-0.69; MT-control: RR=0.31, 95% CI 0.19-0.49)	MT Sham Control Baseline (n, %) 35(100) 35(100) 35(100) 6 Months (n, %) 7(20), 32(91.4) 35(100) MT-sham: RR=0.22, 95% CI 0.11-0.40; MT-control: RR=0.20, 95% CI 0.10-0.36),	MT Sham Control Baseline (median,IQR) 3(2-3) 3(2-3) 3(2-4) 6 Months 0(0-1) 2(1-3) 3(2-30
Gandolfi et al. 2017 T(0) 0 T(1) 8w T(2) 12w EG = Experimental Group (SMT) CG= Control Group (TENS)	**Feasibility based on treatment attendance and efficacy based pain scores** All patients completed the study . No significant between-group difference in pain intensity before (p=.34) and after treatment (p=.14) was measured No significant difference between pre- and post-treatment pain intensity in either group was measured (manipulative group, p=.09;TENS group, p=.96).	**Days (without) Headaches** Mean (SD) T(0) T(1) T(2) EG 13.8(9.8) 10.8(8.7) 13.8(8.8) CG 17.8(10.2) 16.7(9.9) 15.90(8.9)	T(0), T(1), T(2) Mean (SD) EG Mild 33.3 (45.5) 70.4 (106.9) 24.7 (20.2) CG Mild 16.2 (30.5) 17.5 (23.5) 28.3 (35.8) EG Moderate 32.4 (25.3) 31.2 (27.5) 26.1 (25.6) CG Moderate 29.5 (27.7) 24.3 (25.1) 25.7 (28.8) EG Severe 15.3(17.2) 14.8 (15.1) 18.9 (21.8) CG Severe 43.2 (83.7) 43.2 (82.3) 41 (67.0)	**Total analgesia used** Mean (SD) T(0) (T1) (T2) CG 13.1 (9.7) 13.1 (9.8) 13.4 (10) EG 7.50 (6.7) 5.3 (6.4) 3.50 (3.9)	**Change in Disability (HIT6, MIDAS)** HIT6 Mean (SD) [range 36-78], T(0) T(2) EG 62.3 (5.5) 62.0 (6.7) CG 62.0 (7.2) 61.0 (6.5) MIDAS EG 75.6 (44.9) 79.5 (43.4) CG 101.0 (57.6) 79.0 (49.4)

2.5. Discussion

This systematic review identified only two relevant studies, both of which had positive outcomes for MT in CM. This may be seen as too few papers for an RCT, however according to Cochrane handbook, “A systematic review attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question”. Whilst the centre for evidence-based medicine (CEBM) states the purpose of a systematic review as “to provide the best available evidence on the likely outcomes of various actions and, if the evidence is unavailable, to highlight areas where further original research is required”

To this extent, the quality of the systematic review is not solely contingent on the number of papers identified; highlighting gaps in the evidence base may in fact support the need for research (Glasziou et al. 2010). There is no set minimum number of studies required for a systematic review, with one estimate of zero papers in 10% of reviews, which will often be the case in new or immature areas (Yaffe et al. 2012), whilst another study gave the median number of papers as six (interquartile range 3 to 12) (Mallett. 2003). The proposed RCT is in an immature area and as such a systematic review with two papers was considered a valid outcome and consistent with other authors (Chaibi and Russell. 2014; Cerritelli et al. 2016; Moore et al. 2017; Rist et al. 2019) who identified a lack of research in this area. Whilst the number of papers in itself was not seen as a weakness of process, the Cochrane approach to systematic reviews suggests that two people are involved in screening the relevant papers to avoid selection bias. Unfortunately, in this case the resources in a Doctoral PhD did not permit this.

In addressing the impact of potential selection bias and the limitations imposed by only having two papers, it may be useful to revisit the primary aim of this systematic review. It was not, as is usually case, to provide evidence for guidance on the role of MT in CM for clinical purposes but rather to identify the state of current research and provide guidance on the development of the protocol. Thus, the exclusion any papers would have served no useful purpose.

Bettany-Saltikov (2010) suggest that part of the systematic review process is to provide a critical review of the evidence, enabling rigorous conclusions to be drawn from a range of study designs. In this case, whilst the limited number of papers did

reduce the depth of the conclusions to be drawn it did raise issues that were fed into the development the protocol. However, from a quality standpoint, apart from the lack of two people screening the papers, all other components of the process were completed according to the PRISMA guidance.

2.5.1. Risk factors

Both of the studies failed to address the impact of any modifiable risk factors for chronification e.g. stress (Scher et al. 2008). Although Gandolfi et al (2017) measured dietary restrictions and coffee consumption, no analysis was presented. Gandolfi et al (2017) suggested in the discussion that future studies should consider the impact of risk factors on therapeutic response.

2.5.2. Outcomes

Both studies used the validated HIT6 as an outcome measure, although only Cerritelli et al (2015) used it as the primary outcome measure. Gandolfi et al. (2017) presented a non-significant change in HIT 6 score between groups of -3 [95% (CI -5;3)], whilst Cerritelli et al (2015) produced statistically significant differences in changes ($p<0.001$) of -8.74 for the Osteopathic group (MT+'care as usual') compared to 'care as usual'. There was also a difference between (MT+'care as usual') and Sham (MT + 'care as usual') of -6.62; with a non-significant change of -2.32 for Sham (MT+'care as usual') compared to 'care as usual'. Cerritelli et al (2015) used a difference of 5 between groups and 27 within groups to power at 90% (p= 0.05) between baseline and post-treatment HIT6 scores. This resulted in a sample size of 35 per group although no calculations were provided of underlying assumptions on standard deviation in HIT6. However, the small sample size of Gandolfi et al (2017) study made the finding less powerful. Gandolfi et al (2017) also used MIDAS, another validated measurement of migraine disability, as a secondary outcome. However, unlike HIT 6, a minimal clinical difference had not been calculated for MIDAS.

The majority of recent pharmacological studies into chronic migraine used responder categories as outcome measures, despite a lack of consistency in the definition and use of responder rates. The IHS guidelines (Tassorelli et al. 2018) define responder rates as either:

1. The number of headache days with moderate or severe intensity
2. The number of migraine days

3. The number of migraine episodes.

The IHS has suggested a reduction of ≥30% in any of the above measures as clinically meaningful (Tassorelli et al. 2018). Cerritelli et al (2015) also used 4-point Likert scales to assess the severity of pain on headache days and functional ability, whereas Gandolfi et al (2017) used a visual analogue scale (0 = no pain 100 = worst ever). Although these scales were included in the headache diary and are easy to use, it was difficult to correlate the results with changes considered important to the patient. Gandolfi et al (2017) concluded that the primary outcome had been met as the study was successful in terms of attendance for treatment and pain scores before and after each session. All patients completed the study and no significant differences between pre and post-treatment pain scores (VAS) were found (Table 2.7).

Medication use was reduced in both studies although usage was measured differently: Cerritelli et al (2015) used the number of people taking medications in addition to 'care as usual', whereas Gandolfi et al (2017) the consumption by type (Total, Triptans and NSAIDS). The results were statistically significant at $p<0.001$ and $p<0.009$ (Table 2.7) for Cerritelli et al (2015) and Gandolfi et al (2017) respectively in MT groups. However, in Cerritelli et al (2015), the sham MT+'care as usual') and ('care as usual') groups failed to show any significant reduction in medication use. In this case it was difficult to compare the results apart from noting the significant decreases in both.

2.5.3. Gender differences

Whilst both studies included males and females in proportions generally consistent with the population studies of gender and migraine, they did not stratify the results. This limited any discussion on gender differences, despite CM being more prevalent and more disabling in females (Buse, 2012). An important difference that may have influenced the results was the significant variation in the proportion of males in each group in Cerritelli et al. (2015). The (MT + 'care as usual') group had 50% fewer males compared to the 'care as usual' group and 40% fewer than the Sham (MT+'care as usual') group. Coeytaux et al. (2006) found that males had a significantly lower reduction in HIT6 change than females and females are theorised to feel pain differently to men (Scher et al. 2018; Sorge & Strath 2018).

2.5.4. Side effects

Side effects from MT were collected using a diary, with neither study reporting significant side effects. This was consistent with other MT studies despite concerns about the risk and side effects of MT. However, neither study used HVLA cervical rotation manipulations which have often been the focus for attention with regard to stroke (Carnes et al. 2010; MacPherson et al. 2015; Vaughan et al. 2016).

2.5.5. Intervention and process

The TiDier (Template for Intervention Description and Replication) checklist was developed to improve the descriptive reporting of interventions, in part to help clinicians to implement useful interventions, and for other researchers to replicate and build on research (Hoffman et al. 2014).

Both studies provided detail on the intervention in line with the TiDier checklist (TiDier summaries Appendix 7). Although Cerritelli was less prescriptive than Gandolfi in the MT intervention itself, the type and manner of MT was well described in both. However even given the detail in Gandolfi, the exactness of the delivery of intervention will always come down to the manual therapist themselves. Gandolfi et al (2017) also had a planned and actual assessment of adherence – since this was one of the study objectives. Cerritelli et al (2015) on the other hand made no mention of adherence, although all participants completed the study. What is unknown is whether any switched groups. Cerritelli also failed to record any change (modifications) in the care as usual (medication) group regime, which was an important consideration given the impact a change in medication could have on outcomes.

Cerritelli et al (2015) used MT and sham MT as an adjunctive intervention whilst Gandolfi et al (2017) used TENS in one arm as a comparator and MT in the other. The structure of the intervention process also varied with Gandolfi et al (2017) having a four-week run in, a four-week treatment and a four-week phase out compared to Cerritelli et al (2015) with a 24-week treatment phase. Clinical assessments were taken by Gandolfi et al (2017) at the start and end of the MT therapy treatment phase with the Botox being injected at week 0 and again at week 12. Cerritelli et al (2015) made clinical assessment at the start and end of the 24 weeks, concomitant with pharmacological ‘care as usual’ (triptans).

There are no set protocols established for trials of this type although the IHS guidelines (Tassorelli et al.2018) recommend a minimum of 12 weeks for prophylactic migraine studies involving medication with a post-treatment follow up period.

The number and frequency of treatments differed in each study. Cerritelli et al (2015) had 8 out of 24 weeks weighted towards the start whereas Gandolfi et al (2017) had 4 sessions equally spread over 4 weeks. There are no defined or recommended approaches to treatment protocols and other headache studies vary in approach often with no stated rationale. Cerritelli et al (2015) used a “needs-based" protocol, appraised by the osteopathic evaluation, to determine the MT therapy treatment required in each session and used random light touch as the sham treatment. Gandolfi et al (2017) however used a pre-planned approach to using MT therapy and TENS. The issue of a pre-planned protocol and clearly identifying the location of intervention has been cited in the past as a weakness in MT studies, however one of the strengths of the ‘pragmatic’ approach, as adopted by Cerritelli et al (2015), is the similarity to real life clinical situations including the adjustment to each patient (Loudon et al. 2015, Forden & Norrie. 2016).

The issue of tailoring the intervention was not constrained to MT in migraines and headaches, but also to pharmacological and psychological interventions where the need to produce a personalised approach is highlighted in medical literature (Belvis et al 2014; Probyn et al. 2015; Antonuci et al. 2016; Agostini et al. 2019). There is therefore an argument to say the best intervention protocol is one that has a broad evidence-based approach, within which individual pragmatic tailoring is used, based on clinical experience and observation.

2.5.6. Limitations

Despite the overall positive primary and secondary outcomes of the studies included, limitations were noted in both approaches. Firstly, blinding of practitioners or participants to allocation is difficult in MT which can add an increased placebo effect. Cerritelli et al (2015) attempted to address effect of placebo with the use of blinded sham treatment. Another way of reducing the placebo effect is to limit patient interaction to taking necessary clinical information. However, placebo is also large in medication and non-pharmacological interventions, with estimates of between 20%-50%, and thus may not be the comparative issue imagined (Speciali

et al. 2010; De Groot et al. 2011). The diary data were self-reported and no clinical records were used to verify co-morbidities, which are common with migraine, although this is part of a pragmatic approach and endorsed in the IHS guidelines (Tassorelli et al. 2018).

Each study used a different design, 2-arm versus 3-arm, and although there is no consensus on which is better, there is a view that an intervention arm should be compared to a 'real' control. For example, using only Botox or other intervention as a control (Silberstein et al. 2008) with a third sham arm, as in Cerritelli et al (2015), would enable more accurate calculation of the placebo effect and strengthen the validity of the results. The issue of sex- based studies is also a limitation, since neither study focussed on females nor stratified results by sex or gender. This opens the question up as to whether the results are equally applicable to both sexes (MacGregor et al. 2011).

2.6. Summary

In attempting to answer the question on the effect of MT as an adjunctive therapy to 'care as usual' in chronic migraine, the narrative literature review identified a gap in research with a lack of studies on MT and headaches generally and chronic migraine specifically.

Gandolfi et al. (2017) commented that one of the limitations was the lack of a comparison to a control (a group using 'care as usual') and added that there is value in examining MT as an adjunctive to (rather than a replacement for) pharmacological care in chronic migraine. The majority of systematic reviews commented that more high-quality studies are needed to establish the role of MT, and experts within the field suggest that multi-modal approach to a multifactorial disease is the best solution (Jensen et al 2008; Gaul et al. 2016; Cho et al. 2017).

Although this systematic literature review confirmed the need for more high-quality studies into MT and chronic migraine, it also identified a lack of studies that used a pragmatic approach. Patsopoulos (2011) defined this as, "trials designed to evaluate the effectiveness of interventions in real-life routine practice conditions". Although Cerritelli et al. (2015) seemed to be undertaken in clinical practice it was difficult to assess if this was the case, and it was not described as a pragmatic trial. Gandolfi

et al. (2017) on the other hand, was not designed to be a pragmatic study. The analyses confirmed the use of HIT6 as a suitable primary outcome measure, and the value of responder group analyses.

This review did show that good quality studies into MT and chronic migraine were possible and, in the process, informed the methodology proposed for the planned RCT research study, in the following areas:

- The need to check against the methodological quality screen to ensure a good quality approach was taken, wherever possible using guidelines, e.g. CONSORT.
- To ensure the manual therapy protocol was adequately described (TiDier)
- To take into account the risk factors in the chronification of migraine when collecting and analysing data.
- To consider the basis of sample size calculations

CHAPTER 3 METHODOLOGY AND STUDY DESIGN

3.1. Introduction

The literature review highlighted, that whilst many randomised controlled trials (RCTs) exist on the topic of migraine and headaches, there are relatively few investigating the combination of manual, as distinct from physical therapy, and migraine. In particular, there is a paucity of RCTs that involve both MT and chronic migraine (CM). This was an important finding given that CM is the most problematic migraine variant, both for the patient, in terms of symptoms, and the treating clinician (in terms of the available treatment options) (Tepper et al. 2017; Becker 2017; Schwedt 2014).

This chapter describes the methodological approach adopted for a pragmatic RCT which explores the use of MT as an adjunctive treatment to 'care as usual' in CM. Issues discussed in this chapter include: the type and nature of this study; the rationale for choosing a pragmatic RCT; the methods used to collect data, and the statistical approaches used for analysis.

My professional expertise and experience as a registered chiropractor, and lecturer led me to study the impact of co-morbidities and neck pain in migraine and conclude that there is no single solution to the management of migraine. Whilst the presiding view of migraine is as a neurological condition (Andreou and Edvinsson. 2019), there is mounting evidence is that it is a multi-factorial condition consistent with the neurobiological and the allostatic models described in section one (Andrasik et al. 2005; Gaul et al. 2011; Borsook et al. 2012; Diener et al. 2015; Gaul et al. 2016). This helps to explain the known but uncertain relationship between migraine and other conditions that appear to involve similar neurological structures and processes including anxiety; depression; personality disorders; joint hypermobility syndrome, and chronic pain. On this basis, a multi-modal approach to migraine management, addressing the multiple effectors that contribute to chronification, seems the most appropriate treatment model.

3.2. Study hypothesis and objectives

There was extensive empirical evidence as to the benefits of MT for some headache types, particularly tension headaches (Espı-Lopez 2013; Chaibi & Russell. 2014; Clar et al. 2014; Lozano-Lopez et al. 2016). However, at the time of writing there was a lack of RCT studies involving MT for the treatment of headaches, particularly migraine and CM (Cerritelli et al. 2016; Moore et al. 2017; Rist et al. 2019).

Both theory and evidence suggest that migraine, with CM being the most refractory type (Weatherall 2015; Aurora & Brin. 2016) is a multi-factorial condition and would benefit from a multi-modal approach. As such, the overall aim of the study was to examine the use of MT as part of a multi-modal approach, rather than to compare MT against existing treatments (Gaul et al. 2011; Gaul et al. 2016).

3.2.1. Research questions

Based on the literature review, the research questions proposed for this study are:

Question one: Is manual therapy effective as an adjunctive to 'care as usual' in the treatment of females with chronic migraine?

Question two: Do female chronic migraine patients exhibit baseline characteristics that affect treatment outcomes within and between treatment groups?

3.2.2. Primary objective

To measure the effectiveness of adding MT to 'care as usual' in CM over 12 weeks

3.2.3. Secondary objective

To explore the association between baseline participant characteristics and the effectiveness gained from adding MT to 'care as usual' in CM over 12 weeks

3.2.4. Primary outcome measure

The primary outcome measure is the between-group difference in change scores ('care as usual' versus 'care as usual' and manual therapy) from baseline to the end of the 12-week intervention measured using the Headache Impact Test (HIT6).

3.2.5. Secondary outcome measures.

These measures include changes over the 12-week study period in:

- Percentage of participants with a reduction in headache and migraine frequency (days per month),
- Quality of life measure,
- Number of headache-free days,
- Number and type of abortive migraine medications,
- Stress and anxiety levels,
- Allodynia scores and
- Patient Global Impression of Change

Details on the instruments used to measure the above outcome changes are provided in section 3.4.7.

3.3. Study Design

3.3.1. Basis for pragmatic RCT design

One of the main criticisms of headaches studies involving all forms of physical therapy approaches including manual therapy was the low methodological quality (Fernadez-de-las-Penas 2006; Carod-Artal 2014). To address this criticism, an RCT design was chosen for this study as this represents the perceived 'gold standard' in clinical studies (Jones & Podsolsky. 2015). This section sets out the differences in RCT design and explains the rationale for undertaking a pragmatic RCT.

RCTs are positioned to provide support for evidence-based decisions on medical treatment; their systematic methodology provides an unbiased comparison between groups of participants (Speith et al. 2016). The original systematic approach to RCTs is considered to be based on work by Bradford Hill in 1946 (Bhatt 2010). He established a foundation of key tenets: randomisation control groups, and the blinding of everyone involved and outcome analysis (Kendall 2003; CONSORT. 2010). Underlying these tenets is the ability to reduce bias throughout the RCT process (Higgins et al. 2011). It is, in essence, a stable and controlled experiment that is focussed more on the efficacy of the study rather than the effectiveness. Efficacy is defined as the performance of an intervention under ideal and controlled

conditions, with effectiveness related to the intervention's performance under ‘real clinical practice' conditions (Revicki & Frank 1999).

The position of the RCT as the 'gold' standard was enhanced when Guyatt et al (1995) brought a sense of quality to the various types of research approach by proposing a hierarchy (often illustrated as a pyramid) in the quality of evidence. This hierarchy or ‘Levels of Evidence’ established RCTs at the top. This position was further consolidated with the development of Evidence-Based Medicine (EBM) which grew from the idea that many of the established approaches to treatment were often based on poor quality research. Variations of the hierarchy of evidence followed, with systematic reviews of RCTs at the top (Fig 3.1.)

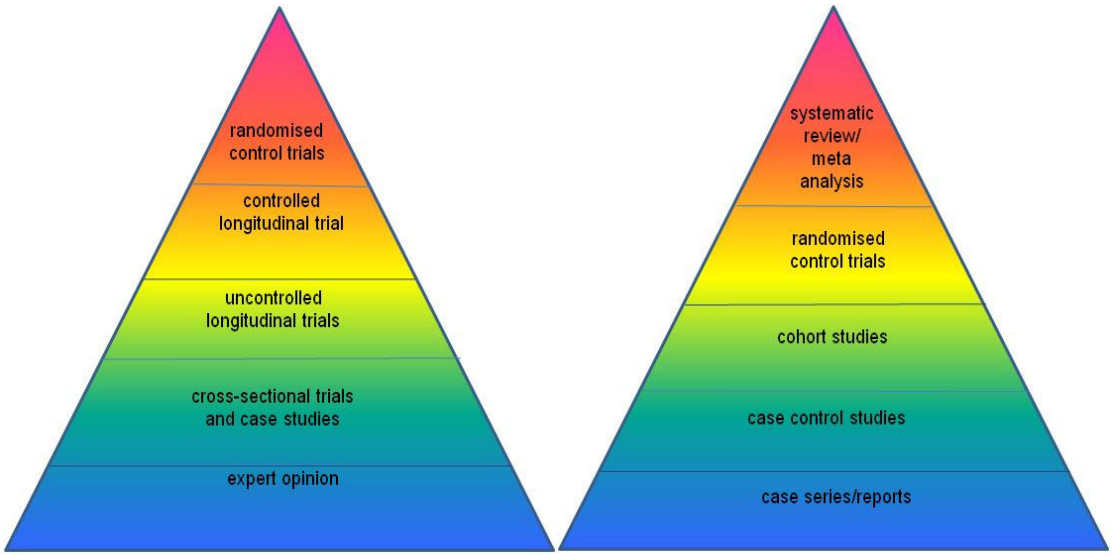

Figure 3-1. Hierarchies of evidence

The strict linearity of quality between levels and the hierarchy was challenged by the development of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (Gradeworkinggroup, 2008). This recognised that the certainty of evidence of studies was based on more than simply the design and reinforced the need to consider other factors, e.g. bias and inconsistency of results. Consequently, changes in the hierarchical schema were proposed (Murad et al. 2016) including “wavy” lines between the types of studies to reflect the movement of rating across the domains according to the quality of evidence. Regardless of these changes, in the hierarchy of evidence, the RCT is still considered the ‘gold standard’ after 70 years, as demonstrated by the growth in the number of studies with RCT in the title [Figure 3.2] (LeFevre 2017).

Image redacted Figure 1 page 411 LeFevre, M., 2017. From Authority- to Evidence-Based Medicine: Are Clinical Practice Guidelines Moving us Forward or Backward? The Annals of Family Medicine, 15 (5), 410-412.

Figure 3-2. Number of Medline articles with 'randomised controlled trial' as key word. (adapted from LeFevre et al. 2017).

A recent study has, however, highlighted the geometric growth in pragmatic RCTs. Despite there being only 615 labelled, 'pragmatic', between 1977 and 2017, 58% of them were published from 2014 onwards, with only 16% involving medicines (Dal-Ré et al. 2018). The next section considers the differences between RCT methodologies and the rationale for this study's design.

3.3.2. Choice of Pragmatic RCT

The choice of a pragmatic design was based on two major tenets. The first, formed from personal experience which informed the study aim; the second, founded on the theories that underpin the explanatory and the pragmatic RCT designs.

As a manual therapist it was paramount that the outcome of a study should inform clinical practice, guiding the approach to the treatment of headache and migraine patients in a working clinic, based on the best evidence. These patients are not a homogenous group, they are not preselected to fit exact criteria and they will not just have one specific intervention, but rather a tailored approach. As a professional in a clinic, the aim is to help reduce patient disability with the tools (interventions) available and not to 'prove' one way is better than another or which specific MT intervention in a multimodal approach makes the difference. This was particularly relevant to those with CM, who were most likely already on a 'care as usual' programme via the or GP or the NHS and thus seeking additional assistance rather than a complete replacement. This situation lent itself to a need to understand the study design options available that would enable good practice to be developed whilst balancing the need for a robust study and everyday clinical situations. Support

for the pragmatic approach came from the UK Back pain, Exercise And Manipulation (BEAM) trial which was at the time of writing, the largest pragmatic RCT investigating the effect of MT interventions in the UK. The BEAM trial was designed to examine whether additional benefits accrued over and above best care from GPs (Vogel et al. 2005) from combinations of MT and PT.

This next section outlines the thought process that led to the decision to implement an adjunctive pragmatic design over the traditional, efficacy based, design.

Despite the success of establishing RCTs as a gold standard, there has been criticism of the approach. Many of these criticisms cite: the reliance of the RCT on a need for an ideal experimental situation; a set environment; a homogenous group of participants; and an exact quantifiable intervention. For many conditions, this does not reflect real-life clinical practice (Moeller 2011; Singal et al. 2014). For MT specifically, maintaining the quality associated with efficacy-focussed RCTs, designed in the main for pharmacological trials, whilst recognising the inherent drawbacks and incompatibility with requirements of MT is a balancing act which has been suggested as being hard to achieve (Milanese 2011).

Koes and Honig (1999) raised issues with implementing an efficacy-focussed RCT approach in physiotherapy, in particular MT. These issues include:

(1) The standardisation of intervention. In pharmacological trials this is straightforward, whereas most MT is not applied as a single intervention;
(2) Blinding. MT interventions can never be double blinded; in all cases the manual therapist will know which intervention is being applied even if the participant does not know. Without blinding, the potential for an increased placebo effect is increased, and
(3) Sample sizes. The relatively small sample sizes possible in MT studies (often fewer than 50 per group) may not affect validity but will influence the precision of the outcome measures.

The above issues become more pronounced when working with MT to aid the management of headaches. Although headache guidelines existed to maintain the quality of pharmacological RCT efficacy-focussed studies, they provided little guidance for non-pharmacological/manual intervention studies (Penzien 2005;

Tassorelli et al. 2018). This led to a question of how research in these areas addressed the required demand for higher quality evidence. One development, proposed by Schwartz and Lellouch (1967), was the concept of the pragmatic effectiveness-focussed trial design to balance the explanatory efficacy-based model. This adapted the standard RCT approach to consider the impact of an intervention in a 'real life' situation, as an alternative to the classical explanatory efficacy-focussed design. In the process, this concept addressed some of the limitations of the efficacy approach which also applies to fields of medicine, e.g. surgery (Das 2011).

Table 3-1. Explanatory versus. pragmatic trials: features.

Table redacted. Table 1 page 139 MacPherson, H., 2004. Pragmatic clinical trials. Complementary Therapies in Medicine, 12 (2-3), 136-140.	

Adapted from MacPherson, 2004

Following on from this, MacPherson (2004) proposed that pragmatic trials could help the manual therapist answer questions on how effective a therapy is when compared to an existing, accepted treatment and not a placebo, as typically occurs in efficacy RCTs.

It was also proposed that this approach would allow the evaluation of complex, multi-modal interventions, and of how well therapies work as an adjunct to conventional interventions. However, this approach would not be able to determine which parts of the intervention provided the benefits as it evaluates a package of care.

Early developments in the pragmatic approach suggested there were distinct differences between the explanatory or efficacy-focussed studies and the pragmatic or effectiveness-focussed studies (Table 3-1). In reality, most RCTs fall somewhere

along the continuum, between the purely efficacy/explanatory and the effectiveness/pragmatic study; a situation acknowledged by the development of the Pragmatic Explanatory Continuum Indicator Summary, or PRECIS, model (Figure 3.3). Developed to support researchers' decision making in trial design (Thorpe et al. 2009; Louden et al. 2017), this model comprises nine key domains that are used to establish the position of the trial along the spectrum and whether the trial design meets the aims. The PRECIS schematic for a very pragmatic trial would be reflected by the scores of five for all domains, whilst a very explanatory trial would be represented by a small circle in the centre of the wheels shown in Fig 3.3.

Image redacted. Figure 1 page 3. Aves, T., Allan, K., Lawson, D., Nieuwlaat, R., Beyene, J. and Mbuagbaw, L., 2017. The role of pragmatism in explaining heterogeneity in meta-analyses of randomised trials: a protocol for a cross-sectional methodological review. BMJ Open, 7 (9), e017887.

Figure 3-3. PRECIS wheel
The extremes of pragmatic and explanatory trials (Aves et al. 2017)

The profile of the current study was mapped using the online PRECIS-2 analysis tool (Zwarenstein et al. 2017), and is shown in Figure 3.4. The analysis indicated this study is of a more pragmatic than explanatory design and, in accordance with

MacPherson (2004), is suitable as an adjunctive study. The full PRECIS-2 explanation and analysis of this study is shown in Appendix 8.

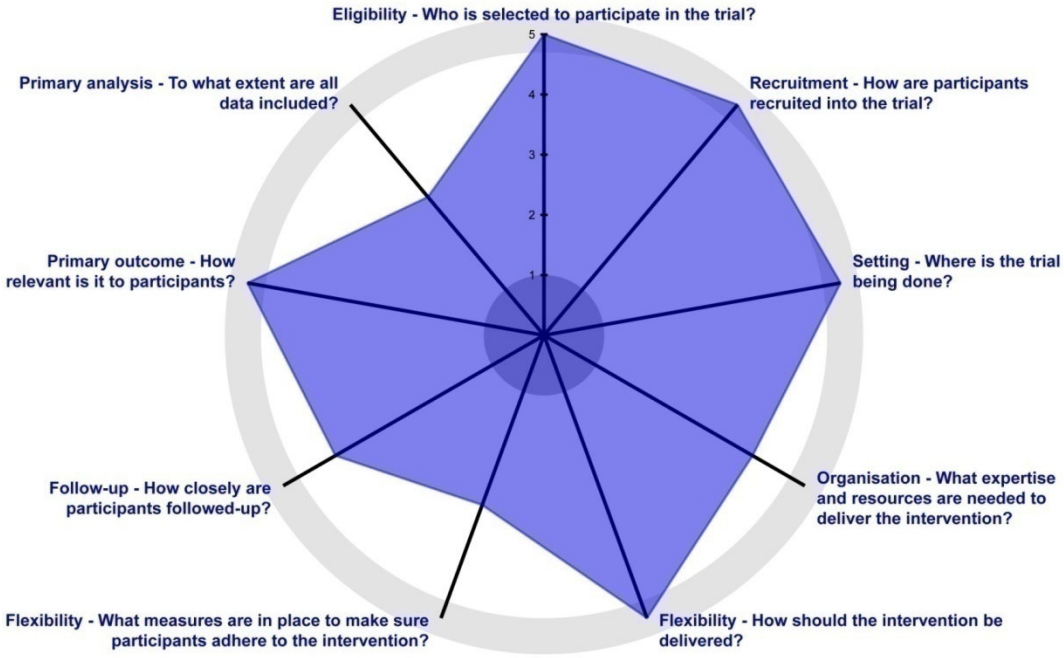

Figure 3-4. PRECIS wheel for this trial

3.3.3. Quality and CONSORT statements

The use of the PRECIS-2 approach helps facilitate avoidance of design decisions that were skewed toward the explanatory end of the spectrum when the trial intent was pragmatic (Zwarenstein et al. 2017). However, PRECIS-2 did not fundamentally address the quality of the methodology. Consequently, a group comprising researchers and editors developed the CONSORT (Consolidated Standards of Reporting Trials) statements to improve the quality of reporting in RCTs. The statements comprised a checklist and flow diagram to be used as a framework for reporting an RCT. This approach has now been endorsed by leading medical journals and international editors. Since the original statement in 1996, that was aimed at purely explanatory RCTs, several extensions have been developed.

These include one designed for non–pharmacological trials (Boutron et al. 2017) and another for pragmatic trials (Zwarenstein et al. 2008). The aim of these extensions was to provide information to include in reports of pragmatic trials,

enabling the researcher to decide if the results have validity for their own situation, and therefore if the intervention was an acceptable option. They also help trial designers to consider these issues when writing the protocol.

3.4. Methodology

The methodology in this study encompassed issues highlighted in the literature review, which included checking the process against a methodological quality screen and adhering as closely as possible to CONSORT guidelines and the International Headache Society (IHS) recommendations (Tassorelli et al. 2018). Specific factors that needed to be included in the trial as a result of this were: ensuring relevant details of the MT protocol enacted was available (Appendix 12) and using validated instruments to collect information related to the risk factors in the chronification of migraine. By embracing the above points, this study would augment the limited quantity of research in the field of MT and CM.

3.4.1. Design

A single centre, pragmatic RCT was employed. The two groups were designated ‘care as usual’ (Group C) and ‘care as usual’ plus MT (Group M). The study design adhered to the IHS and CONSORT guidelines (Zwarenstein et al. 2008; Boutron et al. 2017; Tassorelli et al. 2018).

3.4.2. Participants and Recruitment

Participants were recruited between August 2018 and the end of November 2018 from the Salford Royal NHS Foundation Trust Acute Neurology Clinic. The neurologist and specialist headache nurse identified potential participants from their list of active CM patients. The initial engagement with potential participants began two to four weeks before their next headache clinic appointment by sending a letter of invitation from the neurologist (Appendix 9) along with the participant information sheet (Appendix 10) and their clinic appointment letter. When the potential participants attended their migraine clinic appointment, the specialist headache nurse checked receipt of the invitation letter.

If they had received the letter, and were interested in participating in the study, they were offered an initial assessment meeting with the Principal Investigator (PI) immediately after their appointment. The full study plan is detailed in Figure 3.5.

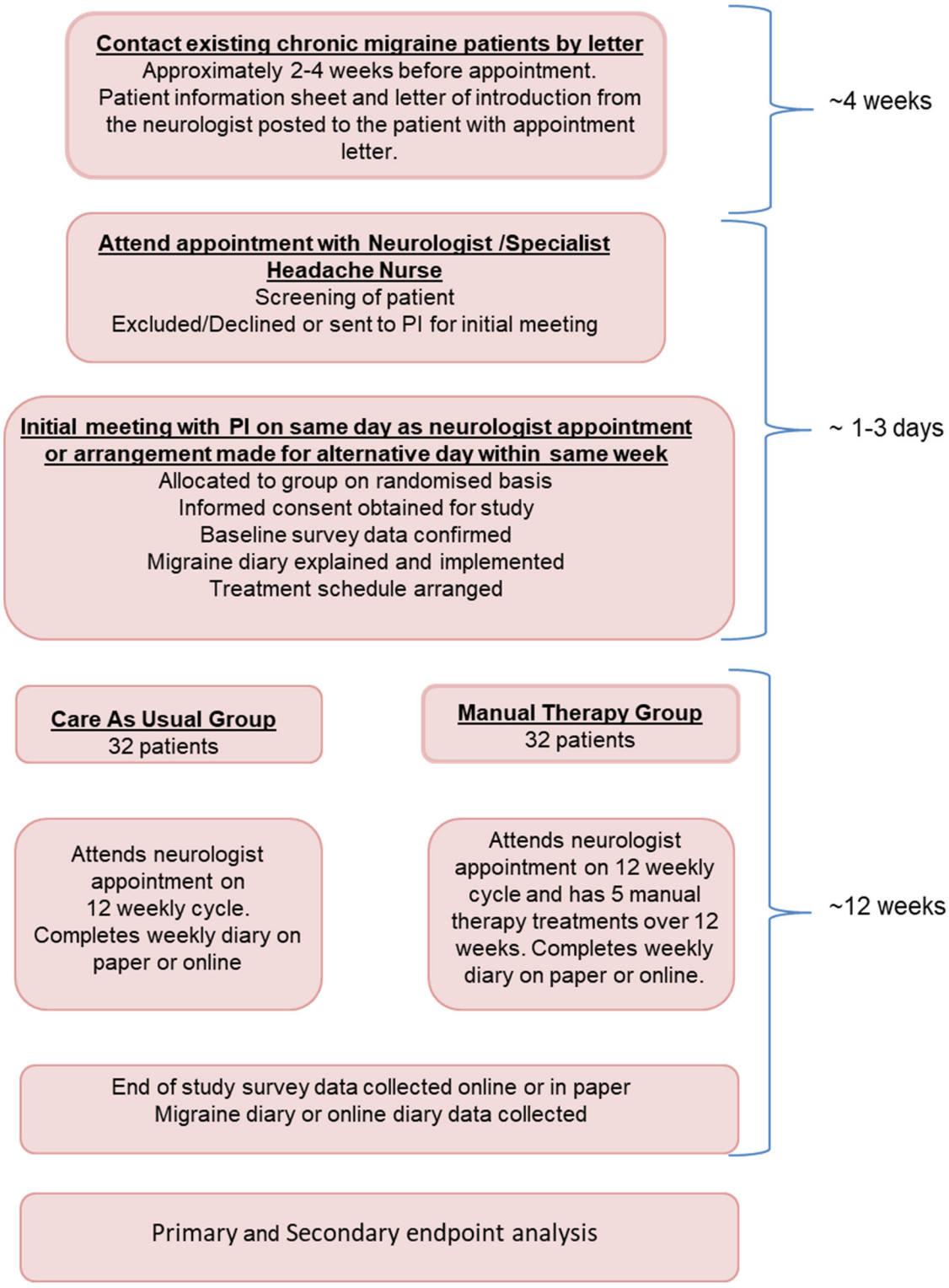

Figure 3-5. Flowchart of study plan

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3.4.3. Inclusion and exclusion criteria

Eligible participants were females aged 18 years or over and diagnosed by their neurologist with CM according to the criteria of the International Classification of Headache Disorders (ICHD-III). To mitigate the potential influence of medication

overuse headache (MoH), which influences the success of an intervention (Schwedt et al. 2017; Rojo et al. 2015), participants were required to have had at least two cycles of tertiary care treatment and be on a consistent 'care as usual' regime to create a more homologous group (Silberstein et al. 2017). Factors for inclusion and exclusion are outlined in Tables 3.2. and 3.3. respectively.

Table 3-2. Inclusion criteria

Female adults over 18 years of age
A good command of English (to enable informed consent)
Existing patients with chronic migraine as diagnosed by a clinical interview with a neurologist in line with the International Classification of Headache Diagnosis criteria (ICHD)
Undergoing 'care as usual' from the neurologist
Must have had at least twos cycle of treatment from neurologist and not be a new patient

Table 3-3. Exclusion criteria

Currently having or had manual therapy for neck, shoulder in the last six weeks.
A new patient without any existing management by neurologist
Having a condition contraindicated for manual therapy including but not limited to inflammatory disorders, severe osteoporosis and tumours.
Identification of any medical ‘red flags’ by the neurologist including: • Evidence of any central nervous system involvement e.g.: • Facial palsy (presence of ptosis/Horner’s syndrome) • Visual disturbance (presence of blurred vision, diplopia, hemianopia) • Speech disturbance (presence of dysarthria, dysphonia, dysphasia such as expressive or receptive) • Balance disturbance (presence of dizziness, imbalance, unsteadiness, falls) • Paraesthesia (presence, location such as upper limb/lower limb, face) • Weakness (presence, location such as upper limb/lower limb) • Known major psychiatric or psychological conditions not under control

3.4.3.1 Rationale for Inclusion and Exclusion Criteria

- **Gender**

The trial included only females for two main reasons. Primarily, CM is much more prevalent in females than males, with approximately 70% of CM tertiary care attendees being female (Jelinski et al. 2006; Wang et al. 2011), with greater than 80% representation in trials of CM medication (Silberstein et al. 2014 Silberstein et al. 2017; Tepper et al. 2019). Furthermore, males are thought to respond differently to treatment than females, potentially skewing the results and negatively impacting transferability of findings to the target population in question (Buse et al. 2013; Vetvik & MacGregor. 2017).

- **Age**

This study followed IHS guidelines (Tassorelli et al. 2018) for enrolment of participants. All were females over 18. Although there are no upper age restrictions on participants in a migraine study the suggestion is that age at onset of EM should be a maximum of 50 years and that the age of onset of CM should be less than 65 years.

- **Diagnosis**

One of the main criticisms of methodology in studies involving headaches/migraine and MT, and the reason for exclusion in the earlier systematic literature search, is the lack of consistent or formal diagnosis in participants. This trial followed IHS guidelines (Tassorelli et al.2018) and only included people diagnosed with CM, by a neurologist, after having failed 3 previous prophylactic interventions.

- **Medication overuse**

The overuse of acute medications (typically opioids) is a known factor in the chronicity of migraine. As this has a significant negative impact on the success of interventions (Raggi et al. 2014; Bigel et al. 2010; Scher et al. 2008) participants were required to have had a minimum two cycles (approximately six months) of intervention, demonstrating CM stability.

- **Current or recent MT on head, neck and shoulders**

As an adjunctive investigation, it was necessary to remove any confounding influence of past or current MT. Six weeks was considered to be the minimum time

period for the effects of any intervention to have subsided. There is no set guideline for the washout period between MT interventions, as such this was a pragmatic decision based upon the period often ascribed to acute injury repair. No new MT was allowed whilst participating in the trial for the same reason.

- **Contraindications to MT**

The main criteria were based on potential adverse effects of MT on the participant (Cambron et al. 2007; Boyle et al. 2008; Church et al. 2016) and red flags for conditions which may be reflected by the presence of secondary headaches (Martin 2010; Schankin & Straube. 2012). To mitigate this, all potential participants on the list were reviewed by a neurologist prior to inclusion on the study and were reviewed at the start of each cycle by the specialist headache nurse and then by the PI.

3.4.3.2 Alteration and outcome in exclusions criteria

Early in the recruitment process it became clear that some of those invited to take part in the trial had ventral shunts in their skull. This group was then added to the exclusion group based on the potential for adverse effects from MT. In all, 17 potential recruits were excluded at the meeting with the PI (Fig 3.6.).

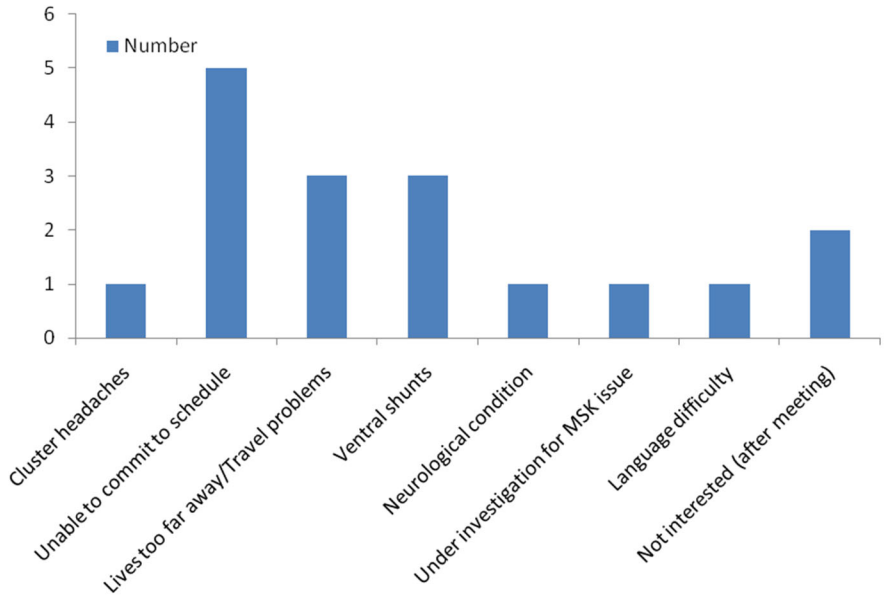

Figure 3-6. Number of exclusions by reason

3.4.4. Randomisation and allocation

3.4.4.1. Random sequence generation

Randomisation is essential in both pragmatic and explanatory randomised control trials and is part of the CONSORT model (Boutron et al. 2017). It comprises two phases:
(1) Generation of a random participant allocation sequence;
(2) Implementing the allocation so the researchers are unaware of the group to which potential participants will be assigned.

There are multiple opinions on the best approach to randomisation (Kim & Shin. 2014) from simple techniques such as putting pieces of paper in a hat and pulling them out through to computer generated block and stratified randomisation. The "paper in hat technique" is not recommended for RCTs due to the ease of compromise, with a computer-generated process generally preferred (Suresh, 2011). However, if simple randomisation is performed samples of fewer than 100 have a strong chance of forming unequal groups. This can be addressed with block sequences but with the potential drawback that the researcher may guess the next allocation (Vickers 2006).

This study employed a randomisation software tool, "Research Randomizer" (Urbaniak & Plous. 2015) to create a randomised assignment sequence; this process was conducted by an independent research assistant, unattached to the project. Pieces of paper with the group allocation were placed in sealed opaque envelopes by the independent research assistant and given to the PI. The master file containing the randomisation sequence was placed in a sealed and secure envelope by the same research assistant without any involvement from the Principal Investigator (PI) or neurology team. With a small sample size, any study is at risk from a higher percentage of dropouts/withdrawals and failure to meet the sample size required. In a recent study of health care trials, only 56% of RCTs achieved their stated sample size (Walters et al. 2017). To mitigate the above issues, the initial randomised sequence of 64 participants was implemented and the balance of group sizes reviewed on an ongoing basis. When it became clear that the number of drop outs and withdrawals would lead to one group not achieving the minimum sample size of 29, the existing randomisation sequence was stopped (at n=50). A new sequence was implemented by the independent research assistant using the

Randomiser software with a block balance (2:1) between both groups designed to ensure both groups met the minimum number.

3.4.4.2 Allocation

Those patients who had been screened from the neurology clinic list were sent a letter of invitation along with a participant information sheet and attended their appointment with the specialist headache nurse as usual (Figure 3.4.1). Once assessed by the specialist headache nurse, the participants meeting the inclusion criteria were then invited to a meeting with the PI. If this was not immediately possible, it was arranged as soon as possible, but no greater than 5 days later enabling those who were assigned to the MT group to have treatment in the first week, in line with the protocol.

At the PI meeting, potential participants were reviewed again with respect to the inclusion criteria and, if still eligible, were informed about the risks, benefits and potential adverse reactions to MT. Potential adverse reactions to MT explained to the participants included temporary local tenderness, aching and tiredness; the potential for higher risk events such as stroke was also explained (Carnes et al. 2010; MacPherson et al. 2015; Vaughan et al. 2016). Verbal and written information about the project was provided to the participants, and written consent obtained (Appendix 11). Participants then opened a numbered envelope which contained the allocation to either the 'care as usual' group or the MT group. The PI explained the process to be followed according to the group to which they were allocated.

3.4.5. Blinding

The neurologist and specialist headache nurse were blinded as to which group the participants were allocated in order to reduce channelling and ascertainment bias potential during the study (Jadad. 2002; Pannucci & Wilkins. 2010). Although it was not possible to blind the PI to the MT group, the PI was blinded to the end of study survey outcomes before analysis. Another member of the research team re-coded the participant reference numbers and stored the key file on a password-protected computer. This ensured the PI was blinded when completing the analysis.

3.4.6. Intervention

Individuals assigned to the 'care as usual' plus MT group were given a 12-week treatment plan as recommended in IHS guidelines (Tassorelli et al. 2018) with 30 minute sessions in weeks 1, 2, 5, 8 and 12. These weeks were chosen to reflect a typical approach in practice and although other studies have used different approaches (Table 3.4), there is much commonality, and this trial followed the same schedule as Cerritelli et al. (2015).

Table 3-4. Study intervention schedules and duration

Study/Headache type	Sessions / week	Time period	Session duration
Chaibi et al. 2017/ migraine	12/1pw	12 weeks	15minutes intervention plus assessment time
Gandolfi et al. 2017/CM	4/1pw	4 weeks	30 minutes
Espi et al. 2016 / TTH	4/1pw	4 weeks	30 minutes
Cerritelli et al. 2015/CM	8 / wk 1, 2, 5, 8, 12, 16, 20, 24	24 weeks	30 minutes
Voight et al. 2011 / migraine	5 / 1 per 2w	10 weeks	50 minutes

Each session comprised 20-25 minutes MT and 5-10 minutes admin/write up. Those in the 'care as usual' group (group C) were managed by the neurology team and reviewed after a period that varied from 12 weeks to 17 weeks. However, final primary and secondary data were collected at 12 weeks from all participants.

This trial investigated the adjunctive effect of MT, generally defined as a subset of physical therapy (Farrell & Jensen. 1992; Bronfort et al. 2010; Moore et al. 2017) which includes the hands-on techniques of mobilisation, manipulation, and soft tissue work (MMS). Consequently, those interventions under the broader label of physical therapy approaches, e.g. the use of equipment, needles and exercise prescription, were not permitted. A pragmatic approach to the MT intervention was adopted whereby the PI used MMS interventions deemed clinically appropriate, after an initial assessment of, and agreement by, the participant at each session. The PI was an experienced chiropractor with over 10 years' experience and postgraduate education and training in headache management, and an author and teacher of soft tissue techniques (Sanderson & Odell. 2012).

Although the key elements of the treatment administered were recorded in the case report file (CRF), there was no attempt to specify the exact location of intervention, e.g. which specific cervical joint was manipulated or mobilised. This approach was taken based on the pragmatic nature of the trial which, as Macpherson (2004) noted, would be unable to identify the specific parts of the intervention that provided the benefits and because studies of manual therapy have shown that there is little specificity when targeting segments of the spine (Ross et al. 2004; Frantzis et al. 2015).

The outline intervention procedure was as follows (Table 3.5)

Table 3-5. Manual therapy protocol

1.	Assess upper body[a] posture in sitting
2.	Assess active and passive neck range of motion
3.	Assess shoulder girdle range of motion by raising each arm sideways from side of body up to ear
4.	Assess the temporomandibular joint
5.	Identify areas to treat in sitting position
6.	Administer MT using mobilisation, manipulation and soft tissue release in sitting position
7.	Assess patient shoulder girdle, neck and head supine and prone
8.	Administer MT in supine and prone position
9.	Following each session an outline of the MT used will be recorded.

A total of 30 minutes will be allocated for each participant at these consultations

[a] *Upper body defined as from thoraco-lumbar junction upwards*

(Details of protocol included in Appendix 12)

Prior to each session participants were asked how they felt after the previous session with details of adverse events, no matter how minor, logged in the CRF. Participants were also asked how they were feeling in terms of the location of any painful areas and headaches.

3.4.7. Data collection

All participants were asked to complete a structured starting, baseline, questionnaire at their first meeting with the PI (Appendix 13). This comprised their demographic information and the validated instruments (Table 3-6). The measurement instruments were not identified individually in the questionnaire but simply supplied

as tables of questions in a professionally designed booklet. This was to reduce the likelihood of participants recognising the instrument from previous experience, particularly HIT6 and HADS, and completing it based on expectation/reward, e.g. a belief that HIT6 or other scores determine their continuation with treatment. The structured questionnaire was available in both paper and online formats, for completion at either the initial assessment with the PI or at home at the discretion of the participant, but had to be completed and returned within 5 days.

Throughout the study, both groups completed a weekly diary either in paper format or online which recorded number and intensity of headaches/migraine; any trigger factors; perceived levels of stress; measures of allodynia, and overall acute medication usage (Appendix 14). After 12 weeks, i.e.at the end of the study, both groups completed the final structured questionnaire (Appendix 15) which duplicated the initial one but with the additional measure of Patient Global Impression of Change (PGIC).

Table 3-6. Data collection instruments validation and utilisation

Measurement instrument	Validation studies	Utilisation studies	Recommended by IHS for migraine trials
Headache Impact Test 6- HIT6	Yang et al. 2010; Rendas and Baum, 2014	Cerritelli et al. 2015	Yes
Perceived Stress Questionnaire PSS-10	Cohen et al. 1983	Radat et al. 2008	No view given
State and Trait Anxiety Inventory- 6- STAI	Marteau & Bekker,1992	Palacios-Ceña et al 2017	Yes
Migraine Specific Quality of Life Questionnaire MSQv.2.1	Rendas & Baum, 2013	Lipton et al. 2016	Yes
Brief Cope	Carver, 1997	Radat et al. 2009	No view given
Hospital Anxiety and Depression Scale - HADS	Zigmond & Snaith 1983	Tomé-Pires, 2016)	Yes
Patient Global Impression of Change Scale_ PGIC	Hurst & Bolton, 2004	Bevilaqua-Grossi, 2016	Yes
Allodynia Symptom Checklist_ASC	Ashkenazi et al. 2007	Louter et al. 2013; Bevilaqua-Grossi, 2016	No view given

3.4.8. Data collection and measurement instruments

The structured questionnaires at the start and the end of the study comprised a number of validated instruments (Table 3.6). All of these questionnaires, excepting MSQv2.1, were freely available in the public domain. Permission was given by the copyright holders to use the MSQv2.1. All of the instruments had been used in major headache studies and validated in the English language.

3.4.8.1 Quality of Instruments

Given the criticism discussed earlier of the methodologies ascribed to headache studies involving MT (Fernández-de-las-Peñas et al. 2006), it was considered essential that all measurement instruments used were high-quality, fit for purpose, specifically the one used for the primary outcome measure. There are two main considerations to assess the quality of instruments used when measuring an attribute or behaviours: reliability and validity.

Reliability is reflected by a consistent or stable measurement over time or in different conditions for which the results obtained should be the same (Drost 2011). One of the most popular measures of reliability, particularly when considering a construct such as disability using multiple questions/items, is the internal consistency of the instrument. This shows how well multiple items/questions in the instrument work together to measure the particular concept /behaviour for which it is designed The most accepted measure for this is Cronbach's alpha(α) which is represented by a number between 0 and 1. An acceptable reliability score of approximately 0.7-0.8 is considered acceptable although too high (0.9) may indicate the instrument is not measuring what it is designed to (Tavakol & Dennick. 2011).

In the migraine setting, the majority of the instruments use multiple questions to measure a 'construct', for example, disability. The extent to which an instrument succeeds in measuring the intended construct is therefore critical. For this reason, Cronbach's alpha(α) was chosen as the main measure of internal consistency for most of the instruments; this is often the one most calculated and available in order to assess the comparative reliability of proposed instruments. However, for the primary and major secondary outcome instruments other measures such as test-retest (ICC) reliability, validity and responsiveness (MDC, MCID) were also considered to address the ability of the instruments to distinguish between

subjects, particularly with the HIT6 as the primary outcome measure. Inter-rater reliability was not addressed in this study as only one person would be involved, and the data would be from self-administered patient reported outcomes. However, it would be a major consideration if a future study, with multiple investigators, involving interviewer-administered instruments were included (Kimberlin and Winterstein. 2008; Ranganathan et al. 2017)

Validity is whether an instrument measures what it is designed to measure and how accurately the concept under investigation is measured e.g. headache disability (Sullivan 2011). There are different components of validity including content validity, construct validity and criterion validity (Table.3.7).

Table 3-7. Components of validity

Components of validity	**Description**
Content validity	Does the research instrument measure accurately all aspects of a construct?
Construct validity	How well does a research instrument measure the intended construct?
Criterion validity	How similar is the research instrument to other instruments which measure the same construct?

Responsiveness is another important component of quality in measurement instruments. There are two ways main ways of reporting responsiveness; the first is the minimum detectable change (MDC), which is the change in a patient's score that is greater than measurement error. The second is the minimum clinically important difference (MCID) which represents the smallest change in an instrument score/outcome that the patient considers beneficial and might bring about a change in clinical management (Jaeschke et al. 1989). The MCID has become more important as patient-reported outcomes have been used to assess the benefits of treatment. Studies have also begun to question the sole use of statistical significance when sample sizes are sufficiently large, despite the effect on patients being of little consequence (Angst et al. 2017). The next section reviews the quality of the instruments used in the study.

3.4.8.2 Measurement Instruments

- **Headache Impact Test (HIT 6).**

The primary outcome measurement instrument is the Headache Impact Test 6 a well-tested and validated instrument and recommended by the IHS as one of the

most valid measures in CM studies (Tassorelli et al. 2018). It comprises six self-answered questions using one of the following five options: “never”, “rarely”, “sometimes”, “very often”, or “always”. These responses are summed to produce a total HIT6 score that ranges from 36 to 78. Anything above 60 is classed as having a very severe impact on life. Between 56 and 59 is classed as having a substantial impact on life, 50 to 55 some impact and less than 49 little impact (Appendix 16). It is generally used to evaluate disability (associated with headaches) over the last 4 weeks although it has been used for longer periods. It has been validated in multiple studies and with different headache types (Appendix 16a). The quality of the HIT6 has been assessed using a range of measures including internal consistency (Cronbach's), test-retest (time stability) and content, construct and criterion validity in different headache conditions.

Kosinski et al. (2003) reported an internal consistency (Cronbach's) of 0.9 on individuals when tested on general headaches. A follow-up study in a specialist neurology clinic, on a primarily female group (77%), had similar results with internal consistency reliability of 0.87 (Kawata et al. 2005). A later, larger (2000 participants) validation study in CM came to a similar conclusion with high reliability reflected by internal consistency over 3 months 0.87 and 0.92 and test-retest reliability (ICC) of 0.77 (Yang 2010). The most recent study evaluated HIT 6 in over 1300 CM patients (87% female). Over 24 weeks, the internal consistency reliability was calculated at 0.91 and the ICC test-retest at 0.71, concluding that the findings were consistent with other studies (Rendas-Baum et al. 2014). Since its inception HIT6 has been used in hundreds of headache studies and translated into at least 27 languages (Gandek et al. 2003). Haywood et al. (2017) concluded in a study of patient reported outcomes in headaches that “only the HIT-6 has acceptable evidence supporting its completion by all ‘headache’ populations.”

The responsiveness of instruments is often measured by the minimal clinical important difference (MCID) for either individuals or between groups under evaluation. The between- group figure represents the smallest difference in mean change score of importance when comparing groups and the individual measure if an individual has experienced meaningful clinical change over time (Lipton 2006). Coeytaux et al. (2006) investigated four different approaches to evaluate a clinically significant change in the HIT6 score in chronic daily headache patients. Using modified versions of the anchor method (Jaeschke et al. 1989) and a linear

regression model, it was concluded that within-person MCID of 3.7 units can be used to assess if an individual patient in a clinic setting experiences a meaningful change. A MCID of 2.3 units was calculated as the smallest difference in change scores between mean HIT6 scores involving two or more groups of individuals over time which represented a meaningful clinical improvement. Castien et al. (2012) calculated the individual MCID for chronic tension-type headaches as a change of 8 points. However, there is currently no MCID for HIT 6 in CM although Smelt et al (2014) looked at primary care practices and concluded for migraine the between-group MCID was 1.5 and within-group between 2.5 and 6 depending on the technique used. Despite a lack of MCID's for CM, the figures from Coeytaux et al. (2006) were used in this study particularly as the MCID for Smelt et al. (2014) were very similar and covered both chronic headaches and migraine.

- **Hospital Anxiety and Depression Scale (HADS).**

HADS (Appendix 17) is a well validated self-assessment instrument. It comprises 14 questions with a score of between zero and three, seven questions for each component (anxiety and depression) with a total score of between 11 and 21 indicating an abnormal level of anxiety or depression, between 8 and 10 borderline levels and between 0 to 7 normal levels (Zigmond & Snaith, 1983; Bjelland et al. 2002). It was initially validated by Zigmond & Snaith (1983) for use in a hospital outpatient setting and has subsequently been validated for many medical conditions and settings. Bjelland et al. (2002) identified 747 studies using HADS and validated HADS in a systematic review comprising 22 trials and 13 languages in a variety of medical conditions and settings. They concluded that the sensitivity and specificity for both anxiety (A) and depression (D) scales were approximately 0.8 with the optimum balance between specificity and sensitivity defined by a score of 8 or above on both the anxiety and depression scales. The internal consistency, Cronbach's alpha for anxiety and depression was measured as between 0.67 and 0.9. The construct validity was calculated for both anxiety and depression subscales respectively, as between .60 and .80. However, despite its prolific use, some recent studies have questioned its bi-dimensional latent structure (measurement of anxiety and depression). However, the anxiety scale is considered to be more valid and acceptable in studies (Martin 2005; Cosco et al. 2012). In answer to this criticism other authors have suggested that whilst there may be some underlying issues with the construct which may require reassessment, these are found in all instruments of this type and other more recent assessments of the validity of HADS are positive

(Norton & Sacker. 2012; Bocéréan & Dupret. 2014;). It has also been suggested that a total score (combination of anxiety and depression) is used to reflect the level of psychological distress on a pro-rata basis to the individual scores hence 0-14 is normal and above 21 abnormal emotional distress/instability (Brennan et al. 2010; Cosco et al. 2012; Iani et al. 2014).

Whilst taking the above views into account one of the earliest migraine studies using HADS to illustrate greater than normal involvement of anxiety and depression in migraine was by Devlen (1994). A recent study involving 300 participants with EM or CM concluded that it was a useful screening tool for depression with Cronbachs's alpha of 0.89 (Amoozegar et al. 2017). Andree et al. (2010) completed a large-scale European study of the burden of primary headaches and concluded that the internal consistency of HADS was 0.9 in the UK and 0.91 in Germany with good construct validity. Thus, despite some controversy over its bi-dimensional latent structure HADS is still a measurement instrument recommended by the IHS for CM studies (Tassorelli et al. 2018). However, to date no measures of its responsiveness to change as determined by the minimal clinical important difference MCID have been calculated for headaches and measures for only a few conditions (COPD, cancer, acute respiratory failure (ARF) were available at the time of writing (Table 3.4.7) (Chan et al. 2016; Corsaletti et al. 2014; Yost et al. 2011; Puhan et al. 2008).

Table 3-8. Recommended MCID hospital anxiety and depression scale (HADS)

Condition	Anxiety MCID	Depression MCID	Combined MCID
ARF	2.5	2.5	-
COPD	1.5	1.5	1.5
Cancer	3-4.5	3-4.5	-
Smokers	8	6	-

- **Migraine-specific quality of life questionnaire, version 2.1 (MSQv2.1).**

MSQ v.2.1 (Appendix 18) is a 14-item, self-administered instrument. It was validated for prophylactic migraine treatment by Cole et al (2007) and for CM in subsequent studies (Bagley et al. 2011; Rendas-Baum et al. 2013). It has three domains: Role Restrictive (RR) which assesses how migraines limit daily social and work-related activities. Role Preventive (RP) which assesses how migraines prevent these activities and Emotional Function (EF) which reflects physical and emotional limitations associated with migraine. The scoring system for each item is based on a 6-point scale: ‘‘none of the time’’ ‘‘a little bit of the time,’’ ‘‘some of the time’’ ‘‘a good

bit of the time,'' ''most of the time,'' and ''all of the time''. The score for each response is scored between 1 and 6 with raw score summed by factor (RR, RP, EF) and converted to a 0 to 100 scale with higher scores indicate better quality of life. Bagley et al (2011) estimated Cronbach's α RP, RR, and EF at 0.90, 0.96, and 0.87, respectively.

Rendas-Baum et al. (2013) examined the psychometric properties of the MSQ2.1 in CM patients (n=1397) from 2 clinical trials which provide a situational analysis appropriate for the current study. The construct validity, its ability to detect clinical indicators change between 2 groups of CM patients having prophylactic treatment, the convergent and discriminant validity and internal consistency were all measured. Cronbach's at baseline was over 0.8 and varied each factor between 0.80 (EF) and 0.93 (RR) and between 0.83 (EF) and 0.93 (RR) in the 2 studies. It also displayed temporal consistency over 24 weeks with Cronbach's of 0.9. Its convergent validity (using HIT 6 correlations) was calculated at between 0.59 and 0.8, well above the recommended 0.4 level. The responsiveness of MSQ2.1 has been estimated for group and individual (within-group) change using different techniques (Cole et al. 2009; Report 2015) (Table 3.4.8). The studies concluded that the MSQ 2.1 is a reliable instrument to assess the impact of headache across the range of headaches including CM. The MSQ2.1 has been used in many of the large-scale CM studies using Botox (Diener et al. 2010; Aurora et al.2014).

Table 3-9. Minimal Important Differences (MCID/MCID) MSQ 2.1

	Range of MCID values		Recommended MCID values	
Domains	Anchor based Group / Individual	Distribution based Group / Individual	Within group Individual	Between Group level
Role Restrictive (RR)	3.2 / 5	3.2 / 8.5	5	3.2
Role Preventive (RP)	- / 10.6	4.6 / 9.2	5 - 7.9	4.6
Emotional Functioning (EF)	7.5 / 10.6	7.5 / 12	8 - 10.6	7.5

MSQ 2.1 Domain Regression-Estimated MCID (95% CI)	
Domain	Within-Group Differences
Role function – restrictive (RR)	10.9 (9.4 to 12.4)
Role function – preventive (RP)	8.3 (6.7 to 9.9)
Emotional function (EF)	12.2 (10.2 to 14.3)

- **State Trait Anxiety Inventory-6 (STAI6).**

The six-item inventory (Appendix 19) was developed from the original larger 40 item inventory (Speilberger 1983) and validated by Marteau & Bekker (1992). The short 6 item inventory measures State anxiety which is a temporary state that reflects how a person is feeling at the time (of a specific threat). These feelings exist on a day to day basis and reflect the overall daily experiences of people to life. There are six questions with four potential answers: Not at all, Somewhat, Moderately, Very Much. Each item is scored between 1 and 4. Positive answers are reverse scored and the total score is converted to a score based on Spielberger's original scoring system where 34-36 is considered normal. The 6-item short-form STAI scale produced scores similar to those observed with the full scale and has been widely used in clinical and basic research with Cronbach's of the STAI 6 of between 0.74 to 0.82,(Marteau & Bekker 1992; Macaluso et al., 1996; Tluczek et al. 2009). Recent validation studies in different areas have supported its use as an instrument to measure anxiety (Bayrampour et al. 2014; Lucibello et al. 2019). At the time of writing, there were no published findings on the responsiveness of STAI6. Despite few clinical studies in headache using the STAI-6 to measure State Anxiety it was selected for this study due to its short length as way to minimise survey fatigue.

- **Brief Cope.**

The Brief Cope (Carver 1997) is a self-report questionnaire to assess the extent of different coping behaviours and thoughts a person may have in response to specific situations (Appendix 20). It has 14 subscales: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioural disengagement, venting, positive reframing, planning, humour, acceptance, religion, and self-blame. The relevant situational specific scenario is placed prior to the questions (in this case migraine specific). There are 28 coping behaviours and thoughts (with 2 items for each subscale) which rated on the perceived use by the participants. The scale comprises 1 (I haven't been doing this at all) to 4 (I've been doing this a lot). Cronbachs α for the 14 subscales range from 0.57-0.90 (Carver 1997), and similar results (α= 0.54-0.93) from Benson (2009). The wording was modified (as is suggested by Carver) for this study to reflect the participant population and their challenges. Brief Cope has been translated into multiple languages and validated across a range of conditions (Brasileiro et al. 2015). Garcia et al. (2015) calculated Cronbach's alpha for each subscale as between 0.53 and

0.82 and the overall scale at 0.6. Monzani et al. (2015) examined the latent structure with respect to personal goal commitment and progression and concluded that the 14-factor structure was a suitable instrument to evaluate coping responses to specific events. Brief Cope has been used successfully in large scale(n=5417 and n=1534) studies involving migraine, CM and chronic daily headache patients (Radat et al. 2005; Radat et al. 2008) and smaller more focussed studies in migraine (n=50) in which reliability of subscales ranged from 0.50 to 0.90 (Chan & Consedine. 2014). At the time of writing, there were no reports of figures for minimal clinical important differences (MCID) for Brief Cope.

- **Perceived Stress Scale (PSS-10).**

The PSS-10 (Appendix 21) is designed to measure perceived stress the preceding month (Cohen et al. 1983). It is one of the most widely used psychological tools for ascertaining the degree to which one's personal life's events are perceived as stressful based on how unpredictable, uncontrollable, and overloaded respondents find their lives. There are two subscales: one, a negative subscale items 1, 2, 3, 6, 9, and 10 and the other a positive subscale items 4, 5,7, and 8. A five-point Likert scale scored from 0 to 4 is used, with a higher summed score indicating higher perceived stress. The unidimensionality of the PSS has been open to question recently and whilst Denovan et al. (2017) concluded the PSS was a short and easy to understand unidimensional stress measure there was a need to test it on a wider audience rather than students. It was originally validated by Cohen et al (1983) and since been validated in multiple chronic headache, tension-type headaches and CM studies around the world (Lipton et al. 2014; Moon et al. 2017; Andreeva et al. 2018). Cronbach's coefficient of this scale ranges from 0.82-0.89 (Lee 2016). Its test–retest reliability was .85 in students after 2 days and 0.55 in a community sample after 6 weeks and its convergent validity confirmed with strong association among the PSS10 total score and the STAI Score. At the time of writing no studies were found that provided minimal clinical difference in headaches and only two linked to other conditions, one was a validation study in a Danish population on work-related stress concluded that 11 points and 28% for absolute and relative change scores were the minimal clinical important change (Eskildsen et al. 2015). The other, in Systemic Lupus Erythematosus (SLE) posited the minimal clinically important difference as 0.5*SD or 4.0 points (Plantinga et al. 2016).

- **Allodynia Score Checklist (ASC).**

Cutaneous allodynia (CA) is a marker for central sensitisation and is usually assessed with quantitative sensory testing (QST) which requires special equipment that is not easily available in a clinical situation and is sometimes complicated to use. The ASC (Appendix 22) was developed and validated by Lipton et al (1983) to measure CA in migraineurs with an easy to use, self-reported measure that reflected the three main types of CA measured by QST: thermal, dynamic mechanical, and static mechanical allodynia. It comprises 12 statements with options – does not apply to me, never, rarely, less than half the time and more than half the time with scoring of 0,0,0,1,2 respectively. Summation scores of 0-2, 3-5, 6-8, >9 represent none, mild, moderate and severe allodynia respectively. Cronbach's has been calculated at between 0.76 and 0.8 in studies around the world (Ashkenazi et al. 2007; Lipton et al. 2008; Florencio et al. 2012; Yalin 2017). The ASC has been used extensively in studies of central sensitisation and in particular with migraine and CM (Bevilaqua-Grossi et al. 2016; Benatto et al. 2017; Young et al. 2019).

- **Patient Global Impression of Change Scale (PGIC).**

The PGIC (Appendix 23) was developed from earlier patient-reported outcome scales although it was Hurst & Bolton (2004) who quantified the clinical change needed in scores rather than the normal statistically significant change. The PGIC is recommended by the IHS as valid measures of patient-centred change in migraine studies. It has seven statements, describing how the patient feels after treatment, which are scored by the participant (0): No change (or condition has gotten worse) (1) Almost the same, hardly any change at all (2) A little better, but no noticeable change (3) Somewhat better, but the change has not made any real difference (4) Moderately better, and a slight but noticeable change (5) Better and a definite improvement that has made a real and worthwhile difference (6) A great deal better and a considerable Improvement that has made all the difference (7). A score of >=5 is considered a significant change. However, despite its use and recommendation by the IHS there are no measures of reliability in headaches or migraine.

3.5. Statistical analysis.

The primary analysis used the Intention to Treat (ITT) method rather than per protocol (PP) or as assigned (AS) as it reduces potential bias, promoting a higher level of evidence for clinical research. However, all approaches have their advantages and disadvantages. The PP approach analyses results excluding all participants who did not follow the protocol, did not adhere to the treatment, changed group, or missed required sessions. The AS analysis uses data based on the treatment participants received, even if they changed group/treatment. Both of these approaches are thought to provide a good measurement of efficacy of treatment, in an ideal situation but both lose the benefits of randomisation required in an RCT (Sainani. 2010). One of the major downsides to excluding the results of participants who failed to complete treatments is that the measure of treatment effect will be exaggerated and will not accurately reflect the outcomes in clinical practice and potentially miss implications for the treatments used, for example, side effects.

The principle of ITT is that all participants in a randomised study should be analysed in their original treatment group, whether or not they stayed in that group or actually received treatment at all. The concept of ITT is founded on two main tenets: firstly, to maintain the benefit of randomisation whereby the baseline factors are balanced between treatment groups and, secondly, that the approach estimates the treatment effect in real-world clinical practice which was an important aspect given the pragmatic design of this study. The first of the above is particularly important when participants can self-select treatment and the second issue when they do not adhere to treatment. In practice, the ITT approach has difficulties (Armijo-Olivo et al. 2009; Sainani. 2010) and although initially recommended by the CONSORT guidelines (Moher et al. 2010) a subsequent update (Moher et al. 2012) replaced the requirement with “a clear description of exactly who was included in each analysis”.

In this study, since participants could not ‘change groups’, as all adhered to their treatment, none withdrew during treatment and all provided complete primary data, the as-assigned and as-received treatment effects could be assumed to be the same regardless of analysis approach. Secondary endpoint/outcomes from the baseline and final questionnaires were analysed on ITT basis without issue since the conditions were the same as with the primary outcome (Ten Have et al. 2008).

However, analysis of the secondary outcomes based on the diary data used a modified ITT (mITT) basis. In this case mITT refers to dealing with missing data and although the approach to take is not defined by any current standards, the use of multiple imputation is considered the most suitable (Bell et al. 2014). In this study any participant who completed over 6 weeks' worth of data for an outcome was included using multiple imputation methods to calculate missing values. (Further detail on handling missing data is provided in section 3.5.3).

Full details of statistical approaches and rationale are provided below with a summary of the main statistical hypotheses and approaches in Table 3.5.2.

3.5.1. Data variable decisions

In medical and many health care RCTs there is often confusion over how to handle the mix of data produced from the measurement instruments. Many of the instruments used to measure complex attitudinal or affective constructs are based on multiple Likert scale items (e.g. MSQoL 2.1, HIT6) others rating scales include adjectival (e.g. PGIC), visual analogue (VAS) and numerical rating (NRS) scales (e.g. pain rating) along with categorical data, both simple and as an output from a Likert based instrument (e.g. ASC) (Carifio & Perla. 2008; Harpe 2015). The confusion is often over how to treat the output from such instruments. Some authors have contended that Likert scales are ordinal data and require non-parametric statistics and the use of mean and SD is inappropriate (Jamieson 2004). However, others have completed substantive studies demonstrating that ordinal data and Likert scales in particular can be analysed with parametric approaches (Norman 2010; Willits et al. 2015). For example, HIT6 has a minimum value of 36 and a maximum of 78 but not every value in between is possible and it is designed in categories (section 3.4.8.2). However, in many major headache studies it is treated as a continuous variable (Buse et al. 2011; Lipton et al. 2019). VA and NR scales are also prone to the same arguments as to whether analysis should use parametric or non-parametric given the apparent ordinal basis of the design. Some authors adhere to the simple construct that they are ordinal and must be analysed with non-parametric approaches (McCrum-Gardner 2008) others suggest that VAS/NRS are suitable as a one-off measure (e.g. pain) but cannot be used to measure change unless transformed to interval data (Kersten et al. 2014).

However, an alternative midway view proposes that normally distributed results can use parametric tests and skewed situation requires non-parametric approaches (Heller et al. 2016; Kim 2017). Dworkin et al. (2008) in Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations support the use of NRS in pain trials and make suggestions for clinically important changes which do not rely on distribution-based statistics.

In this study data variable analysis involved a review of current thinking followed by evaluation of 1. How other headache/pain studies had handled the same outcome measures (or similar if an exact evaluation did not exist), 2. The approach recommended by the questionnaire designers, 3. Confirmation of proposal by the medical research statistician involved at the NHS trust (Table 3.10).

Table 3-10. Study variable definitions

Variable	Design and type of data	Example measures comment / references for supporting information
Headache impact test score - HIT6	Likert type scale Continuous and categorical data	Mean (SD) valid although analysis of proportions in HIT6 categories valid [1,2,3]
Perceived Stress - PSS10	Likert type scale Continuous data	Mean (SD) valid,[1,2,4]
State Trait Anxiety - STAI6	Likert type scale Continuous l data	Mean (SD) valid [1,2,5]
MSQ 2.1 scores	Likert type scale Continuous data	Mean (SD) valid (on total and sub scales) [1,2,6]
Hospital Anxiety and Depression Scores - HADS	Likert type scale Continuous data and categorical	Mean (SD) valid (on total and sub scales) also analysis of proportions in categories also valid [1,2,7]
Allodynia Symptom Checklist - ASC	Categorical	Analysis of proportions in ASC categories valid [1,2,8]
Brief Cope scores (SD) - BCope	Likert type scale Continuous	Mean (SD) valid for sub scales [1,2,9]
Mean body mass index BMI	Categorical and continuous data	Mean (SD) valid although analysis of proportions in BMI categories valid 1,2
Patient Global Impression of Change Scale (PGIC)	Likert Item Categorical	Proportion by category [1,2,10,11]
Stress measure from diary	Numerical rating scale Continuous data	Mean (SD) valid [1, 2,12]
Headache pain from diary	Numerical rating scale Continuous data	Mean (SD) valid [1,2,12]

[1] (Harpe 2015), [2] (Norman 2010), [3] (Usai et al. 2008), [4] (Moon et al. 2017), [5] (Marteau & Bekker 1992),[6] (Wang et al. 2012), [7] (Lantéri-Minet et al. 2005), [8] (Lipton et al. 2008), [9] (Pozzi et al. 2015) [10] (Perrot and Lantéri-Minet 2019) ,[11] (Hurst & Bolton 2004), [12] (Wang et al. 2011)

3.5.2. Normality testing

Study data were analysed for normality using visual assessment of the frequency distributions, skewness and kurtosis, the Kolmogorov-Smirnov test (KT) and the Shapiro-Wilks test (ST) within excel or SPSS as appropriate. Significance levels of $p>0.05$ in these tests were considered to be normally distributed and parametric tests appropriate. If this was not the case and significance was ≤0.05 then non-parametric tests were used. Quantile-Quantile (Q-Q) normality plots were also generated within SPSS and visually assessed. A quantile-quantile (Q-Q) plot compares the quantiles of actual data distribution with the quantiles of a theoretical standardized distribution. The basic normal Q-Q plot should be a straight line of fit between the two distributions. Any variation from these indicating a non-normal distribution and the need for non-parametric tests (Das 2016).

3.5.3. Missing data

Although various approaches are available for coping with missing data some are considered more appropriate than others according to the situation, depending on whether the data are missing completely at random (MCAR), at random (MAR) or not at random (MNAR) (Kang 2013). Opinions vary as to the most appropriate approaches and rules of thumb exist to support each (van Ginkel et al. 2020). One rule of thumb is if data represents fewer than 5% of total cases then ignore it, whilst other authors disagree (Jakobsen et al. 2017). For all missing data the simplest approach is to remove the participant from analysis, although this is not compatible with the ITT approach. It also reduces the sample size and power in MCAR data and introduces biases in the MAR and MNAR. To test if data is MCAR then Little's test can be used, although authors differ on the validity of this approach (McCleary 2002). Although this study could have used a simple approach for missing data, e.g. single imputation including last observation carried forwards (LOCF) partly because it was missing only in a small proportion and considered monotone (simple). However, the single imputation, LOCF approach can add significant bias and is not recommended in many journals (Jakobson et al. 2017; Li and Stuart. 2019). Multiple imputation (MI) is an accepted approach for missing data in RCTs although it has been suggested that using MI separately with each randomised group is a better approach than with the whole sample (Bell et al.2014) As the missing data was only in the diaries the limitation of MI on PROMS with subscales was not an issue where a large (>100) sample size is required (Rombach et al. 2018). The main limitation to implementing MI is its complexity, however with

SPSS this now an automated function. Therefore, in this study it was decided to use Little's test and multiple imputations if the results were MCAR or MAR (which they were in all diaries returned). If MNAR then no methods of replacing are available for the data collected in the diaries and data from the participant was removed before any analysis (for example if a diary was not returned). The final analyses used 27 diaries from each Group M with any weekly data missing from included diaries being replaced using multiple imputation using SPSS (c) version 25 (2018). The range for mean number of imputation points per group over 12 weeks was between 1 and 3.3. The final percentage requiring imputation in any of the outcomes was between 0.01% and 4% percent, so less than the 5% cutoff. This represents a small proportion that was considered not to add to a significant error or bias.

3.5.4. Baseline differences

The use of statistical significance tests in RCTs to identify differences between groups at baseline was considered an “ubiquitous error" in RCTs of the 1970's according to the New England Journal of Medicine. This ‘error’ fell to 38% of RCTs in 2007 (de Boer et al. 2015) although other authors have suggested 50% of RCTs adopt this unnecessary approach (Assmann et al. 2000). However, for many years it has not been considered necessary or useful to produce this analysis as good randomisation should eliminate the issue (Senn 1994). The CONSORT guidelines (Moher et al. 2010) specifically state that significance testing for baseline differences is unwarranted and suggest the preferred approach is to tabulate baseline characteristics with the mean and standard deviation (SD) for normally distributed data and median with interquartile ranges (IQR) for non-normal distributed data. However, it is accepted that when comparing outcomes, particularly the primary outcome, it is good practice to adjust for baseline difference using ANOVA techniques (Egbewale 2015; European Medicines Agency. 2015) but also to provide unadjusted figures (Saquib et al. 2013).

3.5.5. Correlation and effect sizes

Correlation is used to assess the strength of association and direction of relationships between two or more variables. Typically, it is a linear relationship measured by the Pearson Correlation Coefficient (*r*) with a value of between -1 and +1. The most common approach to interpreting the strength or magnitude of these associations is to use Cohen’s (1988) guidelines in which $r \geq 0.10$ indicates a weak

association, $r \geq 0.3$ a moderate, $r \geq 0.5$ a strong association. These figures were set arbitrarily but are established and understood, although Rosenthal (1996) proposed and additional category of $r \geq 0.7$ as very strong. In clinical environments effect size is a term often conflated with Pearson's correlation coefficient when a difference in understanding is required. Kerry and Preacher (2012) define effect size as a *"quantitative reflection of the magnitude of some phenomenon that is used for the purpose of addressing a question of interest*" and suggest there are different categories: a) a statistic, e.g. odds ratio, relative risk, (b) a standardized value, such as Cohen's *d* (c) the actual numerical value of the statistic or (d) the relative interpretation as small, medium, or large. For continuous variables the Cohen's *d* and the correlation coefficient is a common choice and for categorical variables, the relative risk, the odds ratio, and rate ratio are used. However, for ANCOVA there is not an official effect size. A suggested approach to calculate an equivalent Cohen's d is to use the difference between means divided by the square root of the mean square (Maher et al. 2013; Lenhard et al. 2016).

$$\hat{d} = \frac{\overline{X'}_i - \overline{X'}_k}{\sqrt{MS'_{error}}}$$

In other studies (Levine & Hullett. 2002) it is recommended to use Eta^2 for ANCOVA. The basis for comparing the Cohen's d effect size with the r (Eta effects sizes used in this study were based on figures in Lenhard (2016). In pragmatic studies, the smallest effect size which would be considered important is sometimes referred to as the minimal clinical important difference (MCID) (Angst et al. 2017; Fleischmann & Vaughan. 2019). The CONSORT (Moher et al. 2010) reporting approach recommends the use of effect sizes with confidence levels and makes clear that this can include risk and odds ratio, risk difference and, for continuous data, the difference in means.

3.5.6. Multiple test corrections

In this study, the secondary hypotheses are related to the potential impact of participant characteristics, e.g. levels of depression, on the primary outcome. It also considered the impact of the interventions on secondary outcomes (changes in medication, etc). This involved multiple analyses using the same data from both groups to examine the difference between the means. To minimise the potential for identifying effects (statistically significant results) when none exist (Type 1 errors) a

correction to level of *p (normally 0.05)* is required. One of the most common adjustments is the Bonferroni correction, which reduces the stated statistical significance (*p*) to *p* divided by the number of tests undertaken. For example, if 20 tests were undertaken the standard 0.05 significance would be reduced to 0.05/20 giving a new significance level of 0.0025.

However, its use is not universally agreed for a number of reasons, including the potential increase in type 2 errors at the expense of the reduction of type 1 and the lack of consistency in definition of the situations for its use, as it was not designed for the evidence in clinical studies (Perneger 1998). There is an argument that corrections are not needed with small sample sizes; an a-priori hypothesis and, when relatively few comparisons are undertaken and that it may actually penalise in these situations (Armstrong 2014; VanderWeele & Mathur. 2018). The CONSORT guidelines (Moher et al. 2010) do not mention Bonferroni but do state that multiple analysis correction should be applied when needed. In this study it was decided to present both the corrected and uncorrected p values to keep consistency with the only comparative headache study (Cerritelli et al. 2015) which used Bonferroni correction and to allow for consideration of the uncertainty around the necessity given this study's design.

3.5.7. Summary statistical analysis methods

Between-group differences were measured using either the unpaired student's t test or the analysis of covariance (ANCOVA) with adjustments for baseline or the median values with the Mann-Whitney U test depending on data distribution Nominal and categorical data used the chi-squared test. Continuous data, e.g. stress level, from the diaries collected over the 12 weeks, were treated as repeated measures and analysed using the repeated measures mixed ANOVA. Linear regression models were used to evaluate the impact of baseline variables on the outcome measures. For binary outcomes, logistic regression was used to examine the relationship between explanatory variables. All statistical analyses used a probability of <0.05 (two-tailed) as criteria for statistical significance. Bonferroni correction was used when appropriate and presented alongside with uncorrected figures. Numerical data were described by means, standard deviations (SD), standard error of the mean (SE) and 95% confidence intervals (CI) as appropriate and assessed for normal distribution using the Shapiro-Wilks tests.

Table 3-11. Summary statistical analysis

Descriptive	Proposed Statistical Measures
Primary Endpoints	
Differences in migraine-related disability, as measured by the patient-reported Headache Impact Test instrument (HIT6) at end of intervention (12 weeks) between groups	Mean, standard deviations Group comparison of change using: Significance testing (P values) α =0.05 has 80% power to detect a mean difference of 3.7 points in HIT6 before and after treatment ANCOVA Effect sizes: small (0.2–0.5), medium (0.5–0.8) or large (>0.8). Multivariate linear regression, ordinal logistic regression to assess the secondary endpoints relationship with changes in primary end point while adjusting for baseline parameter levels
Secondary Endpoints	
Change in Migraine Specific Quality of Life Questionnaire Score Change in percentage of participants with reduction in headache frequency (days per month) of greater than 50% and 30% Change in number of headache free days Reduction in number and type of abortive migraine medications Change in stress and anxiety levels Patient global impression of change scores Allodynia checklist scores	Means, standard deviations Between group comparison of change in secondary outcomes Students T, Ancova (Mann–Whitney) will be conducted in case of non-normal distribution outcome measures and ordinal data Correlation measures between secondary outcomes using Pearson's coefficient or partial gamma coefficient Binomial, ordinal and multinomial logistical regression ROC charts

3.5.8. Sample size calculation.

A pooled standard deviation (SD) for the Headache Impact Test (HIT6) was initially calculated from the analysis of nine major studies in CM involving a total of 4629 participants and 19 measures of SD (Yang et al 2010; Suh et al. 2012; Aurora et al. 2014; Baum et al. 2014; Negro et al. 2015; Berra et al. 2015; Cerritelli et al. 2015; Rojo et al. 2015; Silberstein et al. 2017). This resulted in a pooled SD of 4.9 for HIT6 in CM. Consequently, this study required 29 participants in each arm to ensure that a two-sided test with α=0.05 has 80% power to detect a mean difference of 3.7 points in HIT6 before and after treatment. However, some SD's in these studies were outliers (>8). Subsequently, a second calculation was made without outliers, involving eight studies and 17 measures of SD with 4400 participants, which gave a pooled SD of 4.7. On this basis the study required 29 participants in each arm to ensure that a two-sided test with α=0.05 has 80% power to detect a mean difference of 3.5 points in HIT6 before and after treatment The project aimed to recruit a maximum of 32 participants into each group to allow for dropout from the study, but also to increase the power to detect a difference in HIT6 of 3.35 (Appendix 24).

3.6. Ethical approval

The online University ethics procedure was initially completed in October 2017. As this project involved an NHS site, a Regional Ethics Committee (REC) submission was required. This took place in February 2018 and was subject to review which resulted in a resubmission in April 2018. The study was given final approval by the UK Heath Research Authority (IRAS 228901), Bournemouth University ethics panel, and R&D at Salford Royal NHS Foundation Trust (SRFT) in June 2018 (Appendix 25) The Declaration of Helsinki was adhered to during this study. All data were anonymised and participants provided written informed consent. Insurance was provided through Bournemouth University. The procedure for withdrawal from the study was in line with the HRA non-CITMP study protocol. Severe adverse events were reported to the CI or the neurologists and resulted in participant withdrawal and appropriate referral to their General practitioner or neurologist. The study was open to monitoring in accordance with SRFT's R &D department's standard operating procedures to ensure compliance with GCP and the Research Governance Framework 2005. All trial-related documents were available upon request for monitoring by R&D monitors. Any changes to the protocol were communicated in accordance with HRA guidelines.

CHAPTER 4 RESULTS

4.1. Introduction

This chapter presents the main study results. The Methodology section introduced the approaches taken with statistics. This section will build on the methodology where necessary when presenting the results. Data from the initial and final questionnaires were used to provide participants' demographics and baseline data for the primary outcome analysis. Secondary outcomes were evaluated using both the initial and final questionnaires along with data from the diaries and the case report file. The project flow, baseline demographics and participant characteristics are presented first. This is followed by the results of the primary and secondary outcome measures and analysis of the differences within and between groups. Finally, correlation and regression analysis are presented.

4.2. Recruitment.

Participants were enrolled between August and November 2018. In total, the neurology clinic sent letters of invitation together with the participant information sheet to 213 patients diagnosed with CM. Of those invited, 124 (58%) declined to take part at the initial screening at the nurse-led appointment; a further 17 (8%) at initial screening with the PI, with 10 (5%) being withdrawn before the end of the study. This resulted in 62 (29%) reaching final analysis stage (Figure 4.1).

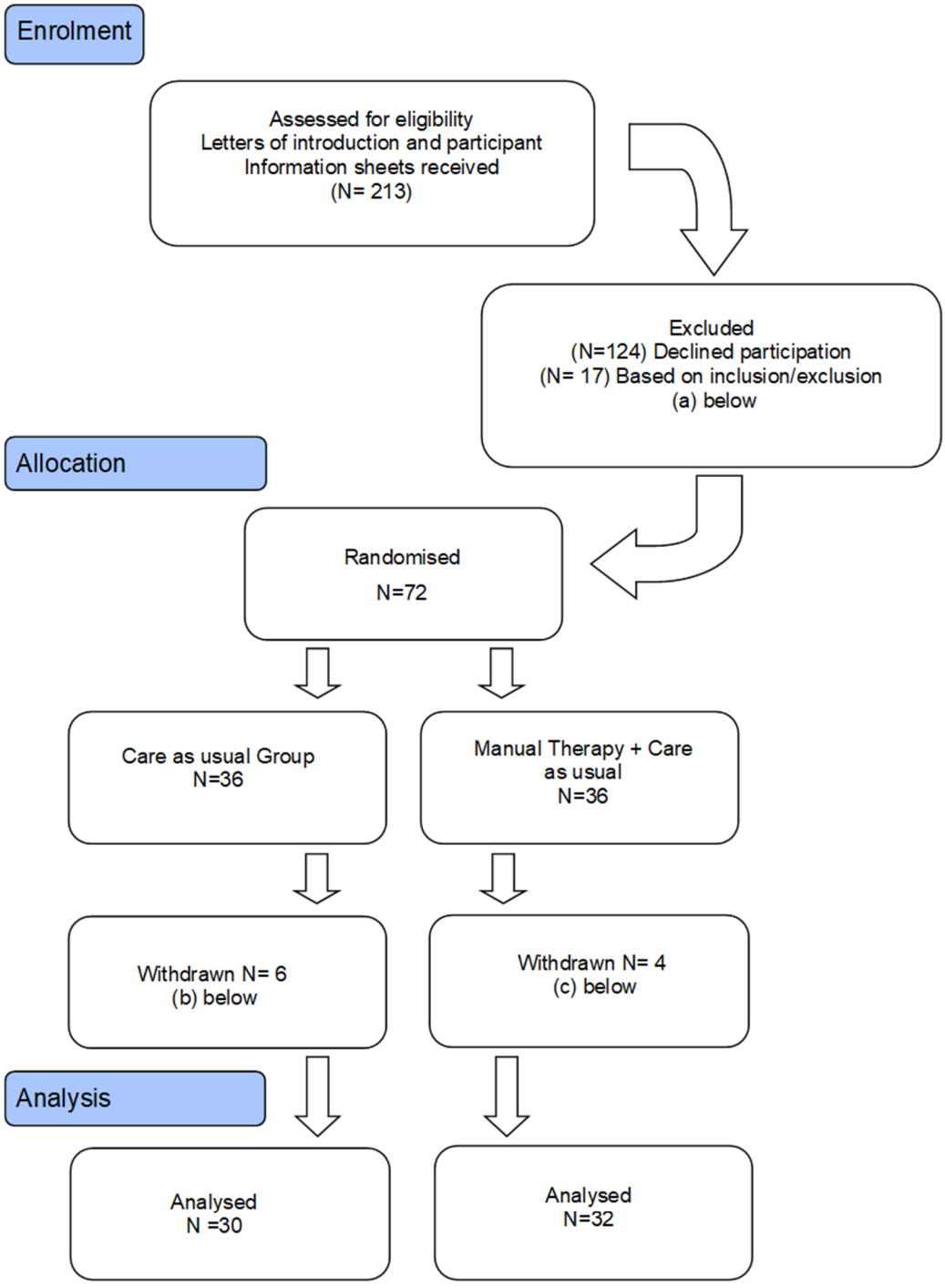

Figure 4-1. Study recruitment process

4.3. Baseline demographics and clinical measures

The baseline demographics and characteristics data were collected from the initial questionnaire (Appendix 13) and measurements made at the time of the PI interview and entered in the case report file (CRF) together with diary data collected at the 12 weeks (Table 4.1).

Table 4-1. Baseline demographics and characteristics

Characteristics Mean (SD)	Manual Therapy + 'Care as Usual' (M)	'Care as Usual' (C)	Data source (n,n)	P value
Participants, n	32	30		
Age, years	43.9 (11.2)	45.6 (13.8)	IQ (32,30)	0.73$
Body mass index	28.2 (6.0)	28.5 (7.3)	C (32,30)	0.86$
Mean number cycles onabotulinum (median, range)	9 (9, 3-15)	9 (8.5, 4-20)	PR (32,30)	
Currently in work/college/retired (%)	28 (88)	28 (93)	IQ (32,30)	0.5[a]
In relationship (%)	24 (75)	23 (77)	IQ (32,30)	0.86[a]
Age first migraine ≤18 years (%)	19 (59)	16 (53)	IQ (32,30)	0.63[a]

n: number of participants,
%: percentage,
SD: Standard Deviation from the mean
Data sources: IQ – Initial questionnaire; C – Case report file; D – Diary data PR = Patient records
$ independent t test [a] Chi square for * significance p ≤0.05.

Table 4-2. Baseline clinical measures

Clinical Measure or patient reported measure Means (SD)	Manual Therapy + 'Care as Usual' (M)	'Care as Usual' (C)	Data source (n,n)	P value T -test
Number medication days per week over last 6 weeks	3.75 (2.2)	4.4 (2.5)	IQ(32,30)	0.28
Number of headaches per month &	17.2 (8.9)	17.5 (9.8)	D (27,27)	0.13
Headache impact test score-HIT6	66.4 (4.7)	62.1 (7.0)	IQ (32,30)	0.006*
% HIT 6 score >60 (severe)	94	60	IQ (32,30)	0.0015*
Perceived Stress - PSS10	20.9 (8.3)	19.3 (7.2)	IQ (32,30)	0.42
State Trait Anxiety - STAI6	52.9 (11.2)	46 (12.7)	IQ (32,30)	0.03*
MSQ 2.1 scores			IQ (32,30)	
Role Function Restriction	49.5 (13.2)	57.5 (20)		0.07
Role Function Prevention	58.2 (16.6)	64.6 (25.4)		0.24
Emotional Function	46 (19.8)	57.6 (26.3)		0.04*
Hospital Anxiety and Depression Scores - HADS			IQ (32,30)	
Anxiety	10.6 (3.2)	10.6 (2.9)		1.0
Depression	9.4 (1.9)	8.6 (2.2)		0.13
Total HADS Emotional Distress	20.0 (3.5)	19.2 (4)		0.20
Allodynia Symptom Checklist - ASC	8.0 (4.1)	7.2 (5.3)	IQ (32,30)	0.51
Brief Cope scores (SD) - BCope			IQ (32,30)	
Self-distraction	5.28 (1.7)	4.93 (1.9)		0.44
Active coping	5.3 (1.8)	5.1 (1.5)		0.63
Denial	3 (1.60)	2.8 (1.5)		0.61
Substance use	2.8 (1.5)	2.6 (1.2)		0.57
Use of emotional support	5 (2.1)	4.3 (1.6)		0.15
Use of instrumental support	3.6 (1.2)	3.4 (1.3)		0.53
Behavioural disengagement	4 (2)	3.1 (1.6)		0.056
Venting	4.3 (1.8)	3.2 (1)		0.005*
Positive reframing	3.8 (1.7)	4.3 (2)		0.29
Planning	5 (1.9)	4.5 (1.9)		0.31
Humour	3.8 (1.8)	4.3 (2)		0.34
Acceptance	6.3 (1.3)	5.9 (1.5)		0.27
Religion	2.8 (1.2)	2.6 (1.6)		0.57
Self-blame	4.5 (1.9)	3.8 (2.1)		0.17

Data sources: IQ – Baseline questionnaire; C – Case report file; D – Diary data PR = Patient records

& Baseline was taken as end of month 1 after start of intervention

$ Chi square * significance p ≤0.05.

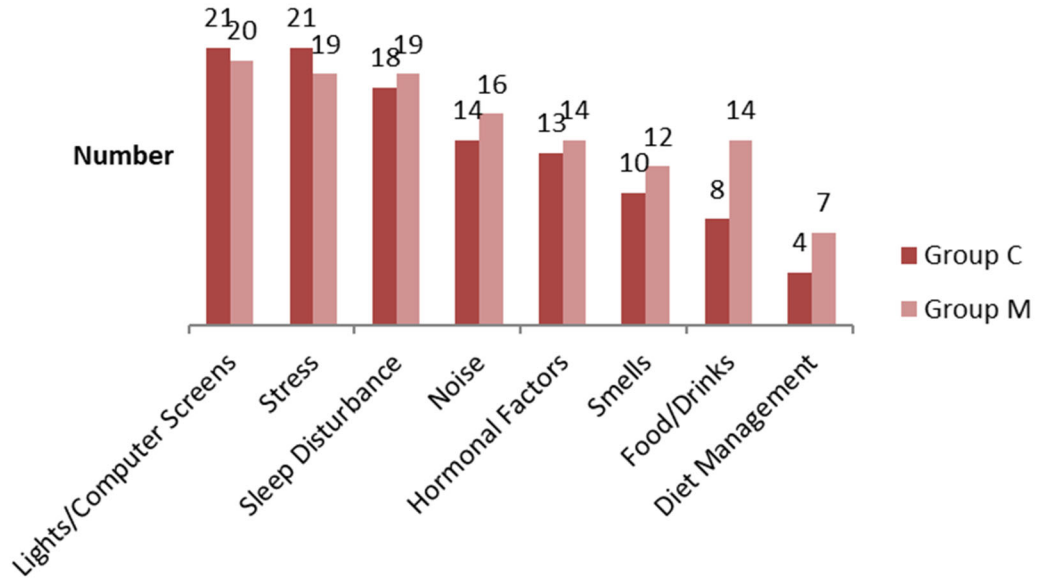

Figure 4-2. Triggers reported in initial questionnaire (multiple responses per participant)

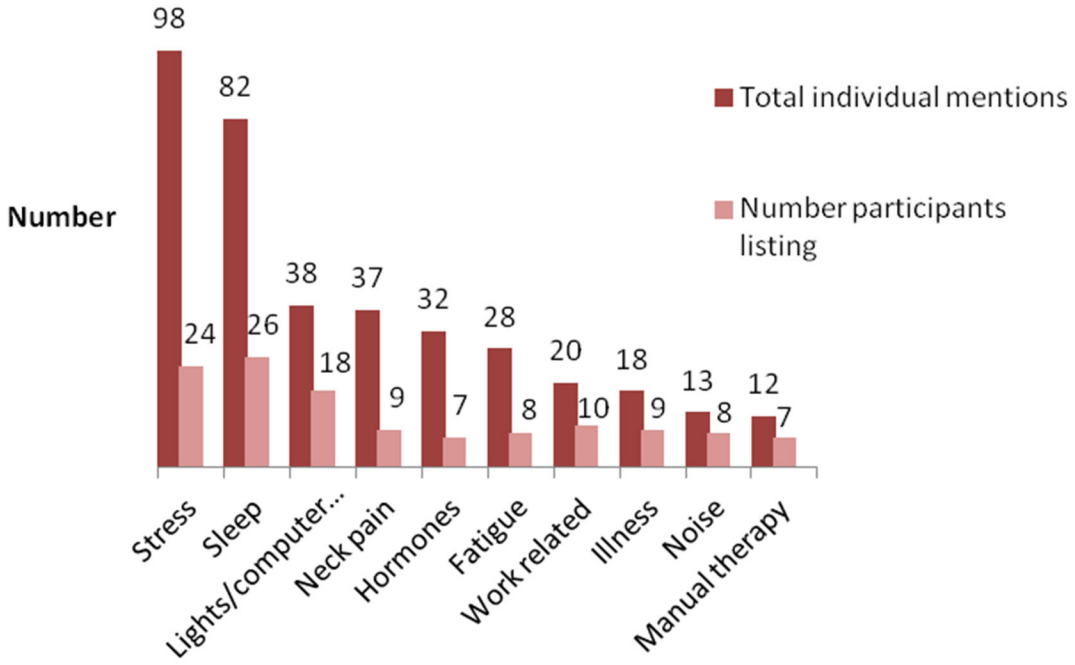

Figure 4-3. Diary data top ten triggers over 12 weeks

Table 4-3. Diary data
Additional triggers by total times reported (number participants reporting)

Total reported	Trigger
12	Shoulder pain (4)
11	Busy life (5)
10	Botox (6), Anxiety (4)
9	Heat/Cold (6)
8	Alcohol (7), Wearing glasses (3), Chocolate (2)
7	Diet (5), Low mood (3), Skin sensitivity (2)
5	Weather (4), Family issues (4), Travel (3)
4	Perfume (2)
3	Dehydration (3), Driving (1), Smoking (1)
2	Darkness (1), Allergies (1)
1	Sun (1), Dental pain (1)

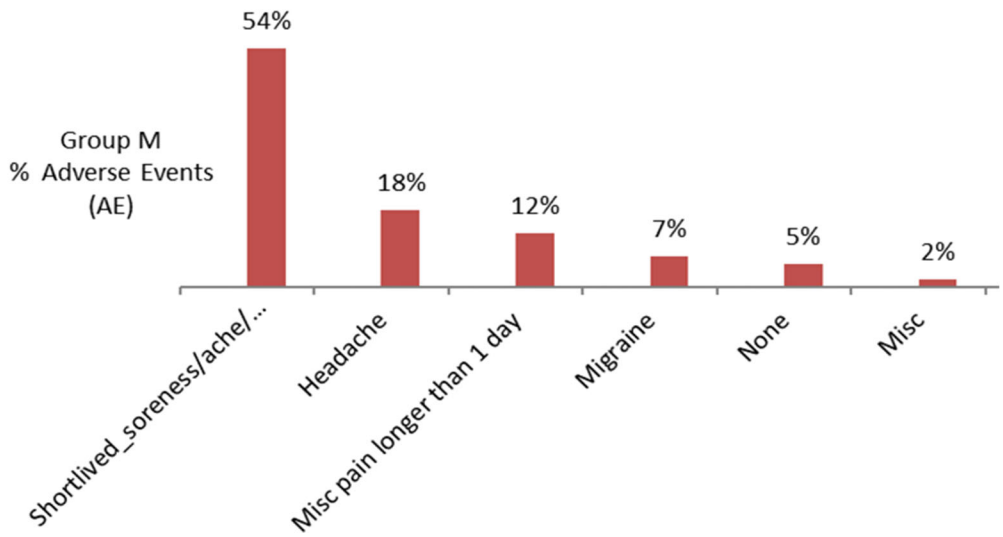

Figure 4-4. Percentage adverse events (AE) in Group M

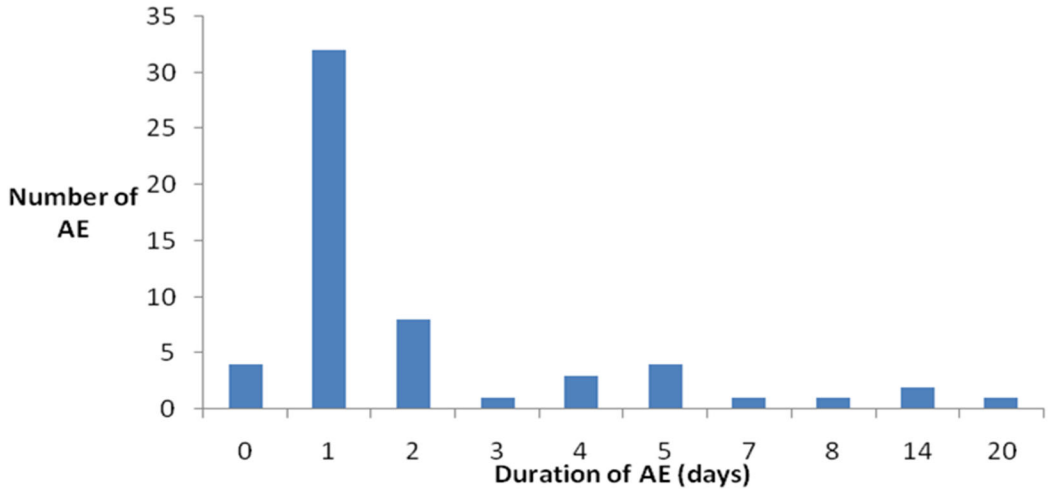

Figure 4-5. Number of adverse events by duration in Group M

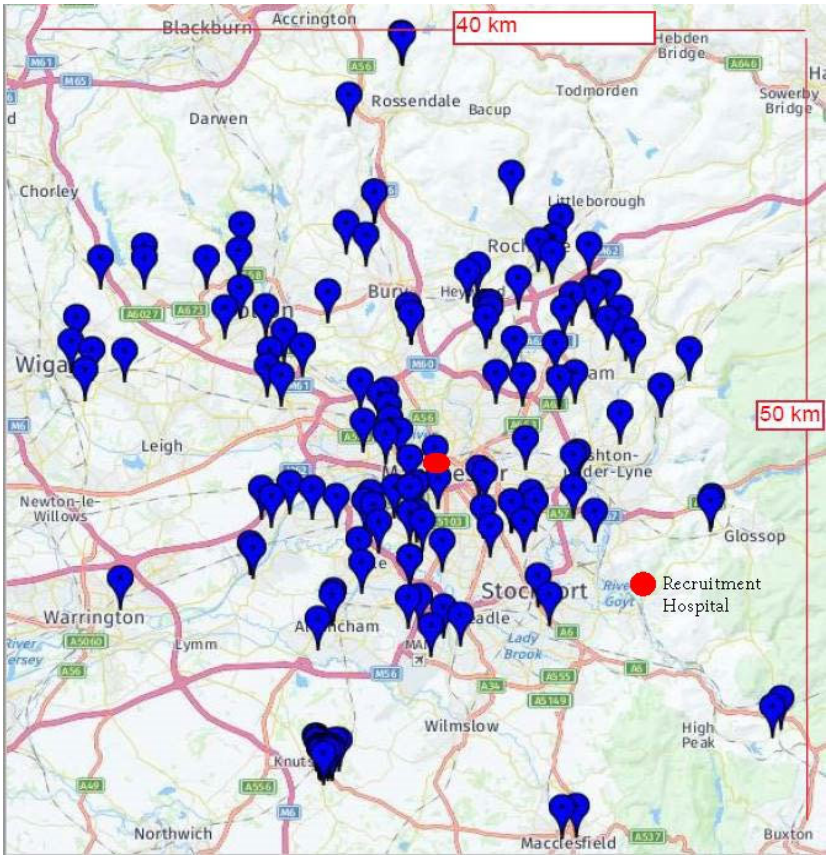

Figure 4-6. Geographic spread of participants

4.4. Adverse events (AE)

The detailed analysis of adverse events was limited to Group M as all participants were experienced users of 'care as usual' and presented immediately after their injections with mild discomfort, considered a normal response. In Group M, a total of 57 adverse events were reported across the 12 weeks. All were of a mild non-serious nature with 77% lasting 48 hours or less, 78% of participants had a maximum of 2 events over the 12 weeks with the majority (92%) being attributable to some degree to the treatment. All were typical of after-effects commonly associated with MT. The most commonly reported were short-lived muscle soreness/aches (54%) followed by headache (18%).

4.5. Research questions and objectives

The research questions proposed for this study were:

> ***Question one: Is manual therapy effective as an adjunctive to 'care as usual' in the treatment of females with chronic migraine?***
>
> ***Question two: Do female chronic migraine patients exhibit baseline characteristics that affect treatment outcomes within and between treatment groups?***

4.5.1. Research question one. Primary objective

To measure the effectiveness of adding manual therapy to 'care as usual' in CM by (1) the change in migraine-related disability (HIT6) at the end of the 12-week intervention and (2) by the proportion of responders at 12 weeks.

Question one: Is manual therapy effective as an adjunctive to 'care as usual' in the treatment of females with chronic migraine?

Question 1, Null hypothesis one*: H1(0) There is no difference in the between-group difference in change scores ('care as usual' [group C] versus 'care as usual' and manual therapy [group M]) from baseline to the end of the 12-week intervention measured using the Headache Impact Test (HIT 6).*

The a-priori outcome measure was the absolute difference between the group change scores from baseline in HIT 6 scores (gain scores) after 12 weeks. Data were tested for normality using SPSS v 25 ©: Q-Q plots were produced and test for normality calculated with Shapiro-Wilk test. These indicated that HIT 6 pre and post for both groups was normally distributed.

4.5.1.1 Absolute within and between group differences in HIT 6

The absolute changes in HIT6 score (Table 4.4) show that group C had a statistically significant increase in HIT6 score compared to a marginally non-significant reduction (p=0.059) in group M. The between-group difference however was statistically significant at p=0.006; the difference in between-group change scores was -3.42 (-5.76, -1.08), greater than the assumed MCID of 2.3.

Table 4-4. Absolute changes in pre and post HIT6 within groups

			Between groups	**Effect size [C]**
(n)	Group C (30)	Group M (32)	**Difference in gain score [B] Group M – Group C (95% CI)**	
Mean Hit 6 Pre (SD)	62.1 (6.95)	66.4 (4.7)	-3.42 (-5.76, -1.08)	**0.51**
Mean Hit 6 Post (SD)	63.9 (7.4)	64.7 (5.8)		
Mean change from baseline (95% CI)	+1.8 (-3.3, -0.13)	-1.7 (-0.73, 3.45)		
P value (*P* ≤ .05)	0.034**	0.059	0.006**	

[a] paired t-test [B] independent t test [c] cohens d
*MCID for HIT 6 between groups 2.3 (Coeytaux et al. 2006)
CI: confidence intervals
** significant p<0.05

4.5.1.2. Between group differences adjusted for baseline HIT 6 score

An ANCOVA determined the effect of adding MT to 'care as usual' (Groups M, C) on post-intervention HIT6 outcomes, controlling for baseline HIT6 measures. Assumptions of linearity, homogeneity, residuals, homoscedascity and outliers were checked and violations noted with the analysis (Laerd Statistics 2017). After adjustment for baseline HIT6 scores, there was a statistically significant difference in post-intervention HIT6 scores between the Groups (M, C), $F(1, 59) = 4.77$, $p = .033$, partial $\eta^2 = .075$. Post hoc analysis was performed with a Bonferroni adjustment.

Post-intervention HIT6 scores were statistically significantly lower in Group M versus Group C with a mean difference of - 2.86 (95% CI, -5.12 to -0.22 *p* = .033) and effect size Cohen's d ~ 0.6 (Table 4-5). We can therefore reject the null hypothesis H1(0).

Table 4-5. Means and variability for post intervention HIT 6: unadjusted and adjusted.

		Unadjusted		Adjusted		Mean Difference Adjusted CI 95%
	N	Mean	SD	Mean	SE	
Group M	32	64.7	5.8	63.01	0.83	[-5.12] to [-.224]
Group C	30	63.9	7.4	65.87	0.85	
Effect size	0.13*			~0.6[c]		

N = number, SD = standard deviation, SE = standard error, * Cohen's d calculated from difference in means, c Cohen's d calculated from η^2

4.5.1.3. Question one, null hypothesis two: H2(0) there is no difference in HIT6 responder rates between groups

Table 4-6. HIT6 responder rates

Group (n)	C (30)	M (32)	Difference proportion	95 % CI	P value for difference
Percentage of Responders[$,b]	10	40.6	0.30	0.11 – 0.50	0.006**

[b] difference of proportion test (chi square of homogeneity)
*MCID for HIT 6 within person = 3.7
CI: confidence intervals
** significant <0.01

The responder rate in this study is defined as the proportion in each group that achieved a reduction of greater than 3.7 in their HIT6 score (within person minimum significant clinical difference) from their base line. In the Group M, 40.6% had a change of more than 3.7 compared to 10% in the Group C. The difference in proportions test (chi square test homogeneity) was statistically significant (p=0.006) indicating a higher response in Group M (Table 4.6). The difference in proportion was 0.3 (CI.95% 0.106 – 0.496.) Using a post-hoc fisher test based on response rates this study was powered at 78% with p=0.05. Thus, for every 100 patients in the population an additional 30 might be expected to achieve the minimal clinically significant change if they were treated with MT and 'care as usual' (Grissom & Kim. 2012). We can therefore reject the null hypothesis H2(0).

4.6. Research question one: Secondary objectives

The secondary objectives resulting from research question one in the study included the post intervention changes in other patient reported outcomes that reflect the disability felt by those with CM. This included Patient Global Impact of Change Scale (PGIC) and the Migraine Specific Quality of Life (MSQ2.1), frequency and intensity of headaches, use of rescue/acute medication and the change in allodynia. The hypothesis for each is listed above the results.

4.6.1. Patient Global Impression of Change

Question one, null hypothesis three: *There is no difference in the PGIC outcomes between the 'care as usual' and the 'care as usual' with manual therapy groups*

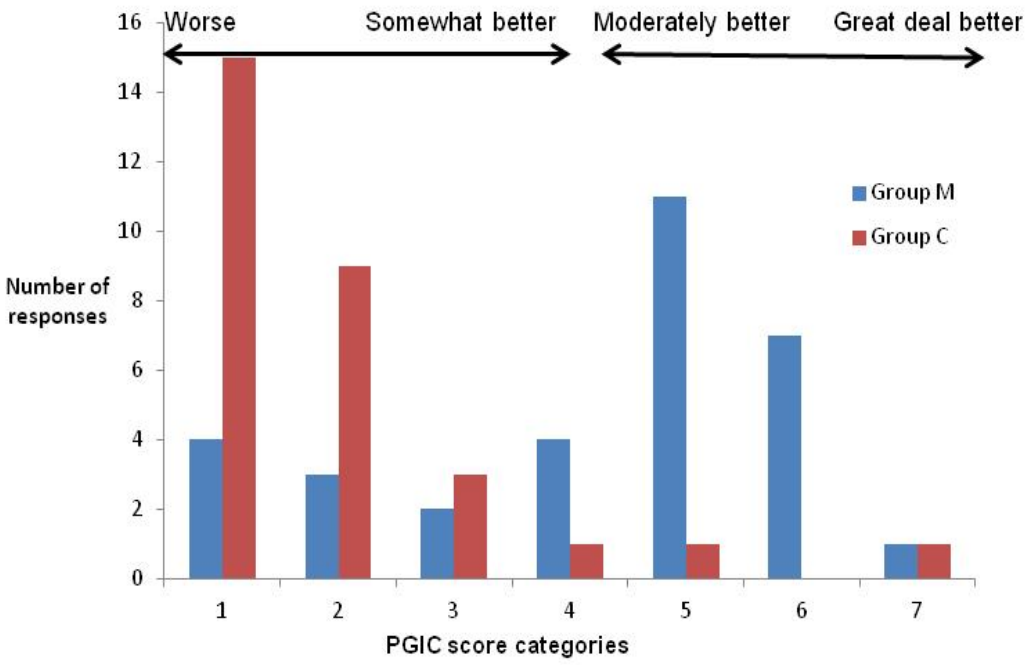

Figure 4-7. Patient Global Impression of Change Scores (PGIC)

A score of 5 or above was a positive change (Hurst & Bolton. 2004). The Chi square test homogeneity (for two proportions) was used to analyse the final outcomes: 19 patients (59%) in the MT group had an improved PGIC classification compared to 2 patients (6%) in the 'care as usual' group with a statistically significant difference in proportions of .53, p = .002. We can therefore reject the null hypothesis H3(0).

4.6.2. Migraine Specific Quality of Life (MSQ2.1)

Question 1, null hypotheses four, five: *H4(0), H5(0) There is no difference between the MSQ2.1 outcome in the 'care as usual' and the 'care as usual' with manual therapy groups for domains and responder rates.*

An ANCOVA determined the effect of being in each group on post-intervention MSQ2.1 domain score after controlling for the baseline measure as a covariate. The data were assessed for linearity and homogeneity of regression; normality; homoscedasticity; homogeneity of variance, and outliers using SPSS © v.25. Any violations were noted alongside results (Laerd Statistics, 2017).

The unadjusted pre and post scores and change in pre and post scores with the group difference compared to the MCID are shown in tables 4.7 and 4.8 respectively.

Table 4-7. Mean MSQ 2.1 scores

Domain	Pre scores (SD)		Post scores (SD)	
	Group M	Group C	Group M	Group C
Role Function Restriction	49.5 (13.2)	57.5 (20)	53.1 (18.2)	54.3 (20.6)
Role Function Prevention	58.2 (16.6)	64.6 (25.4)	62.8 (19.7)	64.7 (25.7)
Emotional Function	46 (19.8)	57.6 (26.3)	51.6 (23.5)	56.5 (25.7)

Table 4-8. Differences in mean change from baseline in domain score

Domain	Group M@	Group C@	P value*	Difference between mean group change $
Role Function Restriction A	+3.6	- 3.2	0.046	6.8
Role Function Prevention B	+4.6	+0.1	0.115	4.5
Emotional Function C	+5.6	- 0.9	0.05	6.5

$ MCID: minimal clinical important difference between groups A =3.2, B= 4.6, C=7.5,
@ MCID: minimal clinical important difference within groups A= 5, B=8, C=10
* P value determined by Mann Whitney U test

The differences in RR and EF mean changes were statistically significant with Group M positive (i.e. improved HRQoL) as opposed to Group C in which they were negative. The difference in RP mean change between groups was not statistically significant although Group C was only marginally positive.

Despite none of the within-group mean changes exceeding the within-group MCID the between group mean differences for RR exceeded the MCID, RF was borderline with EF less than the between group MCID.

4.6.2.1. MSQ2.1 Domain Analysis

An ANCOVA determined the differences in pre and post domain scores between the groups adjusted for baseline. There were some violations to the assumptions for ANCOVA. With Role Restriction there was one outlier at +3.04 (SD) which was ignored due to the robust nature of ANCOVA to these violations. Role Prevention did not meet the normality assumption for Group C using Shapiro-Wilk test p=0.032 (C), p =0.3 (M). The Emotional Function domain did not meet the assumption of normality for Group C with Shapiro-Wilk test p=0.02(C). Levene's homogeneity of variances was also significant (p=0.042). However, as the above deviations were due to a few extreme (but acceptable scores) and close to the critical p=0.05, they was ignored on the basis that ANCOVA is robust to deviation from normality and slight deviations for homogeneity of variances particularly with similar sample sizes (Salsberg et al 1999; Rheinheimer & Penfield. 2001).

Table 4-9. Differences in post intervention means

Domain	Mean post (SD) unadjusted	Mean (SE) adjusted for baseline, 95% CI	Significance
Role Restriction (RR)			*F* (1, 59) =2.1 p=0.15, partial η^2 <0.036
Group C (n=30)	54.3 (20.6)	50.92 (2.5), [45.8 - 56]	
Group M (n=32)	53.1 (18.2)	56.2 (2.46), [51.3 – 61.1]	
Role Prevention (RP)			*F* (1, 59) =0.56, *p* =0.46, partial η^2 = 0.009.
Group C (n=30)	64.7 (25.7)	62.15 (2.89), [56.4 - 67.9]	
Group M (n=32)	62.8 (19.7)	65.12 (2.80), [59.6 – 70.8]	
Emotional Function (EF)			*F* (1, 59) = 0.78, *p* =0.38, partial η^2 =0 .013.
Group C (n=30)	56.49 (25.7)	51.89 (3.18), [45.5 - 58.3]	
Group M (n=32)	51.56 (23.5)	55.87 (3.01), [49.7 - 62.0]	

In contrast to the unadjusted scores there were no statistically significant differences between the group post domain scores when adjusted for differences at baseline.

4.6.2.2. MSQ 2.1 Responder rates

The responder rate was defined as the proportion of participants in each group who had a change in the MSQ2.1 domain greater than the within groups MCID (Table 4.10). For RR the MCID within group has been calculated as a change greater than 5, for RP the MCID greater than 8 and for EF greater than 10 (Cole et al. 2009).

Table 4-10. MSQ2.1 responder rates

MSQ 2.1 Domain	Proportion of Responders		Significance*
	Group M	Group C	
Role Restriction	46.8%	16.7%	p= 0.011$
Role Prevention	46.9%	30%	p= 0.17
Emotional Function	46.9%	20%	p =0.025&

*Chi square test of proportions, $ significant P<0.05 with bonferroni correction, & not significant with bonferroni correction

There were consistent proportions of responders in Group M for each domain, although only RR had a significant difference from Group C after the application of a Bonferroni correction in EF.

As a result, we can neither accept nor reject H4(0) and H5(0) for the difference between groups in the MSQ2.1 domain and for the responder rates respectively.

4.6.3. Frequency of headaches

Question one, null hypothesis six*: H6(0) There is no difference between the frequency of headaches outcomes in the 'care as usual' group (Group C) and the 'care as usual' with Manual Therapy' group (Group M).*

A two-way mixed ANOVA was completed using the data from the diaries (n=54) to examine any differences between groups over the 12-week period. Responder rate analysis in each group was also undertaken using changes from baseline of a 30% and 50% reduction. The assumptions associated with ANOVA were tested. The assumption of sphericity was violated for the two-way interaction, χ^2 (65) = 189.7, *p* ‹ .005. As a result, the Huynh-Feldt correction (epsilon, ε = 0.702) rather than Mauchly's test was used to interpret the results.

There was no statistically significant interaction between the group intervention and time on frequency of headaches, F(7.7,401.8) = 0.62, p=0.75, partial η2 =0.012. In other words, there was no difference in effects of the group interventions (C or M) on mean headache frequency over time. The main effect of group showed that there was no statistically significant difference in mean headache frequency between intervention groups F(1, 52) = 0, p =0.99, partial η2 = 0.0. The marginal mean (SE) for Group C score was 4.056 (0.45) and 4.052 (0.45) for Group M, with a statistically non-significant mean difference of 0.003 (95% CI, 1.28 to 1.286), *p* = .996.

The main effect of time however resulted in a statistically significant difference in mean headache frequency at the different time points, albeit with a small effect size (0.053) F (7.7, 401.8) = 2.93, p = .004, partial η2 = .053. The significant changes were seen in the period between the first and fourth week. The changes in the mean frequency in the following weeks then became non-significant. We fail to reject H6(0).

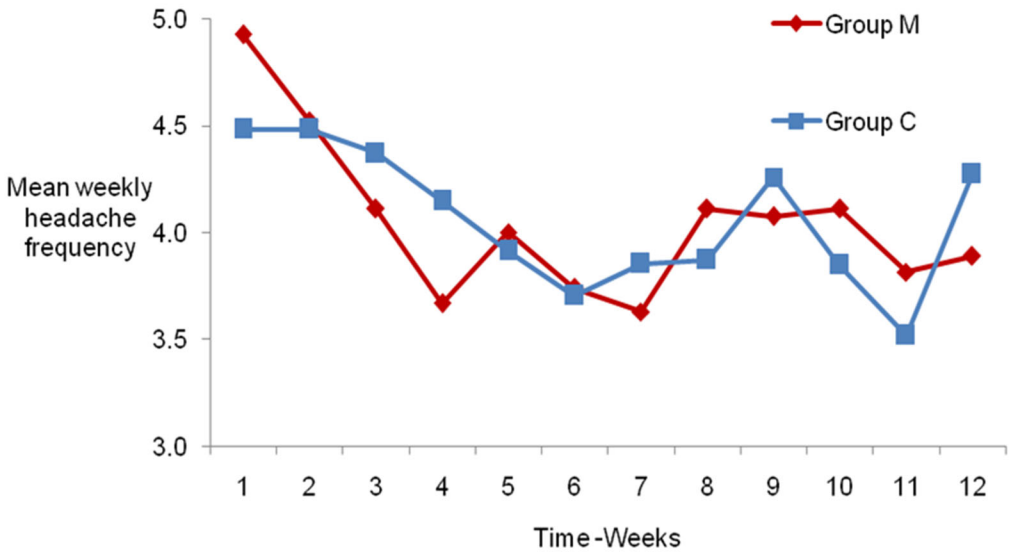

Figure 4-8. Mean headache frequency

4.6.4. Headache responder rate

Question one, null hypothesis seven: *H7(0) There is no difference between the headache responder rate outcomes in the 'care as usual' group (Group C) and the 'care as usual' with Manual Therapy' group (Group M).*

The responder rate is the percentage of participants experiencing a certain percentage reduction in headache frequency from baseline. There is no standardised figure for responder rate analysis although the IHS guidelines for CM (Tassorelli et al. 2018) suggest a 50% and 30% reduction in headache frequency with a focus on headaches classed as moderate to severe. This study analysed the results for headaches classed as moderate to severe headaches and those mild to moderate (Table 4.11)

Table 4-11. Headache frequency responder rates.

Moderate to Severe Headaches (NRS >4)	Group C (n=27)	Group M (n=27)	Significance
>30% reduction	0%	0%	ns
> 50% reduction	4%	0%	ns
Mild to Moderate Headaches (NRS≤4)			
>30% reduction	26%	30%	ns
>50% reduction	15%	22%	ns

ns= not statistically significant

Of the 27 participants in each group, for whom diary data were recorded, a chi square test was run to compare the 50% and 30% responder rates headaches between groups for both mild to moderate and moderate to severe headaches. There was no statistically significant difference in proportion between groups in either the 50% or 30% improvement levels (0.037, p=0.75 and 0.074, p=0.48). (Table 4.11). We fail to reject H7(0).

4.6.5. Intensity of headaches

Question one, null hypothesis eight: *H8(0) There is no difference between the mean intensity of headaches outcomes in the 'care as usual' group (Group C) and the 'care as usual' with Manual Therapy' group (Group M)*

A total of 53 (M= 27, C=26) participants completed data for headache intensity. If the participant indicated that they had no headaches, headache intensity was listed as zero. A mean of the weekly headache intensity was calculated for each participant and used in two-way mixed ANOVA to compare the response between groups over the 12-week period. There were some violations in the test assumptions. There were 6 outliers as assessed by boxplot but all were within

normal values - these were ignored due to the robust nature of the ANOVA to outliers. The -data were normally distributed in 6 of the 24 distributions, as assessed by Shapiro-Wilk's test of normality ($p > .05$) although box plots indicated this was the result of a few outliers. There was homogeneity of variances as assessed by Levene's test of homogeneity of variances was met in all except week 2 ($p=0.0$).Mauchly's test of sphericity indicated that the assumption of sphericity was violated for the two-way interaction, $\chi^2(65) = 92.7$, $p = .14$ therefore the Greenhouse-Geisse correction was used to calculate the results. As both groups had similar distributions, skewness at each time point, and were of similar size the above violations were ignored based on the robust nature of ANOVA in these circumstances (Tabachnick & Fidell, 2007).

There was no statistically significant interaction between the groups and time on headache intensity: $F(8.5, 433)=0.546$ $p=0.832$ partial $\eta^2 = .011$. The main effect of time did not show a statistically significant difference in mean headache intensity at the different time points: $F(8.5, 433) = 1.65$, $p =0.103$, partial $\eta^2 = .031$.

The main effect of group showed that there was not a statistically significant difference in mean headache intensity between groups (Fig. 4-7): $F(1, 51) = 2.2$, $p = .14$, partial $\eta^2<0.042$
The marginal mean (SE) for Group C score was 4.71 (0.452) and 5.4 (0.33) for Group M, with a statistically non-significant mean difference of 0.715 (95% CI, -0.241 to 1.67), $p= 0.14$. We fail to reject H6(0).

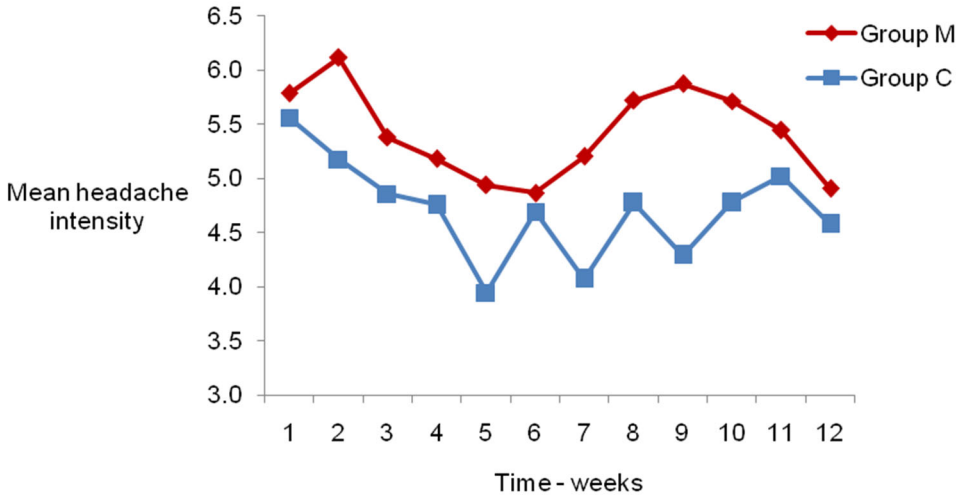

Figure 4-9. Mean headache intensity

4.6.6. Use of rescue medication

Question one, null hypothesis nine: *H9(0) There is no difference between the use of rescue/acute medication outcomes in the 'care as usual' and the 'care as usual' with Manual Therapy groups.*

A two-way mixed ANOVA was run to compare the medication usage between groups at monthly time points, m1, m2 and m3 from the start of the study (Fig.4-10). There were some violations to the test assumptions with 3 outliers but as all were within normal measures, these were ignored due to the robust nature of the ANOVA to outliers. The data were not normally distributed, as assessed by Shapiro-Wilk's test of normality ($p > .05$) although box plots indicated this was the result of the few outliers. As both groups had similar distributions and skewness at each time point this violation was ignored based on the robust nature of ANOVA in these circumstances. Mauchly's test of sphericity indicated that the assumption of sphericity was violated for the two-way interaction, $\chi^2(2) = 7.09$, $p = .029$, as result the Greenhouse-Geisser correction was used to calculate the results. There was no statistically significant interaction between the groups and time on medication usage; $F(1,77, 90.1) = 0.295$, $p = .72$, partial $\eta^2 = .006$, $\varepsilon=0.833$.

The main effect of time did not show a statistically significant difference in mean medication usage at the different time points, $F(1.77, 90.1) = 2.08$, $p =0.136$, partial $\eta^2 = .04$. The main effect of group showed that there was not a statistically significant difference in mean medication usage between groups M and C; $F(1, 51) = 0.13$, $p = .91$, partial $\eta^2<0.001$ Consequently we fail to reject H8(0).

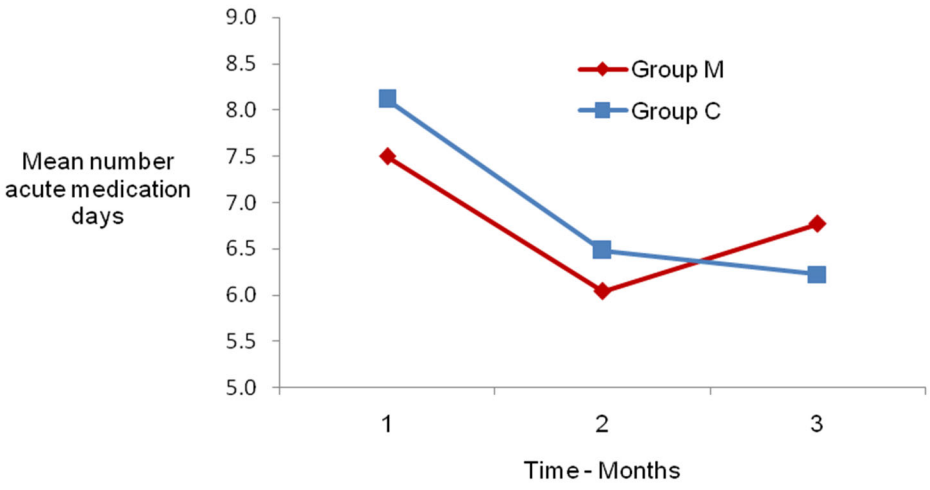

Figure 4-10. Mean monthly use of acute medication

4.6.6.1. Medication Overuse

The ICHD guidelines (Tassorelli et al 2018) define medication overuse headache as headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use over 3 months of one or more:

1. Triptans on 10 ≥ days/month
2. Opioids on ≥10 days/month
3. NSAIDs (other than acetylsalicylic acid) on ≥15 days/month
4. Non-opioid analgesics on 15 ≥ days/month
5. Combination-analgesic medications on ≥10 day/month

Analysis of the 12-week diary data showed that of the 53 total useable responses 31% could be classed as having medication overuse headache: 26% of Group C (n=27) and 37% (n=24) of Group M. A test of proportions found no significant difference between groups with X^2 (1, N = 53) = 0.791, p = 0.374.

The most commonly used medications by participants were NSAIDS (71%), Triptans (65%), miscellaneous (51%) and Opioid (16%). Twenty one (40%) of the 52 participants who supplied data used a single medication with a triptan the most common (17%) followed by Naproxen and Ibuprofen (6% each). Twenty participants (38%) used 2 medications in a regular combination, 7 (13%) used three medications with 2 (4%) on 4 and 1 (2%) on 5 and 6 medications respectively. The most common dual combination was triptan/paracetamol (29%) followed by naproxen/ Ibuprofen (14%) with triptan/aspirin, naproxen/paracetamol and paracetamol/ibuprofen combinations each on 10%.

4.6.7. Allodynia checklist scores (ASC)

Question one, null hypothesis ten: *H10(0) There is no difference in the allodynia score outcomes between the 'care as usual' group (Group C) and the 'care as usual' with Manual Therapy' group (Group M).*

Analysis of the ASC (used as a measure of central sensitisation) between groups was completed using two approaches: The first used the difference in the proportion by severity (none, mild, moderate, severe) between groups and the second the difference in those reporting allodynia (Score > 2) or not. Figure 4.11 illustrates the change in ASC category distribution between categories pre and post intervention and figure 4.12 highlights the movement between the categories.

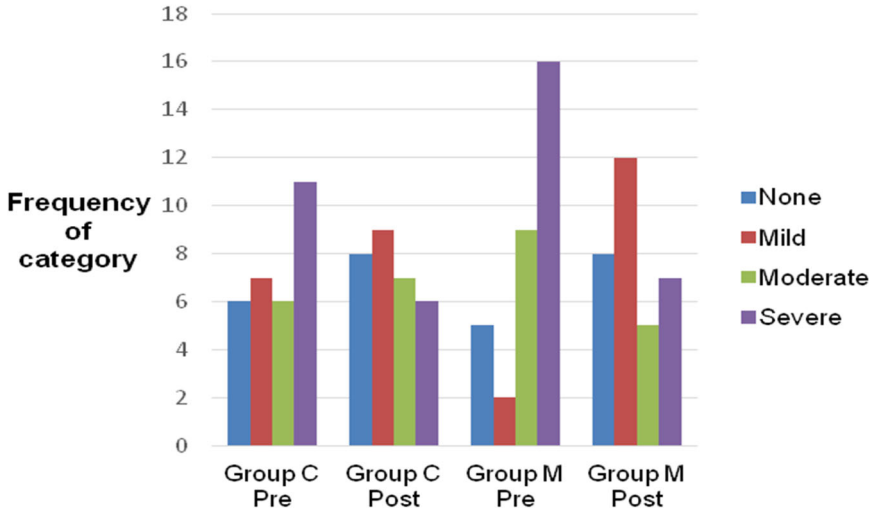

Figure 4-11. Pre–Post ASC category by group

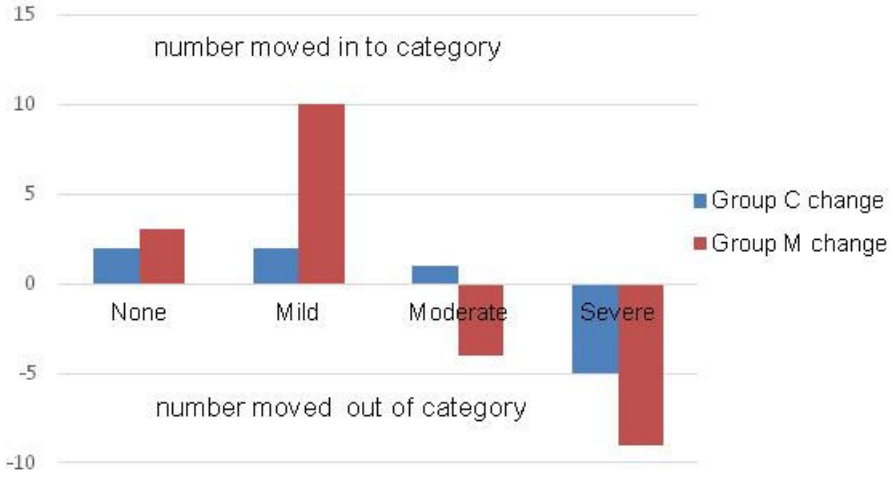

Figure 4-12. Movement between ASC categories

Chi square test was completed on the above category proportions post intervention which was not statistically significant (p=0.86) indicating there was no difference between the balance of categories in the groups after intervention. However, an analysis of the movement between the categories (Figure 4.12) highlighted that a

higher percentage of the severe category moved into the mild group in Group M (n=6) compared with Group C (n= 1 (35% versus 9%).

Conversely the percentage moving from the severe to moderate category was higher in Group C (n=4) compared to M (n=4) (36% to 24%) whilst 12% of the Group M moved from the severe to none category compared to 0% in Group C. No statistical tests including the test of proportion, chi square or Fisher's exact test were suitable to analyse the difference in movement between groups due to the population size and test assumption conditions. The proportion of those in each group experiencing allodynia (ASC score > 2) after the intervention was assessed using a test of proportions. The findings were not significant (p= 0.81) with 73.3 % (n=30) of Group C having allodynia compared to 75% (n=32) of Group M. However, given the other findings this meant that H10(0) can be neither rejected nor failed to be rejected.

4.7. Research question two

Do female chronic migraine patients exhibit baseline characteristics that affect treatment outcomes within and between treatment groups?

Previous studies have demonstrated the potential for participant characteristics at baseline (e.g. level of depression) to influence patient reported outcomes and in some cases to be influenced themselves by interventions. The generic null hypotheses for research question two can be summarised as follows:

H(0) Treatment outcomes are not affected by baseline characteristics
H1(0) The probability of being a responder is not affected by baseline characteristics

This next section presents an analysis of differences in characteristics, within and between groups, pre and post and, in the case of diary data longitudinally, as a precursor to examining the results of their influence on the primary outcome(s).

4.7.1. Brief Cope (BC)

The non-parametric Mann-Whitney U test was used to examine the distribution of change scores between groups for each variable in Brief Cope and then for the French four factor variables. The full results can be found in Appendix 25. The only individual variable in Brief Cope with a statistically significant difference (p=0.036) in scores pre and post between groups was Behavioural Disengagement. In Group C the mean score increased whilst decreasing in Group M.
This can be interpreted as those in Group C becoming more likely to shy away from difficult situations compared to those in Group M. The effect size, η2 =0.07 is equivalent to a moderate effect when converting to Cohen's (d ~0.55) (Lenhard & Lenhard, 2016). The French four factor version of Brief Cope (Baumstarck et al. 2017) groups the individual variables in four composite factors as shown in table 4.12. The change in factor scores were assessed using independent t test.

Table 4-12. French four factor cope

Original Brief Cope variables	French four factors variables	T-test results (p= 0.05)
Self-distraction	Avoidance	t(60)=1.473 p=.146 Mean Diff = 2.72 95% CI (0.97, 6.4)
Denial		
Substance use		
Behavioural disengagement		
Self-blame		
Use of emotional support	Seeking social support	t(60)=0.689 p=.493 Mean Diff =1.02 95% CI (1.93, 3.97)
Use of instrumental support		
Venting		
Religion		
Humour	Positive thinking	t(60) =-1.178 p=.243 Mean diff = -1.6 95% CI (-4.32, 1.12)
Acceptance		
Positive reframing		
Planning	Problem solving	t(60) =-1.089 p=.281 Mean Diff = -1.18 95% CI (-3.3, -0.99)
Active coping		

There were no statistically significant differences in the change in factors scores between groups when using the French four factors variables.

4.7.2. Perceived Stress Scale (PSS 10)

Table 4-13. Perceived Stress Scale 10 ANCOVA

	Mean pre (SD)	Mean post (SD) unadjusted	Mean post (SE) adjusted for baseline: [95% CI]
Group C (n=30)	19.3 (7.2)	19.2 (6.59)	19.83*(.865) [18.10, 21.56]
Group M (n=32)	20.9 (8.3)	19.6 (8.37)	19.03*(.837) [17.36, 20.71]

*Covariates appearing in the model are evaluated at the following values: Pre PSS = 20.1613
The norm for females =13.7 (Dietrich et al. 2008)

The difference between the post PSS scores for the groups was calculated with ANCOVA adjusted for the baseline score. There were 2 minor violations of assumption for the test: Group M did not meet the Shapiro Wilks condition for normality ($p<0.05$) and there was one outlier. These two violations were ignored on the basis of the robust nature of the ANCOVA.

After adjustment for baseline perceived stress, there was no statistically significant difference in post-intervention PSS score between the Groups C and M, $F(1, 59) = 0.443$, $p = 0.51$, partial $\eta^2 = .007$.

4.7.3. Hospital Anxiety and Depression Scale (HADS)

A one-way ANCOVA test was run on the HADS for each of the following factors: anxiety, depression and the total score (which is seen as a measure of emotional stability) with the baseline score of each acting as the covariate. However, the data failed the assumptions of homogeneity of regression and thus it was decided to use a two-way mixed ANOVA on the grounds that the baseline figures between each group were similar and that the covariance error would be small in the between group differences. A Bonferroni correction was applied to the three ANOVA tests (p= 0.05/3 = 0.016). A Chi square test of homogeneity was also used to compare the proportions in each category between Group M and C post intervention. If the assumptions were not met then the Fishers exact test was used.

4.7.3.1. HADS: Anxiety

Table 4-14. HADS anxiety Score*

	Mean Pre (SD)	Mean Post (SD)	Difference	Significance
Group C (n=30)	10.57(2.9)	9.8 (2.46)	- 0.77	p= 0.27
Group M (n=32)	10.56 (3.2)	10 (2.26)	-0.56	P=0.42

* Score 0 - 7 Normal, 8 -10 mild , >10 severe

Assumptions for the mixed ANOVA were performed. There was one outlier, as assessed by boxplot and the data were normally distributed, as assessed by Shapiro-Wilk's test of normality ($p > 0.05$) except for a slight variation in the pre-C score (p=0.03). These variations were ignored due to the robust nature of the ANOVA. Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(0) = 0$, $p< 0.00$, resulting in use of the Greenhouse-Geisser correction. There was no statistically significant interaction between the groups and time on anxiety, $F(1, 60) = 0.02$, $p = 0.89$, partial $\eta^2 < .001$ (Table 4.14).

The main effect of time did not show a statistically significant difference in mean anxiety score at the pre and post time points, $F(1, 60) = 1.68$, $p = 0.2$, partial $\eta^2 < 0.02$. The main effect of group showed that there was no statistically significant difference in mean level of anxiety between intervention groups $F(1, 60) = 0.017$, $p = 0.89$, partial $\eta^2 < 0.001$.

The data for anxiety was tested using a Fisher exact test. There was no significant difference between the two groups in the proportion of categories for anxiety (p=0.182) (Figure 4.13).

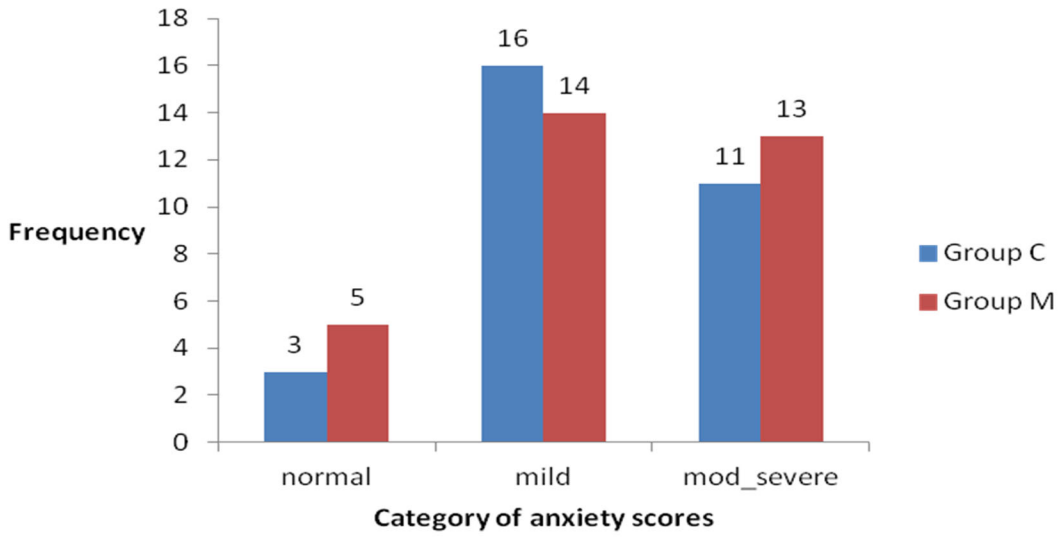

Figure 4-13. Anxiety categories

4.7.3.2. HADS: Depression

Table 4-15. HADS depression score*

	Mean Pre (SD)	Mean Post (SD)	Difference	Significance
Group C (n=30)	8.63 (2.19)	9.07 (2.51)	0.44	P = 0.47
Group M (n=32)	9.44 (1.88)	9.31 (1.57)	-0.13	p = 0.76

* Score 0 - 7 Normal, 8 -10 mild, >10 severe

Assumptions for the mixed ANOVA showed there was one outlier, as assessed by boxplot which was ignored based on the resilience of the test to this condition. Box's M test assumption was violated (p=0.007) and on this basis the Anova was continued but without an analysis of interaction simply the difference between groups. The main effect of group showed that there was no statistically significant difference in mean level depression between intervention groups at the end of the study $F(1, 60) = 2.064$, $p = 0.16$, partial $\eta^2 < 0.033$ (Table 4.15). A chi square of homogeneity was run to compare the proportions in each category for depression (none, mild, moderate-severe). The results showed there was no statistically significant difference in proportions between groups. $\chi^2(2) = 3.24$, $p = 0.198$.

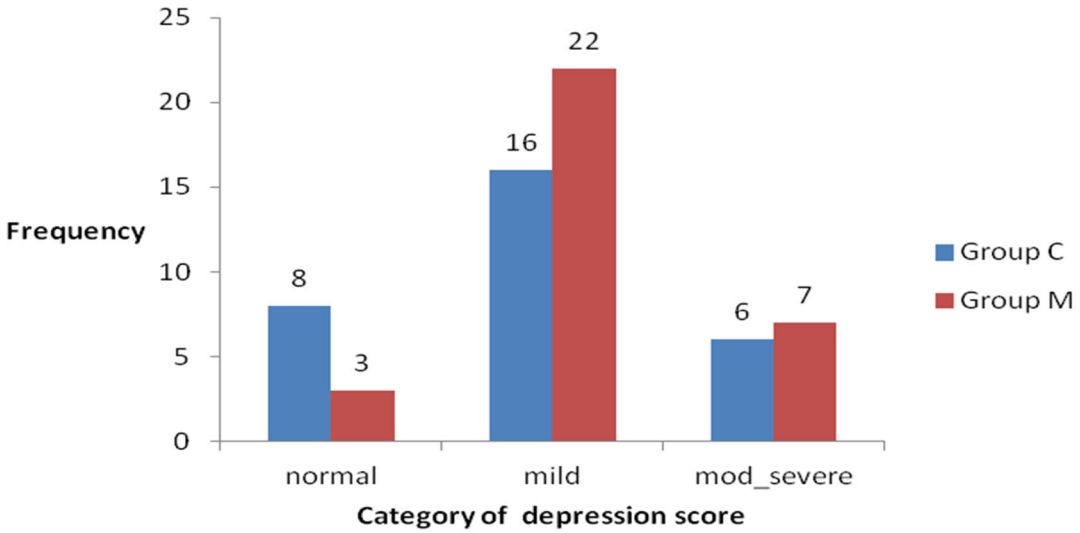

Figure 4-14. Depression categories

4.7.3.3. HADS Total Score

The total score is considered a measure of emotional stability (or distress) with a higher score being more unstable and any score ≥ 16 considered abnormal.

Table 4-16. HADS Total score*

	Mean Pre (SD)	Mean Post (SD)	Difference	Significance
Group C (n=30)	19.2 (3.96)	18.93 (3.63)	-0.27	p=0.78
Group M (n=32)	20 (3.45)	19.3 (2.46)	-0.7	p=0.35

*Score ≥16 is cut off for emotional instability/distress

The mixed ANOVA assumption tests found two outliers, although both were acceptable scores, as assessed by boxplot. The data were normally distributed, as assessed by Shapiro-Wilk's test of normality ($p > .05$) except in the case of the post total score in Group C. These violations were ignored due to the resilience of Anova to minor deviations. Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(0) = 0$, $p< 0.05$ necessitating the use of the Greenhouse-Geisser correction.

There was no statistically significant interaction between the groups and time on the Total_HADS score, $F(1, 60) = 0.113$, $p = 0.74$, partial $\eta^2 = .002$. The main effect of time did not show a statistically significant difference in mean Total_HADs score at the pre and post time points, $F(1, 60) = 0.58$, $p = 0.45$, partial $\eta^2 = 0.01$. The main effect of group showed that there was no statistically significant difference in mean Total_HADS score between intervention groups $F(1, 60) = 0.967$, $p = 0.329$, partial $\eta^2 < 0.016$ (Table 4.16).

A test of 2 proportions was used to compare the groups for the proportion of total scores over the cut off score (16) which showed no statistically significant difference in the proportion (0.077, *p*=0.443) of participants in each group (figure 4.15).

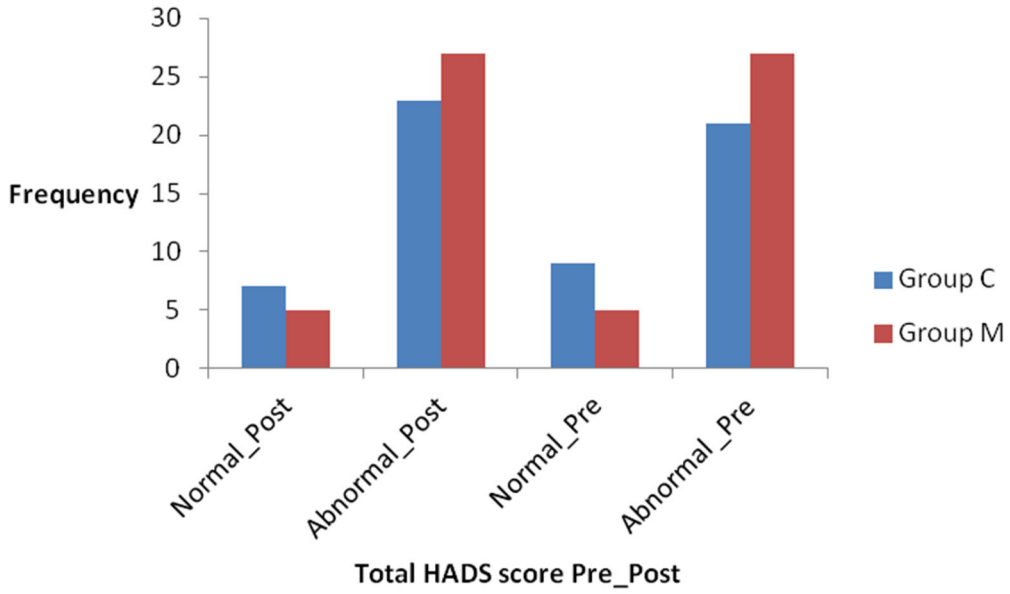

Figure 4-15. Total score pre and post HADS_Total

4.7.4. Stress

The level of stress was recorded weekly for each of the 12 weeks using the diary using a NRS scale (Figure 4.16). A two-way mixed measure ANOVA was run using the 12-week data. The assumptions for ANOVA were checked and found to be violated for outliers. However, these are within normal values and given the robust nature of the ANOVA to outliers they were included. The assumption of sphericity was also violated and therefore the Greenhouse-Geisser correction was used. There was not a statistically significant interaction between the interventions and time on stress, F (7.2, 376) = 1.3, p = 0.243, partial η^2 = 0.025. The main effect of time showed did not show a statistically significant difference in mean stress at the different time points, F (7.2, 376) = 0.944, p =0.474, partial η2 = 0.018. The main effect of group (M, C) showed that there was not a statistically significant difference in mean stress between intervention groups F(1, 52) = 0.19, p = 0.667, partial η^2 = 0.004

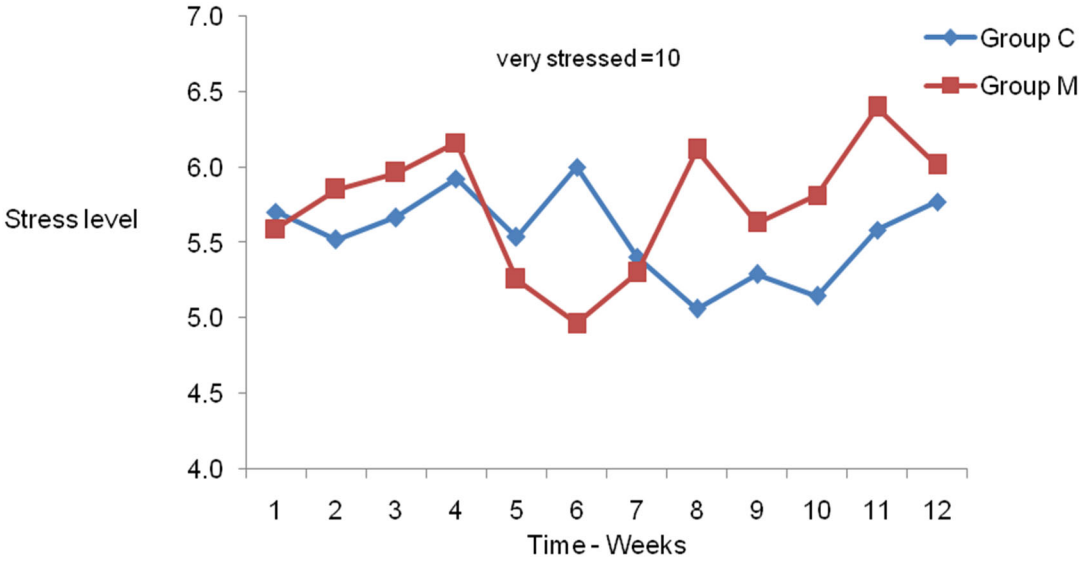

Figure 4-16. Mean stress score

4.7.5. Body Mass Index (BMI)

The body mass index (BMI) was recorded for each participant at the start of the study (Figure 4.17.). In total 64.5% of all participants were overweight or obese. A chi square test showed no statistically significant difference between groups in the proportion of participants in each BMI category. $\chi^2(2) = 2.68$, $p = 0.26$.

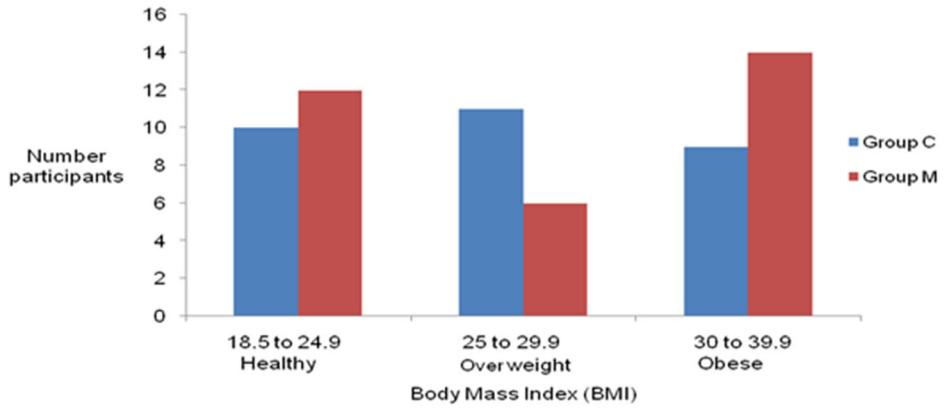

Figure 4-17. Body mass index by group

4.8. Correlations

To determine if any baseline factors correlated with the primary and secondary outcome measures (change in HIT6 and PGIC score) correlation analyses were completed between the continuous variables (Appendix 27) using the Pearson's coefficient (r) bivariate matrix for both groups.

4.8.1. Continuous patient reported outcomes measures by group

Analysis of each group highlighted differences in the correlation figures for the outcome results. Group C had statistically significant correlations between the change in HIT6 score and the baseline variables: Substance abuse (r=-0.404 p=0.027) positive reframing (r=0.367 p=0.046), planning (r=0.439 p= 0.015). Group M had no statistically significant correlations between the change in HIT6 and the baseline variables.The secondary outcome measure, the PGIC was correlated with baseline variables in both groups. Group M was significantly correlated with Emotional support (r =0.363 p=0.04), Instrumental support (r =0.469 p=0.007), Behavioural disengagement (r =- 0.384 p=0.03) and Planning (r =0.488 p=0.005). Group C had statistically significant correlations between PSS10 (r =0.466, p=0.014), Denial (r =0.362 p=0.049), Behavioural disengagement (r = 0.37 p=0.044), Acceptance (r = - 0.464 p=0.01) Religion (r =0.41 p=0.024), Self blame (r = 0.496 p=0.005) and ASC (r =0.458 p=0.011).

4.9. Baseline variable response predictors

Two approaches were employed to identify potential relationships between baseline characteristics and outcomes. The first approach considered baseline variables that have been shown in previous studies to be associated with chronicity or treatment response outcomes (Mathew et al. 2007; Schwedt et al. 2014; Schiano di Cola et al. 2019; Dominguez et al. 2019). The second evaluated between groups outcomes using t-tests on all baseline variables, in the HIT6 and PGIC responder groups, to identify significant differences as an indicator for predictive variables (Tables 4.17, 4.18). Hierarchical linear regression was used to examine the baseline relationships with the change in HIT6 scores and multinomial logistic regression with the PGIC outcome. Due to the limited sample size, a maximum of four variables (where n=62) were chosen when the outcome was a continuous variable (Tabachnick & Fidell. 2001).

Binomial logistical regression was used to evaluate the relationship between mixed categorical and continuous baseline variables and dichotomous responder the responder/non responder outcomes for HIT 6 and PGIC. Finally, to evaluate the potential impact of abnormal levels of baseline variables the proportions of responders/non responders of these baseline variables were also examined using the chi square test.

Table 4-17. Baseline characteristics between HIT 6 responder groups

Responder / Group	Y	N	Within group variables with significant mean differences	Significance
M (n=32)	13	19	Planning, Emotional support	P= 0.06 P=0.07
C (n=30)	3	27	Substance use Self-distraction	P=0.034 P=0.046
Between group variables with significant mean differences	Venting	STAI RR_MSQ Behavioural disengagement EF_MSQ		
Significance	P=0.05	P=0.009 P=0.037 P=0.06 P=0.06		

Table 4-18. Baseline characteristics between PGIC responder groups

Responder / Group	Y	N	Within group responder variables with significant mean differences	Significance (t-test)
M (n=32)	19	13	RR_MSQ RP_MSQ Behavioural disengagement	P=0.024 P=0.06 P=0.059
C (n=30)	2	28	Denial Instrumental support Religion ASC	P=0.005 P=0.065 P=0.001 P=0.008
Between group responder variables with significant mean differences	Acceptance Religion ASC	a. PSS10 b. STAI c. RR_MSQ d. RP_MSQ e. EF_MSQ f. Behavioural disengagement g. Venting		
Significance	P=0.08 P=0.001 P=0.027	a. P=0.049 b. P=0.025 c. P=0.014 d. P=0.07 e. P=0.04 f. P=0.022 g. P=0.006		

4.9.1. Hierarchical linear regression

4.9.1.1. Headache impact test

The initial regression equations for the change in HIT6 were examined based on variables identified in previous studies as factors likely to impact treatment outcomes. These included substance abuse, medication overuse, levels of anxiety, depression, coping and stress (Biaggianti et al. 2014; Schwedt et al. 2014; Probyn et al. 2017; Bottiroli et al. 2018). Prior to conducing a hierarchical regression, the assumptions of this statistical analysis were checked. A sample size of 62 was deemed adequate given four independent variables (IV) to be included in the analysis (Tabachnick & Fidell. 2001). Since substance use accounted for a statistically significant variation in the change in HIT6 a regression process was used that maintained the maximum number of additional variables at 2 per group, or 3 for the combined groups, to evaluate other variables as potential predictors. The assumptions of linearity, independence of residuals, homoscedasticity, multicollinearity, studentized deleted residuals greater than ±3 standard deviations, leverage value greater than ~0.33 (3k/n, k = number factors, n = sample size), Cook's distance above 1 and assumption of normality were checked with violations highlighted with each model.

4.9.1.2. Final hierarchical models

In Group C 40% of variation in the change in HIT6 was accounted by the variables, substance use, planning and Total_HADS. The full model was statistically significant, $R^2 = 0.43$, $F(3, 26) = 7.45$, $p = 0.001$, adjusted $R^2 = 0.40$. There were a few high centred leverage values, however removal of these cases did not affect the model significantly. In contrast, in Group M, no individual variables or models were found that could be regressed to account for a statistically significant variation in the change in HIT6. The same model as Group C above was statistically insignificant, $R^2 = 0.14$, $F(3, 28) = 1.5$, $p = 0.231$, adjusted $R^2 = 0.039$.When the combined groups (C and M) were regressed using the same model as above only substance use entry was significant which accounted for 6.2% of variation in the change in HIT6. $R^2 = 0.078$, $F(1,60) = 5.05$, $p = 0.028$, adjusted $R^2 = 0.062$. The optimum model for the combined group, accounting for 20% of the variation in the change in HIT6 score comprised substance use, planning, active coping and intervention (dichotomous variable). $R^2 = 0.25$, $F(4, 57) = 4.85$, $p = 0.002$; adjusted $R^2 = 0.20$.

4.9.2. Multinomial logistic regression

4.9.2.1. PGIC category outcomes

The PGIC categories for perception of change (1-7) were regrouped as: None (score 1, 2) Little (score 3, 4) Moderate (score 5) Much (score 6, 7). Multinomial regression was used to identify those baseline factors that produced the optimum predictive model. Assumptions were checked and violations noted with summary. Two models were constructed to identify those factors which best predicted the positive categories, Moderate (=5) and Much (>5) into which responders are likely to fall based on baseline factors when compared to no change (none) category. Given the relatively small sample size these models were taken as a guide for discussion. Future larger studies are needed to provide more robust data.

Table 4-19. Predicting PGIC 'Moderate' change versus 'No' change category

Base = No change		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Moderate Change	Intercept	0.13	1.25	0.01	1	0.92			
	Denial	0.86	0.35	6.19	1	0.013	2.37	1.20	4.66
	Behavioural disengagement	-0.59	0.31	3.67	1	0.055	0.56	0.31	1.01
	[MT_Y=.00]	-4.90	1.51	10.52	1	0.001	0.001	0.00	0.14
	[MT_Y=1.00][a]	0[b]			0				

a = group M b = redundant as is comparator

The main predictors of gaining "Moderate" improvement were: MT therapy plus 'care as usual' (Group M), Denial and Behavioural disengagement score. The predictors in the model for "Much" improvement were: MT therapy plus (Group M), Planning and ASC.

These results (Table 4.19) suggest that participants in Group M were statistically significantly more likely to be in the Moderate PGIC group compared to Group C, with almost no increase in the probability of being in the moderate category in Group C. With increasing denial score there was a significantly more likely probability (137%) of participants being in the Moderate category compared to the no change (None) category.

Although just over the significance level (p=0.05) an increase of one unit in behavioural disengagement decreased the odds of the participant being in the Moderate compared to the No change (none) category by ~45%. This model successfully predicted 75% of the Moderate category, 11% of the Much, 20% of the Little and 84% of the No change category outcomes and had an overall success rate of 61.3% for all categories.

Table 4-20. Probability of PGIC 'Much' change versus 'No' change category

Base = None		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Much	Intercept	-5.75	2.23	6.64	1	0.01			
	Planning	0.63	0.30	4.48	1	0.034	1.87	1.05	3.33
	ASC	0.32	0.15	4.71	1	0.030	1.38	1.03	1.84
	[MT_Y=.00]	-4.63	1.56	8.81	1	0.003	0.01	0.00	0.21
	[MT_Y=1.00][a]	0[b]			0				

a = Group M b = redundant as is comparator

The best model for predicting the participants being in the PGIC "Much change" compared to the "No change" (none) category (Table 4-20) suggested that those participants in Group C had a significantly less (almost zero) probability of being in the "Much change" category those in Group M. The model also suggested that for each unit change in Planning and ASC there was an 87% and 38% greater probability respectively of being in the "Much change" compared to the "No change" category. This model predicted 56% of the Much change, 67% of Moderate change, 0% of the Little and 87% of the No change categories successfully and had an overall predictive rate of 64.5%.

4.10. Binomial logistical regression

The probability of predicting the outcome of treatment on a responder basis used binomial regression with the baseline characteristics as the variables. Variables were selected using a combination of evidence of impact on outcome from previous studies and the differences identified in Tables (4.21, 4.22). Assumptions for the regression included: A linear relationship between the continuous independent variables and the logit transformation of the dependent variable. No substantial multicollinearity and outliers, high leverage points or highly influential points. Any violations and how handled are listed with the model.

4.10.1. HIT6 responders combined group

A binomial logistic regression for HIT6 responders found that a model comprising treatment group, self-distraction, ASC and baseline HIT6 score affected the likelihood of being a HIT6 responder. A Bonferroni correction to p=≤ 0.05 was not applied in the model (Tabachnick & Fidell. 2014) as these findings were to be taken as a guide and correcting at this level may have removed potential important predictors. There was one standardized residual with a value of 2.3 standard deviations, which was kept in the analysis. The logistic regression model was statistically significant, $\chi^2(4) = 17.4$, $p = 0.002$.

The model explained 36% (Nagelkerke R^2) of the variance in responder group and correctly classified 77.4% of cases. Sensitivity was 89.1%, specificity was 43.1%. The baseline HIT 6 score was the only variable not to add significantly to the model (Table 4.21).

The odds of being responder decreased by 83% by being in Group C compared to Group M, whilst a unit increase in ASC decreased the odds of being a responder by 17% and a unit increase in self-distraction increased the odds of being a responder by 67%. The area under the ROC curve was .837 (95% CI, .738 to .936) (Figure 4.18.), which is an excellent level of discrimination (Yang & Berdine. 2017).

Table 4-21. Logistic regression predicting likelihood of being HIT6 responder

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.Exp(B)	
								Lower	Upper
Step 1[a]	HIT6_base	0.09	0.06	1.89	1	0.17	1.09	0.96	1.24
	MT_(Group C)	-1.79	0.81	4.88	1	0.03	0.17	0.03	0.82
	ASC	- 0.19	0.09	3.97	1	0.046	0.83	0.69	0.99
	Self_distraction	0.51	0.24	4.73	1	0.03	1.67	1.05	2.65
	Constant	-7.65	4.41	3.00	1	0.08	0.00		

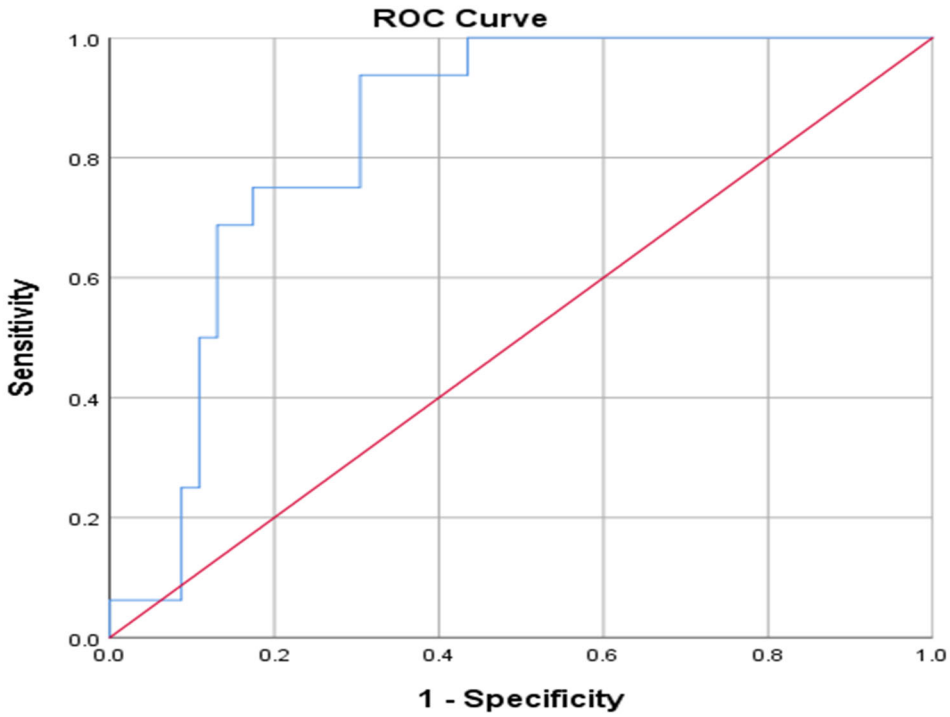

Figure 4-18. ROC curve HIT 6 responders

4.10.2. Patient global impression of change (PGIC) responders

A binomial logistic regression found that a model comprising treatment group, behavioural disengagement and denial affected the likelihood of participants being in a PGIC responder group. A Bonferroni correction to p=≤ 0.05 was not applied in the model (Tabachnick & Fidell. 2014) as these findings were to be taken as a guide and correcting at this level may have removed potential predictors. There was one standardized residual with a value of 2.2 standard deviations, which was kept in the analysis. The logistic regression model was statistically significant, $\chi^2(3) = 35.7$, $p < 0.001$.

The model explained 61% (Nagelkerke R^2) of the variance in responder group and correctly classified 85.0% of cases. Sensitivity was 80.1%, specificity was 88.1%. The three predictor variables were all statistically significant (Table 4.22).

Table 4-22. Logistic regression predicting likelihood of being PGIC responder

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for (Exp) B	
							Lower	Upper
Intervention (Group C)	-4.94	1.43	11.85	1	0.001	0.01	0.000	0.119
Denial	0.75	0.32	5.50	1	0.02	2.120	1.132	3.972
Behavioural disengagement	-0.48	0.24	4.19	1	0.04	0.617	0.389	0.979
Constant	0.19	1.06	0.03	1	0.85	1.215		

The odds of being a responder if in Group C decreased significantly by a factor of 0.01 compared to Group M. A unit increase in denial increased the odds of being a responder by 112%, whilst a unit increase in behavioural disengagement decreased the odds of being a responder by 38%. The area under the ROC curve was .91 (95% CI, .83 to .98) (Figure 4.19), which is an outstanding level of discrimination (Yang & Berdine. 2017).

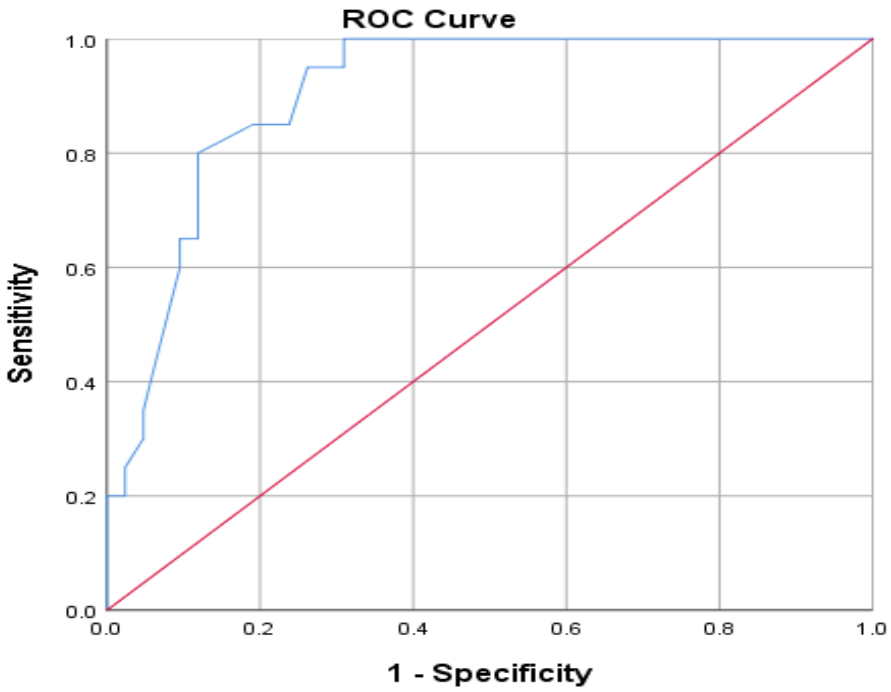

Figure 4-19. ROC curve PGIC responders

4.11. Baseline characteristics outside normal range

A number of baseline variables when present at above normative levels have been shown to be associated with poor treatment outcomes in migraine studies (Mathew et al. 2007; Schwedt et al. 2014; Schiano di Cola et al. 2019; Dominguez et al. 2019). These include depression, anxiety, medication over-use, allodynia and stress. Test of proportions or Fishers exact tests were used to compare the proportion of these variables in HIT6 and PGIC responder groups.

Table 4-23. Combined groups: PGIC Responders

Base line variable / Responder		Y	N	Chi square test of proportions (*Fishers exact test)
HADS_Depression Score (>10)	Y	6	8	*p =0.33 (n=62)
	N	14	34	
HADS_AnxietyScore (>10)	Y	7	17	p =0.68 (n=62)
	N	13	25	
Medication Overuse Present (Y/N)	Y	5	11	p =0.646 (n=53)
	N	14	23	
Allodynia (ASC) Score (>2)	Y	16	35	* p=0.735 (n=57)
	N	4	7	
Stress (PSS10) Score (>13.7)	Y	16	33	* p =1 (n=62)
	N	4	9	

There were no statistically significant differences in the proportion of scores above normative values in the PGIC responder/non responder groups for any of the variables (Table 4.23).

Table 4-24. Combined groups: HIT6 Responders

Baseline variable /Responder		Y	N	Chi square test of proportions (*Fishers exact test)
HADS_Depression Score (>10)	Y	2	12	*P=0.322 (n=62)
	N	14	34	
HADS_Anxiety Score (>10)	Y	8	16	*P=0.374 (n=62)
	N	8	32	
Medication Overuse (MO) Present (Y/N)	Y	13	29	
	N	8	3	*P=0.017 (n=53)
Allodynia (ASC) Score (>2)	Y	11	40	*P=0.151 (n=57)
	N	3	3	
Stress (PSS10) Score (>13.7)	Y	15	34	*P=0.154 (n=62)
	N	1	12	

In table 4.24 only medication overuse had a statistically significantly difference in proportions between HIT6 responder groups with less probability of being a responder if MO was present.

4.12. Summary

Table 4-25. Summary hypotheses			**Outcome**
Question one: Is manual therapy effective as an adjunctive to 'care as usual' in the treatment of females with chronic migraine?			H^0 outcome
Hypotheses (H^0)	1	*There is no difference in the between-group HIT6 change scores from baseline in the 'care as usual' (Group C) and the 'care as usual' with manual therapy' group (Group M)*	Rejected
	2	*There is no difference in HIT6 responder rates between Group C and Group M*	Rejected
	3	*There is no difference in the PGIC outcomes between Group C and the Group M*	Rejected
	4	*There is no difference in the MSQ2.1 domain outcome between Group C and Group M*	Inconclusive
	5	*There is no difference in the MSQ2.1 responder rate outcome between Group C and Group M*	Inconclusive
	6	*There is no difference in the frequency of headaches outcomes between Group C and Group M.*	Not rejected
	7	*There is no difference in the headache responder rate outcomes between Group C and Group M*	Not rejected
	8	*There is no difference in the mean intensity of headaches between Group C and Group M*	Not rejected
	9	*There is no difference in the use of rescue/acute medication outcomes between Group C and Group M*	Not rejected
	10	*There is no difference in the allodynia score outcomes between Group C and Group M*	Inconclusive
Question 2: Do female chronic migraine patients exhibit baseline characteristics that affect the treatment outcomes within and between treatment groups?			H^0 outcome
Hypotheses (H^0)	1	*Treatment outcomes are not affected by baseline characteristics*	Rejected
	2	*The probability of being a responder is not affected by baseline characteristics*	Rejected

CHAPTER 5 DISCUSSION

5.1. Introduction

The original idea for the study evolved from extensive professional experience working in the field of musculoskeletal therapy with people who had headaches and migraines. It became increasingly evident that the outcomes for people with certain headache types were consistently good, whereas with other types the results varied without an obvious reason. Those with migraine, particularly uncontrolled episodic or chronic migraine, experienced the least predictable response.

Prior to undertaking this study, a narrative literature review explored the current state of research in the area of MT and headaches both generally and, more specifically, chronic migraine (Chapter 1). This review provided evidence that there was both a biopsychosocial and pathophysiological basis for investigating the use of MT in the treatment of chronic migraine. This evidence suggested migraine is a neurological condition with multiple-factorial drivers and consequently likely to benefit from a multi-modal approach to treatment including physical therapy and psychotherapy (Nicholson et al. 2007; Gaul et al. 2011; Diener et al. 2015; Gaul et al. 2016). Following this, a systematic literature review was undertaken that identified a limited base of existing research. No studies of MT and CM had attempted to assess the effect of ‘care as usual’ i.e. Botox and adjunctive MT, compared to Botox alone, and none had focussed solely on the primarily affected population, i.e. females.

Only two studies describing MT as an adjunctive intervention with chronic migraine were identified: a three-arm RCT (Cerritelli et al. 2015) and a two-arm pilot RCT (Gandolfi et al. 2017). Neither study reflected current clinical practice in the UK, where most CM patients in tertiary care are managed with the existing ‘gold standard’ treatment, i.e. Botox. Despite receiving Botox, the outcomes in these patients can be extremely variable, with a significant proportion remaining severely affected (Silberstein et al. 2014; Ahmed & Gooriah. 2015; Sarchielli et al. 2017). This may have been due to the multi-factorial nature of chronic migraine and the limited use of multi-modal interventions. Since both CM studies identified in the literature review demonstrated positive results in the use of adjunctive MT, the question raised was whether the outcomes from the ‘care as usual’ intervention (i.e.

Botox) might be improved with the use of adjunctive MT rather than MT as an alternative competing mono-therapy.

As a result of the narrative literature review highlighting the low quality of many MT and headache studies, this study was designed as an adjunctive RCT methodology to mitigate some of the quality issues e.g. heterogeneity of participants, lack of detail on interventions, missing sample size calculations (Fernadez-de-las-Penas 2006; Carod-Artal 2014). The design comprised a pragmatic methodology, reflecting normal clinical practice and followed CONSORT and IHS guidelines (Boutron et al. 2017; Tassorelli et al. 2018). It recruited only female CM participants undergoing Botox treatment from a specialist tertiary headache clinic, representative of the most affected group of migraine patients (Jelinski et al. 2006; Buse et al. 2012; Dodick et al. 2016; Deneris et al. 2017). For the purpose of this study, 'care as usual' in this study was treatment with OnabotulinumA (Botox (R)) given as per the PREEMPT protocol (Appendix 12a): this is currently the gold standard for CM in the UK (NICE.org. 2020). Manual therapy was defined as a hands-on approach utilising mobilisation, manipulation and soft tissue work singly or in combination (Bronfort et al. 2010).

Accordingly, this study's methodology used outcome measures recommended by the IHS guidelines, reflecting those used in major CM studies (Tassorelli et al. 2018) and recruited participants with CM being treated with a defined intervention (Botox) in a tertiary clinic setting.

The research questions addressed in this study are:

> ***Question one: Is manual therapy effective as an adjunctive to 'care as usual' in the treatment of females with chronic migraine?***
>
> ***Question two: Do female chronic migraine patients exhibit baseline characteristics that affect treatment outcomes within and between treatment groups?***

The terms 'the study' or 'this study' in this chapter refer to the data collected as part of this RCT and reported within this thesis.

This chapter begins with a discussion of the baseline characteristics of the two groups in the context of successful randomisation, moves on to explore differences between this and other studies, and follows with a discussion of the findings in relation to the research questions and their null hypotheses (for a reminder of the hypotheses, see Chapter 4, section 4.12). The chapter concludes with implications for clinical practice, challenges and the strengths and limitations of the study.

5.2. Group characteristics

One of the reasons for an RCT is to achieve a balance in participants' characteristics between treatment arms at baseline, facilitating more accurate comparisons of outcomes between groups and with similar studies (Efird 2010; Spieth et al. 2016).

This study differs to other CM studies by involving only females whereas the majority of CM studies have a small proportion of between 10% and 20% male participants (Lipton et al. 2016; Tepper et al. 2019). This typical balance was reflected in Gandolfi et al. (2017), but differed significantly from Cerritelli et al. (2015), in which the male proportion varied between 23% and 43% in the three groups. This is an important difference, as males are thought to differ from females in presentation and responses to migraine and other pain conditions (Buse et al. 2013; Sorge & Strath. 2018). As such, the outcomes of mixed-sex studies may not be generalisable to either sex and may explain some of the differences in outcomes between studies (Peterlin 2011).

The average age of the participants in this study was 44.7 years, typical of the majority of chronic migraine studies where mean ages vary between 41 and 51 years (Lipton et al. 2016; Washington State Health Care Authority. 2017; Tepper et al. 2019; Ahmed et al. 2019). This age range was expected since the majority of migraine sufferers are often initially misdiagnosed (Dougherty & Silberstein. 2014) and consequently not diagnosed with CM until they are in their mid 20's, after which they must wait several years to access to the 'gold standard' of the time (Dodick et al. 2016). However, in Cerritelli et al. (2015), the average age was less than 40 years; this difference in average age may have been a contributing factor in outcome variations between this study and Cerritelli et al. (2015).

In this study, there was a statistically significant difference at baseline between the control, Group C, and the intervention, Group M, in the proportion of participants in the HIT6 severe category. Despite this, both groups had a high proportion in the severe category and were typical of the majority of people recruited to CM studies with Botox as an intervention (Frampton & Silberstein. 2018; Lipton et al. 2019). However, in people using Botox for the first time there is often a 30% reduction in the proportion of those in the severe category, with further reductions in cycles two and three of the Botox intervention, until a stable level is reached (Silberstein et al. 2014; Guerzoni et al. 2017). All of the participants in this study had between three and 20 (median nine) cycles of Botox treatment and thus confirmed that participants were in a stable treatment state, as intended in the methodology. Furthermore, the participants were also representative of the most refractory migraineurs with potentially unidentified and/or unaddressed underlying biopsychosocial co-morbidities that may limit further improvement (Schiano di Cola et al. 2019; Ozge et al. 2018; D'Antona & Matharu. 2019). Therefore, any change in HIT6 score /response was likely linked to the intervention.

There were two important baseline outcome variables with a statistically significant difference between the two groups: HIT 6 score and Emotional Function (MSQ2.1).

The mean baseline HIT6 scores in groups M and C (66.4 and 62.1) respectively indicated that Group M was slightly more disabled than Group C. However, while both group scores were in the severe HIT6 category, consistent with major pharmacological studies of CM (Washington State Health Care Authority. 2017), they were not consistent with the participants in Cerritelli et al. (2015). The mean HIT6 scores in the Cerritelli groups range from 58.5 to 59.9 which is not in the severe HIT 6 category, suggesting that the participants were not in the same refractory state as those in this study, highlighting another potential reason for differences in outcomes. In contrast, the HIT 6 scores of 62 (severe category) in Gandolfi et al. (2017) were similar to this study.

The greater similarity of Gandolfi et al (2017) HIT6 scores to this study may have been due to Gandolfi following IHS guidelines on inclusion and exclusion criteria, as did this study, whereas Cerritelli et al (2015) did not appear to have done so. This highlights the importance of following guidelines in future studies to enable useful comparisons.

The MSQ2.1 sub domain of Emotional Function had a marginal statistically significant difference between groups, indicating that Group M was slightly more disabled than Group C as a result of feelings of frustration and helplessness linked to their migraine. However, these baseline factor measures were consistent with large CM studies and represented substantial disability (Blumenfeld et al. 2010; Bagley et al. 2011; Rendas-baum et al. 2012; Dodick et al. 2015; Lipton et al. 2016).

In summary, despite the slight baseline differences, the characteristics of both groups were relatively balanced and both groups comprised severely disabled participants consistent with a wide range of previously published CM studies. The relatively small sample size may have had an impact on the final balance between the groups' baseline characteristics but overall, the outcome demonstrated that the randomisation process worked well.

5. 3. Clinical effectiveness: Primary outcome

RQ1: Is manual therapy effective as an adjunctive to 'care as usual' in the treatment of females with chronic migraine?

5.3.1. Change in HIT6

The primary outcome measure was the between group difference in HIT 6 change scores with an initial hypothesis H1(0) that there was no difference between the two groups.

Although the HIT6 outcomes were positive for Group M, and the statistical power approximately 80%, some authors consider that the evaluation of treatment effect in clinical studies should examine the effectiveness of a treatment based on a broader evaluation. This includes clinical significance, effect size and confidence intervals rather than simply a-priori power and statistical significance (Sullivan & Feinn. 2012; Page 2014; Nahm 2017).

In this study the between-group difference in HIT6 change score was greater than the MCID, with the point estimate and confidence interval in favour of Group M (Figure 5.1) and a moderate effect size. This result is also of the same order as the Botox PREEMPT 1 and 2 studies in CM that reported smaller positive differences in change scores in HIT6 between Botox and placebo but with smaller confidence

intervals, as a result of a much larger sample (Aurora et al. 2010; Diener et al. 2010). A recent systematic review also reported statistically significant differences in HIT 6 change scores with migraine and other primary headaches that favoured MT in line with this study, although caution was noted due to the low quality of evidence (Falsiroli Maistrello et al. 2018) (Figure 5.1).

This result suggests that being in Group M is moderately more beneficial than being in Group C for females with CM and, being of the same order as, concurs with other CM studies.

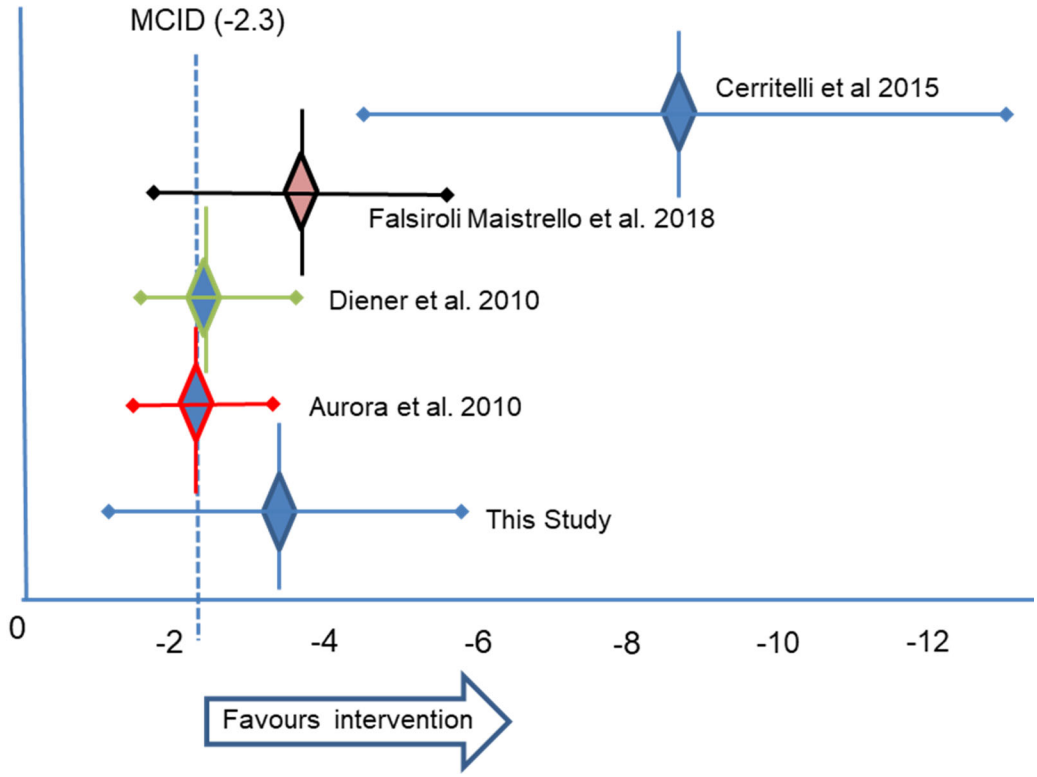

Figure 5-1. CM studies. HIT6 change differences (with 95% CI)

The only adjunctive MT study into CM for which a direct comparison can be made to this study is Cerritelli et al. (2015); although Gandolfi et al. (2017) used an adjunctive treatment approach and reported a non-significant change in HIT6 it did not have a 'care as usual' comparator. Cerritelli et al. (2015) reported much greater difference in change score for HIT6 between the ‘care as usual’ control group, and the MT plus ‘care as usual’ in favour of the MT (Fig 5.1).

The significantly greater difference in the HIT6 change between groups reported in the Cerritelli et al. (2015) study raised questions as to why it was much greater than

both this study and major pharmaceutical studies against placebo. Risk et al. (2019) also questioned the extent of the effect size found in the Cerritelli et al. (2015) study in their systematic and meta-analysis review of SMT and migraine, and decided to exclude it from their final analysis during peer review. Some of the differences between Cerritelli et al. (2015) and this current study, which may provide an explanation for these substantial differences, will now be explored, including the participant characteristics, the study design and the method of analysis.

Firstly, the HIT6 MCID is normally calculated on the absolute difference in change (gain score) between groups (Deiner et al. 2010) whereas Cerritelli et al. (2015) chose to use ANCOVA, adjusting for multiple baseline covariates except, unusually, the baseline HIT6 which is recommended by the CONSORT guidelines (Boutron et al. 2017). This approach answers a different statistical question about “the difference between final measures, based on starting at the same theoretically calculated baseline” (adjusted for covariates). If the standard approach, used in the majority of CM studies, had been used this would have reduced the difference only slightly to 8.3 (Royale et al. 2011).

One argument is that ANCOVA is statistically more valid than an absolute gain score in a randomised trial (Fitzmaurice 2001), another is that experimental design and research question matter more in terms of the test used (Petscher & Schatschneider. 2011; Smolkowski 2019). However, the importance here is that it highlights the need for guidelines on how data are collected; results analysed and presented for comparative purposes in future MT headache studies. In this study, both the absolute and ANCOVA results were provided and demonstrated a statistically and clinically significant difference with both analytical approaches, highlighting the stability of the outcome.

Other factors that may have influenced the difference in HIT6 outcome measures in this study, when compared to both Cerritelli et al. (2015) and the PREEMPT CM Botox studies (Aurora et al. 2010; Diener et al. 2010; Lipton et al. 2016), include the study duration, participant selection, medication/dosage and intervention frequency.

Both this study and Gandolfi et al. (2017) were of 12 weeks duration (one Botox cycle) compared to Cerritelli et al. (2015) and the PREEMPT (Aurora et al. 2010; Diener et al. 2010; Lipton et al. 2016) studies which were 24 weeks. The CM PREEMPT studies used naïve participants and two cycles of Botox, 24 weeks, i.e.

potentially benefitting from the early stage repeated dose effect. An inclusion criterion for Cerritelli et al. (2015) was that the acute or prophylactic intervention had to be stable for only four weeks, thus the longer study period of 24 weeks may have also enhanced the repeated dose/temporal effects that have been shown to exist for CM medications over the initial cycles (Silberstein et al. 2014; Silberstein 2016; Guerzoni et al. 2017).

This current study involved the most refractory CM participants thus limiting the potential for change; the participants in Cerritelli et al (2015) were generally less disabled and younger, suggesting some may not have CM or had a strong component of cervicogenic or tension-type headache, which have shown to be amenable to MT (Clar et al. 2014; Wandereley et al. 2015; Espi-Lopez et al. 2016; Ferragut-Garcias et al. 2017).

The composition of the groups in Cerritelli et al (2015), having higher than typical proportion of male participants, may have also influenced the group outcomes. The current consensus is that males and females experience pain differently, including headaches, although the mechanisms and factors involved have yet to be fully elucidated (Popescu et al. 2010; Buse et al. 2013; Scher et al. 2018; Sorge & Strath. 2018). No studies could be found that reported how males and females differ in outcomes to treatment with MT or Botox regardless of having CM. However, two studies involving physical and psychological therapy identified that males were less likely than females to benefit from interdisciplinary programmes for chronic pain (Burns et al. 1996; Racine et al. 2019). Coeytaux et al. (2006) also found that males had a significantly lower reduction in HIT6 change than females when comparing 'care as usual' and 'care as usual' combined with acupuncture. This may explain why the control group in Cerritelli et al (2015) with 42% males performed worse than the MT group with only 23% males and potentially increased the HIT6 difference outcomes. The gender difference in treatment effect is an area that warrants further investigation.

Cerritelli et al. (2015) further increased the potential differences for change between groups compared to this study and that of Gandolfi et al. (2017) by not presenting the medication or regime used in the groups. This meant that each group potentially had different medications, with those in the worst performing groups possibly on the least effective medications, and more in the MT group on the gold standard, including topiramate and Botox. In addition, unlike this study and that of Gandolfi et

al. (2017), Cerritelli et al. (2015) allowed the control group to change their medication regime throughout the study as directed by the physician whereas the MT group were not. This introduces a potentially significant confounder to the Cerritelli et al. (2015) study outcomes, as the control group may not have benefitted from the long-term effect of medications and may have been negatively impacted by the changes, thus artificially increasing the reported differential benefit of the MT group.

Cerritelli et al. (2015) also excluded participants with medication overuse headaches and significant psychological signs on examination. There is no specific detail whether this meant anxiety, depression or other common comorbidities or how they were evaluated by the physician. The PREEMPT studies (Aurora et al. 2010; Diener et al. 2010; Lipton et al. 2016) also exempted those overusing opioids and anyone with a score ≥ 24 on the Beck depression inventory or with fibromyalgia.
In contrast, neither this pragmatic study nor Gandolfi et al. (2017) screened participants for any common comorbidities (except known severe uncontrolled psychiatric conditions) or medication overuse prior to randomisation as the study was designed to examine treatment response in patients attending a typical tertiary clinic, and likely to be most chronic and least responsive to existing treatments. This is important; a relationship between medication over-use and psychological co-morbidities has been proposed, with them both independently and jointly established as risk factors in chronification and reduced treatment response (Negro & Martelletti. 2011; Riederer et al. 2013; Biagianti et al. 2014; May & Schulte. 2016; Bottiroli et al. 2017; Seng et al. 2017).

This study used one chiropractor compared to Cerritelli et al. (2015) which involved six osteopaths. Importantly, no details were provided on variations in outcomes between osteopaths in each group. Whilst this study had less participant contact than Cerritelli et al. (2015), the frequency of five MT sessions in 12 weeks versus eight in 24 weeks, was higher than Cerritelli et al. (2015). However, Pasquier et al. (2019) concluded that, whilst further study is required, the frequency of spinal manipulative therapy (SMT) did not significantly influence the clinical outcomes during or following SMT treatment period. The effect of treatment dose with MT therapy in CM is an area for future research.

In summary, the greater between group differences in HIT6 mean change seen in Cerritelli et al (2015) when compared to this study can be explained by a number of factors, although both studies favour MT an adjunctive intervention in CM.

5.3.2. HIT 6 responder rates

The secondary group of hypotheses in research question one considered the outcomes of the within-individual changes or responder rates.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group emphasised that the interpretation of results of randomised trials of treatments for chronic pain involve two components: interpreting the clinical importance of both group differences, and the individual patient improvements. Part of the rationale for responder analysis is that the change in group means downplays individual patient improvements and, to really understand the therapeutic benefit associated with a treatment, a broader overview should be taken. The responder rate analysis for all outcome measures requires an MCID and there are also differences in the values of MCID at the group mean difference level and at the individual level responder level (with-in individual) which require different calculations to establish clinical benefit of one treatment over another. However, neither identifies which participants are likely to benefit more from each treatment as each group was only exposed to a single intervention. Conversely, reporting only the difference in proportions responding can also be misleading since it may be possible that many of the responders needed only a small improvement to tip over the MCID. There is also the question of the value of the dichotomised variable i.e. the cut off from non-responder to responder. In the absence of a validated MCID for a measurement instrument the value may be arbitrary and not clinically significant. Therefore, the balance was struck by presenting each group means difference outcomes against MCID and individual outcomes against MCID to gauge overall statistical and clinical patient benefit. (Snapinn and Jiang. 2007; Dworkin et al. 2008, 2009; Moore et al. 2009; Cates & Karner. 2015)

The within-individual MCID for HIT6 used was as 3.7 (Coeytaux et al. 2006) and can be used to assess if an individual participant has experienced a meaningful improvement in their headache condition. In this study the figure used was ≥ 4 as the HIT6 change results were expressed as a whole number.

However, in Lipton et al. (2014), the proportion of responders decreased after the first and second cycle of Botox until only 7.5% responded by cycle three, leaving almost 25% as non-responders. Other studies have also concluded that there are approximately 30% non-responders to Botox after approximately four cycles (Cernuda-Morollón et al. 2014; Matharu et al. 2017; Parrales Bravo et al. 2018). Given the high proportion of participants in this study categorised, by the HIT6 score, as severely affected, it is probable that the majority of the were poor responders to Botox since the median number of cycles of Botox was nine, with a minimum of three in Group M and four in Group C. A similar effect may have accounted for the small mean change in HIT6 in Gandolfi et al. (2017) where the median number of Botox cycles was six with a range of three to ten. Thus, the participants in both this study and that of Gandolfi et al. (2017) could be classed as having refractory chronic migraine, and consequently less likely to benefit from ongoing treatment (Guerzoni et al. 2017; D'Antona & Matharu. 2019). This situation would also suggest any difference in this study was treatment effect.

The results in this study demonstrated a statistically significant 30% difference in proportion of responders in Group M compared to Group C (Table 4.6). It was not possible to compare this result with Cerritelli et al. (2015) or Gandolfi et al. (2017) as neither presented HIT6 responder figures, and a meaningful comparison to other Botox studies in CM was confounded by their use of an MCID of ≥5 which is not a recognised MCID and would favour CM patients who are naïve to Botox rather than long term users.

The difference between Group M and Group C responder rates was not only statistically, but clinically, significant as it represented a change in a group of patients that are likely to have been classified as non-responders in much larger Botox studies. However, as with the change in HIT6 score, there was the likelihood that responder rate outcomes were due to the placebo effect which is known to be high in all headache studies (de Groot et al. 2011; Hougaard & Tfelt-Hansen 2016). The exact mechanism of placebo in headache is unknown, although it has been postulated that there are three components of treatment effect (Speciali et al. 2010). One is the specific effect on the mechanism of headache, the second a placebo effect linked to the idea of having had the known treatment and finally a non-specific psychological covert intervention, such as empathy, listening, understanding.

An aspect of all MT interventions often cited as a source of placebo, is physical touch despite the evidence in headache studies being inconclusive (Autret et al. 2012; Benedetti. 2014; Meissner et al. 2013

Consequently, to minimise the potential differential placebo effects, this study attempted to reduce the difference between the groups in social interaction and the project team by making weekly contact with all participants for data collection. This was helped by all participants having a strong relationship with the headache nurse, built over a number of years with an expectation of benefit from Botox every 12 weeks. Schwedt et al. (2007) highlighted factors associated with increased placebo in migraine prophylaxis treatment that included younger age, lower severity and being male (odds ratio of placebo response 5.8 times that of females).

Although the relative values of these factors in this study should have decreased the placebo effect compared to Cerritelli et al. (2015), and minimised it in overall terms, the exact extent of the placebo effect in either study cannot be ascertained.

Whilst a ‘novel’ or new treatment is thought to increase the placebo effect, the novelty or newness itself is not the factor in question, it is the construct of the novelty which drives the expectations of the participant. For example, a new procedure with a dramatic delivery (injected, sham surgery or involving more complexity) is likely to create a greater placebo effect than a new drug with a normal delivery (Hedges and Burchfield. 2005; Lipton et al. 2020).

In this study the participants were all aware of MT and some had tried it before and so although the ‘newness’ factor was not high; the expectation factor may have added to the effect. However, since there was little difference between groups for many of the common outcome measures, such as headache frequency and intensity, this would tend to suggest a limited additional placebo effect over and above that of the botox injections.

However, whilst one view is that placebo controlled trials establish whether a new intervention is better than ‘care as usual’ by more than a placebo, there is an alternative view: If adding a new intervention to ‘care as usual’ is better than ‘care as usual’ alone - even if the element of placebo cannot be measured - then is it right to withhold the treatment from patients that it may benefit, particularly if few other options are available and risks are low (Avins et al. 2012)?

In this study, the participants fitted the criteria for the most affected, refractory, chronic migraine patients and consequently most resistant to treatment with few other options. The difference in HIT6 responder rates was statistically and clinically significant in favour of Group M. In summary these results suggest a potentially beneficial treatment effect for those females most severely affected by CM with the use of MT as an adjunctive therapy to Botox.

5.4. Research question one: Secondary outcomes

Guidelines for CM studies (Tassorelli et al. 2018) recommend the use of a number of outcome measures that reflect the change in disability felt by those with CM, and consequently, the success of an intervention. In this study the main outcome measures included Patient Global Impact of Change (PGIC); the Migraine Specific Quality of Life (MSQ2.1); frequency of headaches; use of rescue/acute medication and change in allodynia.

As such there are hypotheses to be considered for each outcome (section 4.12). *The generic null hypothesis H(0)n: There is no difference between the [measurement] outcomes for 'care as usual', Group C and 'care as usual' with Manual Therapy, Group M.*

5.4.1. Patient Global Impression of Change (PGIC)

The proportion of much or very much improved PGIC outcomes (responders) in Group M was 59%, equalling the best of the new calcitonin gene related peptide (CGRP) medications (Lipton et al. 2019) and significantly higher than Group C, at 10%. The PGIC is a well validated instrument for examining the patient's perception of how they have improved after an intervention. It has been used in a wide range of chronic pain studies, is recommended by IMMPACT (Dworkin et al. 2008) for clinical trials in chronic pain and was recommended in the latest CM trial guidelines as a secondary outcome (Tassorelli et al. 2018). Despite this, in the original literature search, the author was unable to find the PGIC used in any major CM or migraine study, whether or not MT was involved, against which to compare the outcomes of this study. In a subsequent search, one recent trial of Eptinezumab, a new calcitonin gene related peptide (CGRP) for CM (Lipton et al. 2019), was found to have used the PGIC. This was a large study, involving 92 sites around the world with 1072 participants. The PGIC responder rates for the medication and placebo were 59% and 32% respectively.

As with all patient reported outcomes, the placebo effect is a consideration and, although a completely different study to this one, some aspects of the Lipton et al (2019) design were reported to have increased the chances of a higher responder rate due to the placebo effect. These included; the novelty and administration of the treatment, with evidence suggesting that a more dramatic intervention increases the placebo effect (Meissner et al. 2013; Dodick et al. 2019); and importantly, 54% of participants were naïve to the treatment and may have had CM for only one year, which provided the opportunity for greater expectancy from a new medication, reinforced by the higher early phase response (Guerzoni et al. 2017). There was also intensive patient contact with migraine experts during the trial that included supervised intravenous administration and frequent contact by telephone and face to face. Additionally, the PGIC was recorded every 4 weeks rather than once at the end of the 12-week intervention period, as in this study, and potentially increased the placebo response through learning mechanism (Bishop et al. 2016).

These reported effects are not as relevant to this PhD study and consequently suggest that the 59% responder rate in this current study may have benefited less from placebo effect than the Eptinezumab study.

As a comparative, the difference between placebo and the Eptinezumab responder rates was 27% compared to 49% in this study, assuming an additive model of placebo (Enck et al. 2011). Therefore, taking into account a placebo response, the PGIC outcomes in this study were consistent with existing, albeit limited, findings from large clinical studies and in favour of MT as an adjunctive to Botox.

5.4.2. Migraine Specific Quality of Life (MSQ2.1)

The MSQ2.1 measures how migraine impacts on the participant's life using 3 domains: Role restriction (RR): Do migraines reduce involvement in social and work activities; Role prevention (RP): Do they prevent these activities, and Emotional freedom (EF): How emotions are involved with migraines. A higher score (range 0-100) reflects a better the quality of life. Cerritelli et al. (2015) did not use the MSQ2.1 so a comparison cannot be made, although many Botox studies have used MSQ2.1 and can provide a comparison to the differences between groups M and C to evaluate the study outcomes.

The mean baseline domain scores (RR, RP and EF) for both groups in this study were consistent with initial MSQ2.1 validation studies, CM-Botox studies and the latest CRGP studies (Bagley et al. 2012; Rendas Baum et al. 2013; Tepper at al 2019) and female only studies (Talarska et al. 2014). The mean within-group changes from baseline were small compared to the major Botox studies (Frampton 2012; Silberstein et al. 2013; Aurora et al. 2014) suggesting a negligible benefit for both groups. However, difference between group means for role restriction (RR) exceeded the clinically meaningful difference, and placebo differences in recent studies of new CM medications (Detke et al. 2018), in favour of Group M.

These results were surprising as the expectation was that Botox alone (Group C) outcomes would improve the MSQ2.1 score, as was the case in almost all studies of Botox referenced above. One explanation is that it may reflect both the stable and refractory nature of the participants. This is supported by long term studies of Botox in which the difference in MSQ2.1 change between Botox and placebo in all domains is insignificant after 4 to 5 cycles (Aurora et al. 2013) despite having started with large change differences. This suggests that the MT did have a small positive effect over and above Botox on Group M participants' daily social and work-related activities (RR).

However, conversely, the long-term reduction in difference between groups (Aurora et al. 2013), did not appear to be true of the MSQ2.1 responder rate. The proportion of responders (those exceeding the with-group MICD) was almost 50% for each domain in Group M; statistically significantly different to a responder rate of approximately 20% for RR and EF domains in Group C.

Although this type of responder analysis is often completed for HIT6, figures for MSQ2.1 are rarely reported which limits any comparison to other studies. In a systematic review involving 35 studies associated with CM, no examples of this analysis could be found (Washington State Health Care Authority. 2017) and the latest Botox studies failed to produce comparative or placebo MSQ2.1 responder rates (Blumenfeld et al. 2015; Young et al. 2019; Ahmed et al. 2019). Why this is the case is unknown, but it identifies an area for consideration in future analysis, given that MSQ2.1 is widely used and has validated within and between group MCIDs (Tassorelli et al. 2018). However, the MSQ2.1 responder rates in this study tend to support the view that the quality of life was improved clinically and statistically in a greater proportion of Group M participants than Group C.

5.4.3. Medication usage

A reduction in use of acute medication is recommended in the IHS guidelines (Tassorelli et al. 2018) as a secondary outcome measure. The monthly medication usage from the diary was analysed to identify whether there was a change between groups in the use of acute medications and to calculate medication over use headache (MO) in participants.

The analysis showed a non-significant drop in usage of acute medication in both groups with no statistical difference between groups. This was consistent with Gandolfi et al. (2017) but could not be accurately compared to Cerritelli et al. (2015) as only the number of participants using medications was recorded in their study.

However, even on this basis, the result of this study appeared to differ markedly from Cerritelli et al. (2015) in which 80% of the MT group stopped using acute medication altogether compared to none of the 'care as usual'. The Cerritelli et al. (2015) result for the MT group was also far superior to the pooled analysis of three major Botox studies which reported a non-significant reduction in both acute medication and change from placebo (Washington State Health Care Authority 2017). It also differed to a study comparing MT to amitriptyline, in which there was a reduced usage overall but no significant difference between groups (Nelson et al. 1998). The reason why the MT group in Cerritelli et al. (2015) differed so much from its own control and sham groups, as well as from this current and other studies, cannot be ascertained exactly. However, it is likely a combination of the differences in participant characteristics between studies and between groups in Cerritelli et al. (2015) and also a failure to record how many days and what type of medication was used, as recommended in CM trials (Tassorelli et al. 2018). Other potential explanatory factors include an overall lower disability in Cerritelli et al. (2015) and therefore less dependency on acute medications (Mehuys et al. 2012), a lower percentage of males (in MT) which would tend to decrease the likelihood of medication over use (Schwedt at el. 2018), and the exclusion of participants with psychological signs, who tend to use more medication and be more dependent (Bendtsen et al. 2013; Kristoffersen et al. 2015). The results of this current study are consistent with Botox studies and did not provide support for the view that adjunctive MT reduces acute medication use over and above the use of Botox alone. However, the differences between Cerritelli et al. (2015) and other studies highlights the need for future MT studies to follow guidelines to enable better comparison of outcomes.

5.4.4. Medication over use headaches (MoH)

The diary data were also used to calculate the presence of MoH which is considered one of the risk factors in the chronification and poor treatment response in CM (May & Schulte. 2016; Vandenbussche et al. 2018). Overall, a third of participants were classed as having MoH with no significant difference between groups. These findings were consistent with other studies of CM which have suggested that between a third and two thirds of those with CM have MoH (Natoli et al. 2010) and even after detoxification between 20% and 40% of CM patients have MoH (Biagianti et al. 2014).

Some studies have proposed that Botox reduces the use of acute medications, both in those with MoH and in those without (Silberstein et al. 2013), whilst others' views are that it does not help any more than placebo when MoH is present (Olsen 2012; Pijpers et al. 2019). Although Chiang et al. (2017) highlighted the heterogeneity in design and reporting between MoH studies as a cause for the differences, there is agreement that in the long term (>2 years) a cohort of patients still exhibit MoH regardless of withdrawal therapy, the use of Botox, or a combination. Although a small study, Schiano di Cola et al. (2019) concluded that after 3 cycles of Botox almost half of the participants still had MoH. In this study the presence of medication overuse was also the only single baseline factor that reduced the probability of participants being a HIT6 responder regardless of intervention which concurs with existing CM Botox studies as to its effect on outcomes.

The findings from this analysis suggested that the participants in this study were the most refractory to Botox treatment (Negro et al. 2015) and that there was no adjunctive benefit from MT, for long-term users of Botox, in reducing the proportion classified as having MoH.

5.4.5. Headache days

The IHS guidelines (Tassorelli et al. 2018) for CM trials recommend the change in number of headache days per month be used as a primary outcome measure and if not, then as a secondary outcome along with the responder rates based on change in intensity of headaches. In this study, diary data over the 12 weeks collected mean headache frequency and intensity, from which responder rates were calculated.

There was no statistically significant difference in the change in mean headache frequency per week between groups and, although the frequency decreased and remained lower than baseline in both groups, there was not a statistically significant change over the 12 weeks.

There was no significant difference between this study and Gandolfi et al. (2017) in the baseline frequency of headaches days per month. In contrast, Cerritelli et al. (2015) reported significantly higher baseline monthly frequencies of *migraine days* in the MT and control groups than the *headache days* in both groups in this study. The author could find no CM study that reached the mean number of migraine days per month cited in Cerritelli et al. (2015). This level of migraine day frequency was also at odds with the mean HIT6 scores reported by Cerritelli et al. (2015), which were lower than all major CM studies investigated, Gandolfi et al. (2017) and this study.

However, regardless of migraine or headache days, in the MT group there was a surprisingly large, 70%, reduction in days per months down to 7 migraine days per month at week 12 and 95% reduction to 1.2 days per month in 24 weeks (Cerritelli et al. 2015). In comparison this study had approximately seven percent reduction in headache days for groups M and C over 12 weeks, with less than one percent reduction reported by Gandolfi et al. (2017). The reduction in Cerritelli et al. (2015) was also significantly greater than those reported by major Botox CM studies where, despite high baseline migraine days, the reduction was only 36% over 24 weeks for headache days (Blumenfeld et al. 2018) and 40% over 12 weeks (Pijpers et al. 2019). A systematic review reported that the mean change with Botox compared to placebo was only three headache days per month over 12 weeks (Herd et al. 2019). One longer term CM Botox study produced similar reductions to Cerritelli et al. (2015) but over 36 weeks and in a group of known responders which added a large selection bias (Vikelis et al. 2018).

Although it was possible that the mode of MT in Cerritelli et al. (2015) had a much greater effect on the number of headache and/or migraine days than the MT in this study, or than medications in pharmacological interventions for CM, there are other possible explanations for these large differences in both baseline and change. The definition of migraine days given to, or used by, the participants may have been subject to recording error with participants recording a mixture of headache and migraine days, which has been the subject of discussion (Tassorelli et al. 2018). Also, the lower mean HIT6 baseline scores in Cerritelli et al. (2015) was suggestive

of participants with episodic migraine and/or mixed headaches (Buse et al. 2011). These, by their nature, would have altered in the 24 weeks, and may have shown a greater response to MT and or medications. In addition, no details on the 'care as usual' intervention were provided which may have been a major confounder. However, some of the differences between this study and Cerritelli et al. (2015) might reflect a smaller sample size. These potential explanations raise the issue of consistency, clarity of measurement and reporting in CM studies to enable accurate comparisons between studies.

Whilst the changes in outcomes of this study were less than the major CM studies, this was not surprising since these larger Botox CM studies have the greatest reduction in headache and migraine days during the first two cycles of treatment. This study comprised participants with long term Botox use, a group in which stabilisation has occurred, with a non-significant change from one cycle to the next after 6 cycles/18 months (Guerzoni et al. 2017; Vernieri et al. 2019; Pijpers et al. 2019).

Both groups in this study had the most significant drop in headache days between weeks one and four, with the decrease in Group M marginally statistically greater, albeit with a very small effect size. This is consistent with other studies where the largest reduction in number of headache days was seen over the first four weeks (Dodick et al. 2010; Blumenfeld et al. 2018; Pijpers et al. 2019). Some authors have concluded this is a placebo effect (Aurora et al. 2010; Cernuda-Morollon et al. 2015). If this was the case, then it was an interesting outcome as it would seem to indicate that the Group M did not have a significant additional placebo effect over and above that of Group C, which conflicts with some theories of placebo in MT but is consistent with the PGIC responder placebo theory posited earlier in this study (Autret et al. 2012; Benedetti.2014; Meissner et al. 2013).

The findings in this study were consistent with existing long-term Botox studies and Gandolfi et al. (2017). The overall reduction in headache days supports a view that MT as an adjunctive to Botox does not reduce headache days in female, long-term, users of Botox.

5.4.6. Headache frequency responders

A CM participant is generally a responder if they have a 50% reduction in migraine days or in overall and severe to moderate headache days, although a 30% reduction commonly used (Bendtsen et al. 2018; Tassorelli et al. 2018). The NICE guidelines consider a reduction of 30% in moderate to severe headache days per month, after two cycles, as a responder (NICE.org. 2016). Many CM studies use both recommended IHS (Tassorelli et al. 2018) percentages although few specify if a headache is moderate or severe in the analysis, preferring to simply use the reduction in days per month (Khalil et al. 2015; Blumenfeld et al. 2018; Stark et al. 2019; Young et al. 2019). In this study, mild to moderate severity was a score of less than or equal to four, using a NRS, with moderate to severe severity a score greater than four. However, issues in comparison between studies occur because there is no consistency in agreed percentage figure, nor what constitutes a severe and moderate headache if an VRS or NRS scale is used (Sjaastad et al. 2002; Tassorelli et al. 2018). There is also no official guidance for responder rates in adjunctive studies or MT studies, which makes comparative analysis with this study difficult. There was no significant difference in responder rates between groups in this current study regardless of severity of headache, although overall, approximately a third of both Group M and C had a ≥30% reduction in frequency of all headaches and a fifth had ≥50% reduction, but almost all were in the mild to moderate severity.

Gandolfi et al. (2017) used a categorical scale and also found a significant reduction in the MT plus Botox group in the mild to moderate headache category but failed to present any responder rates and was limited by a very small sample size. It was difficult to compare this study with Cerritelli et al. (2015) as responder rates were not reported. In Botox studies with experienced Botox users the cumulative responder rates have been estimated at 70%-85% over more than 3 cycles with the trend for fewer participants to achieve a 30% reduction in headache days over more cycles (Silberstein et al. 2014; Stark et al. 2018; Schiano di Cola et al. 2019) which again suggests the relative lack of significant change in the headache frequency in this study was to be expected.

Although the quantity of data collected in this section of the study was limited, the findings were consistent with larger Botox studies of experienced users. The most likely rationale for any reduction in headache is the waxing and waning nature of CM (Manack et al. 2011) in combination with a placebo effect. The placebo responder rates for Botox studies over the same and longer periods have also been estimated

at between 30% and 50% (Ahmed & Gooriah. 2015; Frampton et al. 2018). The non-significant difference in responder rates in this study also tends to supports the earlier view that the MT did not add to the level of placebo over and above Botox (Enck et al. 2011). Clinically, it confirms the view of some authors that the definition of responder over the long term (e.g. for experienced users of Botox) may need revisiting as decisions on stopping the treatment are often based on these outcomes (Ahmed & Gooriah. 2015; Santoro et al. 2017; Schiano di Cola et al. 2019).

5.4.7. Allodynia

Cutaneous allodynia (CA) is considered a measure of central sensitisation (Burstein et al. 2000; Landy et al. 2004; Tommaso et al. 2017) and has been identified as a risk factor in chronification and refractory treatment response (Louter et al. 2013) via changes in two processes: sensitisation of nociceptive structures, and deficiency of anti-nociceptive systems in the ascending and descending pain pathways (Filatova et al. 2008; Woolf 2011; Su & Yu. 2018). In this study, the validated allodynia symptom checklist (ASC) was used to measure changes from baseline to investigate the effect of MT on central sensitisation. No comparison could be made between this study and Cerritelli et al. (2105) or Gandolfi et al (2017) as measures of allodynia or central sensitisation were not reported.

Both groups had a high proportion of participants in the moderate and severe allodynia categories with no statistically significant difference between them. At the end of the study, there was no statistically significant difference between groups; a non-significant reduction from baseline in the proportion classified as having CA, and three-quarters of participants still reporting a score of two or higher (meaning allodynia is present).

This was an expected outcome as participant characteristics in this study were similar to those in other studies in which CA was present in 90% of CM patients (Mathew et al. 2016; Yalin et al. 2017). Risk factors for CA included being female, having depression, a high frequency of headaches (>15 days month), being overweight and having had migraine for a long time (Bigel et al. 2008; Lipton et al. 2008; Tietjen et al. 2009; Benatto et al. 2017).

However, there was an interesting difference between the groups in the movement of participants within the severity categories that has not been reported before in any previous migraine or CM study.

In Group M over half of the participants moved from the 'severe' category to 'mild' or 'no allodynia' compared to less than a tenth in Group C, with a third of Group C moving to 'severe' to 'moderate' allodynia compared to a quarter in Group M.

The pattern of movement from the severe category to mild and none in Group M versus to moderate in Group C suggests that MT added to the effect of Botox. A plausible explanation for this additive effect can be made from the similarities between the proposed mechanism of Botox in CM, and other musculoskeletal conditions, via peripheral nociception (Aoki 2003; Burstein et al. 2014; Do et al. 2018) and the theories of MT influencing central sensitisation via nociceptive mechanisms (Bialowski et al. 2009; Nijs et al. 2010; Vigotsky et al. 2017). This finding is also consistent with the allostatic model (Borsook et al. 2012), in which the individual effects of Botox and MT might be summated to reduce a common stressor (e.g. musculoskeletal pain) in the allostatic load, providing potential for reduced chronification and symptoms. However, for some participants the results were not positive. The reason for this is unclear but one possibility is that the intensity/mode of MT in some individuals determines whether the effect gained is beneficial via a reduction in noxious stimuli, or detrimental via an increase in nociception (Vigotsky et al. 2017). Whilst these findings must be taken in the context of a small sample size, the results support the use of MT as an adjunctive to Botox in CM to reduce signs of central sensitisation in a significant proportion of participants but not all. Larger studies to identify modes of MT that most reduce allodynia in this group of CM patients could be considered.

5.5. Impact of participant baseline characteristics

RQ2: Do female chronic migraine patients exhibit baseline characteristics that affect the treatment outcomes within and between treatment groups?

Despite Botox being the gold standard for treatment of CM, its mechanism of action is still unclear, as is an understanding of which patients will benefit (Matak and Lackovic 2014; Schafer 2015; Jaime Kalach-Mussali and Mondlak Algazi 2018). Given the cost, the sometimes relatively small benefit over placebo and the individual differences in response, the focus of research has turned to identifying predictors of response (Lin et al. 2014; Russo et al. 2016; Vikelis et al. 2016; Probyn et al. 2017 ; Escher et al. 2017; Domınguez et al. 2018; Schiano di Cola et al. 2019; Parrales Bravo et al. 2019).

To explore patient characteristics that might predict treatment response, or identify individuals who are more or less responsive to an intervention, baseline characteristics were gathered on a range biopsychosocial factors and headache characteristics that have been identified as risk factors for chronification and reduced treatment response (Holyroyd et al. 2009).

The next section of the discussion starts by addressing correlations between factors and outcomes, briefly introducing potential models of mechanism. This is followed by a summary review of the results for HIT6 change and PGIC outcomes; the responder results for each of these, and an overall discussion that brings together common strands in the findings. It is important to note that the sample size is small for the type of analysis and therefore these discussions are exploratory and provide a basis for identifying future avenues of research in the context of research question two.

5.5.1. Correlations

Initial correlations between baseline variables and outcomes were calculated, to establish potential relationships, as a starting point to explain differences between groups in the context of current theories and for inclusion in later analyses.

The correlations between baseline variables and change in mean HIT6 differed between groups. Group C had moderate positive correlations with adaptive coping behaviours but a greater negative correlation with the maladaptive coping behaviour, substance use. In contrast, the change in HIT6 in Group M did not correlate significantly with any baseline factors. Therefore, this seemed to indicate an alteration in the mediation and/or moderation relationships which led to a differential effect on the HIT6 change between groups.

The PGIC outcome had significant moderate positive correlations in Group M between baseline adaptive coping behaviours whilst Group C had moderate positive correlations with stress, allodynia score (ASC) and maladaptive coping behaviours, but a negative correlation with acceptance. Interestingly the maladaptive behaviour, behavioural disengagement, was the only coping factor that had a statistically significant change between groups over the 12 weeks and was negatively correlated to Group M, yet positively to Group C. This could be interpreted as those in Group C being less likely to engage with difficult actions than Group M and thus reflect a possible mediating role for behavioural disengagement in treatment response. This

finding is consistent with studies in pain that examined psychological factors involved in mediation of treatment outcomes, particularly the role of active engagement, reflected by the MT in this study (Leeuw et al.2006; Turk & Wilson. 2010; Werneke et al. 2011).

Despite the variations between groups, the correlations in this study are consistent with previous findings relating biopsychosocial and pathophysiological factors to headache disability and treatment outcomes: The ASC score is a measure of central sensitisation which has been found to correlate with chronification, poor treatment response and increased disability (Burstein et al. 2000; Bigal et al. 2006; Louter et al. 2013; Dodick et al. 2019). Stress (anxiety/depression) factors are also a commonly correlated with greater disability in CM studies (González-Quintanillet al. 2015; Moon et al. 2017; Cha et al. 2017) and coping behaviours, particularly avoidance behaviours including substance use, have been linked to CM disability and treatment response (Radat et al. 2008; Weiser et al. 2012; Biagianti et al. 2014).

One possibility for the variation in correlations in Group M and C is error resulting from a small sample size. However, the differences in PGIC and change in HIT6 outcomes might also reflect the underlying constructs of the measurement instruments, with the PGIC more likely influenced by biopsychosocial factors compared to HIT6 (Oh et al. 2014; Das Mahapatra et al. 2015; Scott & McCracken. 2015). Alternatively, any differences in treatment outcomes between the groups may have indicated a difference in the mediation and moderation relationships between patient characteristics and treatment outcomes. This proposition will be explored in the next section.

5.5.2. Moderation and mediation

Various authors have described moderators and mediators of treatment effect (Baron & Kenney. 1986; Kraemer et al. 2002; Holroyd et al. 2009; Kraemer 2016; Hayes & Rockford. 2017). This study adopted the definitions provided by Kraemer (2002, 2016).

(a) To be a moderator of effect of intervention (Group M or C) on outcomes, a factor must be a baseline characteristic that suggests on whom the intervention choice has differential effects on the outcome(s). Predictors are baseline factors that affect outcomes but do not change with intervention.

(b) A mediator of intervention outcomes changes over time and suggests how or why one intervention might be preferred over the other in the population sampled. Intervening factors are those that change, or occur, after randomisation but before the study outcome and may be independent of, or moderated by treatment

At the time of writing there were no mediation/moderation RCTs with adjunctive studies in CM, although there was one of drug and psychological intervention SM (stress management) in CTTH. This suggested that presence of mood disorders has a mediating effect on headache disability outcomes (Holroyd et al. 2009). Kokonyei et al. (2016) also showed increased psychological distress (equivalent HADS_TOTAL) in migraine is partially attributed to (mediated by) maladaptive avoidant behaviour.

Consequently, this study was the first to explore the potential influencers of response to MT as an adjunctive intervention to Botox compared to Botox alone in CM. Based on the results, a post-hoc premise was formulated that treatment outcomes may be moderated differently by some of the baseline characteristics(s). The discussion here must be seen in the context of a small sample size and the absence of a standalone MT group and should be viewed as a tentative step for the basis for future studies.

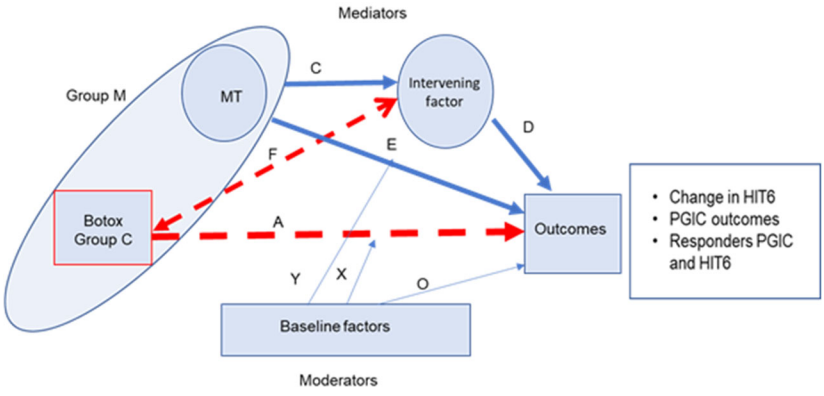

Figure 5-2. Generic mediation – moderation model

Using initial results, the variables correlated with treatment outcomes could be grouped into three themes: Allodynia (ASC); Stress related; Coping behaviours.

Although there were correlations to baseline variables with differences in outcomes between groups, the findings did not provide evidence of causation. However, they

did demonstrate a consistency with existing studies on the factors that might be involved in mediating and moderating CM outcomes (Lin et al. 2014; Russo et al. 2016; Vikelis et al. 2016; Probyn et al. 2017; Escher et al. 2017; Domınguez et al. 2018; Schiano di Cola et al. 2019; Parrales Bravo et al. 2019). The next section will build on this initial analysis to explore those characteristics that may influence outcomes.

5.5.3. Summary outcomes

This section begins with a brief review of main findings, in the key outcomes of interest, before discussing in detail the main themes that emerged from the analysis.

5.5.3.1. Change in HIT 6

The change in HIT 6 score is a key outcome in many CM studies (Tassorelli et al. 2018) and at the time of writing the author could find no studies that investigated predictors of change in the HIT6 score. There were significant differences between the predictors for Group M and C. In Group C, three factors: substance use, planning and the HADS_Total accounted for 40% of the variation in the change in HIT6, whereas in Group M, no model could be regressed to account for a statistically significant variation in the change in HIT6.

Although the major contributor to variation in groups M and C was substance use, the strong influence of HADS_Total in Group C and its absence in Group M was an interesting finding given that previous CM studies in Botox have found that depression/anxiety (HADS_Total), in association with medication overuse (substance use) lead to poorer outcomes (Disco et al. 2015; Schiano di Cola et al. 2019). It would therefore be expected that these factors should be similar in both groups if no effect was involved. The finding in this study indicated that the baseline HADS_Total may have moderated the effect of Botox in Group C (Figure 5.3 path XA) possibly with other, different/unknown mechanisms, reducing its effect on the combined MT and Botox in Group M (Fig 5.3 path YE), and via intervening variables.

Medication (substance) use may also have acted as independent intervening influencer on outcome regardless of intervention (Figure 5.3 path D), which is consistent with the results from this study in which medication overuse was the only baseline factor that had a negative impact on the probability of participants being a HIT6 responder regardless of intervention. The role of HADS_Total in this study

seemed to mirror studies that concluded: 'in the presence of mood or anxiety disorders', headache disability was likely mediated by variables including coping behaviour (e.g. substance use) (Holroyd et al. 2009; Kokonyei et al. 2016). A more detailed analysis would require a much larger sample size and is an area for development.

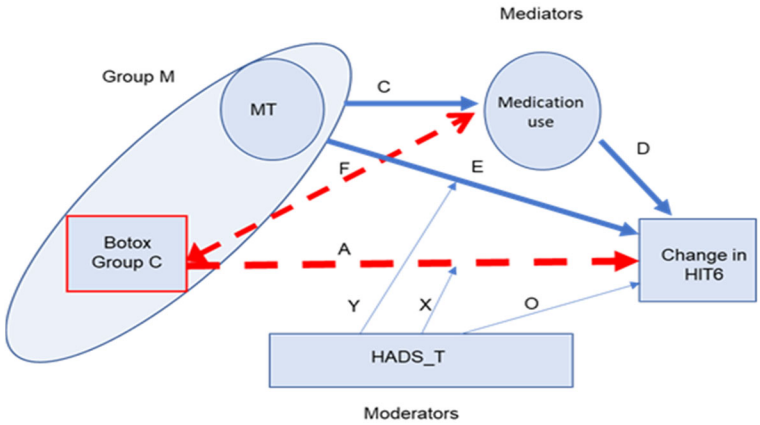

Figure 5-3. Change in HIT6 potential moderation - mediation model

5.5.3.2. HIT 6 Responders

This was the first study to examine HIT6 responder group outcomes and their relationship to predictive factors. Binomial logistic regression for HIT6 responders produced a model comprising treatment group, self-distraction, ASC and baseline HIT6 score that explained 36% of the variance in responder outcome and correctly classified three-quarters of cases. The odds of being a responder decreased significantly if in Group C compared to Group M, with an increase in ASC score decreasing the odds of being a responder substantially, and conversely an increase in self-distraction increased the odds of being a responder marginally. The area under the ROC curve had an excellent level of discrimination suggesting this could provide a useful test for distinguishing the responder outcomes in this group of patients (Yang & Berdine. 2017).

5.5.3.3. PGIC category outcomes

Multinomial logistical regression was used to estimate the predictive factors for gaining "Moderate" and "Much" improvement over no change. For moderate improvement the factors were: being in Group M, denial and behavioural disengagement and for much improvement: being in Group M, planning and ASC score. The best model for predicting the participants being in the "Much change" compared to the "No change" (none) category suggested that those participants in

Group M had a significantly greater probability (90%) than those in Group C. The model also suggested that for each unit change in planning and baseline ASC there were significant increases in the probability of being in the "Much change" compared to the "No change" category. Although these findings must also be seen in the context of a small sample size and therefore as a preliminary evaluation, they support the secondary outcomes presented earlier on the benefit of MT as an adjunctive over Botox alone, providing a basis for future research to investigate the effect of baseline variables on patient reported treatment outcomes in CM.

5.5.3.4. PGIC responders

A PGIC responder was categorised as having a score of five or higher. The optimum model comprised intervention, behavioural disengagement and denial. It explained 61% of the variance in responder group and correctly classified 85.0% of cases with the area under the ROC curve having an outstanding level of discrimination (Yang & Berdine. 2017). The odds of being a responder decreased significantly with an increase in behavioural disengagement and by being in Group C relative to Group M, conversely an increase in denial improved the odds of being a responder. It was difficult to say if these results are consistent with any existing research as the PGIC has only recently been used for headaches or CM and no previous studies have addressed the biopsychosocial factors involved. And despite limiting the number of variables used in the model, the results must be considered as only an initial step towards larger studies.

5.6. Themes

The main factors highlighted in the above analyses were cutaneous allodynia (CA), stress (depression/ anxiety) related, coping behaviour and intervention. These are now discussed in the context of the main research questions.

5.6.1. Central sensitisation (CS)

Cutaneous allodynia (CA) is believed to be a result of central sensitisation and was measured using the allodynia score checklist (ASC). It was no surprise to find CA as a main theme in outcomes since the likelihood of having allodynia has been associated with factors representative of this study's participants, including female gender, lower age at onset, high frequency of attacks, as well as comorbid depression/anxiety and increased medication usage (Bigal et al. 2008; Lipton et al. 2008; Louter et al. 2013; Mathew et al. 2016; Young et al. 2019).

The proportion of participants with CA at baseline was very high in both groups, consistent with previous studies (Bigal et al. 2008; Dodick et al. 2019) and neither group had a significant change in proportion of participants with CA at 12 weeks. However, what did alter significantly was the proportion of participants in each ASC category for each group. Group M moved half of participants from severe to mild or no CA, compared to less than a tenth in Group C, and both groups moved at least a quarter from severe to moderate.

The explanation for this outcome might lay in studies of the mechanisms of Botox and MT in pain and migraine. One established theory is that CA results from the activation of the trigeminovascular neurons which, over time, leads to sensitisation of second-order neurons in the spinal trigeminal nucleus. These can then become self-maintaining without the initial noxious sensory input from the internal and external neck and head structures, including the muscles, joints and cervical nerve roots (Bartsch & Goadsby. 2003; Bigal & Lipton. 2007; Bernstein & Burstein. 2012; Tietjen et al. 2019). Therefore, if this pattern of sensitisation can be inhibited, CA should reduce and disability along with it.

Two relevant mechanisms of action have been proposed for Botox; one that it relaxes muscles by inhibiting acetylcholine (Ach) release resulting from the muscle trigger points and the two, that it inhibits nociception in the peripheral trigeminovascular system by the reduction of mechanical pain signals to the spinal trigeminal nucleus, which begins a cascade of other neurophysiological effects (Burstein et al. 2014; Do et al. 2018). Jakubowski et al. (2006) also concluded the success of Botox with migraine pain involves extracranial sensory fibres near the injection sites and speculated the involvement of activation of extracranial nociceptors of scalp tissues, bone and periosteum. Both of these mechanisms of action for Botox have commonality with the proposed mechanisms and potential neurophysiological effects of MT in migraine and pain.

Firstly, the relaxation of muscle trigger points and secondly the reduction in nociception, via mechanical pain signals, in structures around the head and neck (Bialosky et al. 2009; Nijs et al. 2010; Fernández-de-las-Peñas & Dommerholt. 2014; Bishop 2015; Vigotsky et al. 2017; Falsiroli Maistrello et al. 2018).

Consequently, a greater reduction in nociceptive input from the combination of MT and Botox may explain the increased benefit over Botox alone in this study, with MT adding to the action of Botox (Ghanbari et al. 2015; Gandolfi et al 2017; Kumar et al. 2018).

However, despite the movement of participants from a higher level of ASC category to a lower one, a substantial proportion of participants still exceeded the cut off score of two in the ASC, which indicates the presence CA. One explanation may be that since Botox and MT are believed to influence just mechanoreceptors, and not thermal nociceptors (Burnstein et al.2014; Paterson et al. 2014; Matak et al. 2019), the ASC components of thermally induced CA would have been unaffected by either intervention and therefore potentially limit the ability of the ASC score to move below the cut off of two. This finding raises questions on the use of the ASC as a dichotomous measure of CA in studies of MT and Botox, for which it may be better to examine movement between categories as an outcome rather than a cut off score.

There was also an unexpected result in which the higher baseline ASC positively correlated with a move to the ‘much change’ PGIC category, which seemed to conflict with higher levels of ASC being a negative factor for the HIT6 responder outcomes.

However, there is some evidence from previous studies that offered a possible explanation. Young et al. (2019) reported that the presence of CA in CM could affect Botox treatment outcome measures differently, e.g. headache frequency compared to quality of life measures, and concluded that the effect of CA on treatment outcomes remained unclear. Since HIT 6 is a measure of disability, and PGIC a measure of how the participant feels they have improved, the different construct validity of each may lead to different outcomes from changes in the same variables, as observed with other rating scales (Holroyd et al. 2009; Lati et al. 2010; Mannix et al. 2016). Although the role of psychological stressors in mediating allodynia is a subject of debate (Lovati et al.2009; Crettaz et al. 2012; Dodick et al. 2019), there is agreement on a strong association between depression and CA, with depression found to mediate patient ratings of migraine severity to MIDAS outcomes (Tietjen et al. 2009; Ashina et al. 2012; Louter et al. 2013; Mendonca et al.2016;Sajobi et al 2019).

It is therefore possible that a different mediating relationship exists between depression (or HADS_Total) and the HIT6 and PGIC constructs, resulting in the inconsistent outcomes observed (Young et al. 2019). To the knowledge of the author, this is the first study to report the potential relationship between ASC and PGIC outcomes in CM.

The findings suggest support for a potential relationship between psychological stressors e.g. depression, and the development of allodynia. The results are also consistent with existing theories on the reduction in nociception from both MT and Botox, and suggest a new proposal that they work in combination to create an enhanced reduction in central sensitisation and consequently in CA. However, this was a small study for this type of analysis and conflicting evidence for the role of allodynia in CM, specifically its treatment with Botox, remains an area for further investigation.

5.6.2. Coping behaviours

Coping behaviour is as an important factor in chronic pain, as well as the management and chronification of headaches and migraines (Gamsa 1994 a,b; Siniatchkin et al. 1999; Rollnik et al. 2001; Samwel et al. 2007; Radat et al. 2009; Borsook & Kalso. 2013; Ruscheweyh et al. 2019). In this study the main coping behaviour reported was maladaptive avoidant, involving self-distraction, denial and behavioural disengagement. One of the key and unexpected findings, in both the HIT6 and PGIC responder outcomes, as well as PGIC categories, was the association of denial and self-distraction as beneficial to positive outcomes despite both being maladaptive avoidant, coping strategies. The Fear-Avoidance (F-A) model of pain (Appendix 28) developed out of musculoskeletal pain concluded that two modes of coping existed: avoidant maladaptive and adaptive (Lethem et al. 1983). Those with an adaptive approach challenged the acute phase and actively performed actions designed to improve, whereas the avoidant people restricted activities and physical performance with over predictions of pain and strong correlates with self-reported disability (Black et al. 2015). The F-A model also recognised that behaviours, such as withdrawing from daily activities, common in migraine, can contribute to the symptoms of depression and that it is possible these symptoms stimulate F-A pathways (Zale & Ditre. 2016). In CM, there is also a history of reinforcing avoidant behaviour in the form of advice to avoid triggers (Hoffman & Recober. 2013). Moreover, there is a view that this process builds a pattern of distraction and sensitisation that reduces tolerance and encourages a

greater use of medications (Martin et al. 2009; Gandolfi et al. 2019). The high levels of medication use and disability, with higher than normal levels of anxiety and depression in this study, regardless of group, is therefore consistent with F-A model studies that suggest avoidant behaviours might contribute to increased levels of anxiety / depression in CM and vice versa (Buse et al. 2010; Baskin & Smitherman. 2016; Seng et al. 2017).

In this study, higher baseline denial scores significantly increased the probability of participants being in the PGIC moderate change category, and substantially increased the odds of being a PGIC responder. Likewise, higher baseline levels of self distraction significantly increased the probability of being a HIT6 responder. This was an unexpected outcome, as denial and self-distraction are avoidant behaviours and generally considered negative influences on a variety of pain condition treatment outcomes (Norton & Asmundson. 2004; Castelnuovo et al. 2016; Edwards et al. 2016). In common with increased use of acute medication, they have also been found to be negative reinforcers of the F-A pattern (Siniatchkin et al. 1999; Vlaeyen & Linton. 2000; Ruscheweyh et al. 2019). Conversely, some studies have found those with higher levels of disability use avoidant coping behaviours to benefit outcomes in the short term, or in differing conditions, particularly if they feel the situation is not going to change (Philips 1987; Turk & Wilson. 2010; Biagianti et al. 2014; Garcia et al. 2018).

This mechanism and the F-A model may explain some of the unexpected findings in this study. Because the expectation of these highly disabled participants is almost certain access to Botox every 12 weeks, they can use avoidant coping behaviours, including significant levels of medication, to manage in the short-term. Therefore, this short-term coping strategy essentially avoids the need to develop a long-term strategy, and perhaps access to more beneficial long-term adaptive coping behaviours (Leeuw et al.2006; Cosio and Lin 2018). Therefore, in this study of refractory CM patients, the continued use of Botox may be a long-term enabler of chronicity rather than a short-term solution to help break the F-A pattern. Consequently, the possibility of a multi-modal solution for some participants, who might benefit from adjunctive psychological or active therapy is missed (Norton and Asmundson. 2004; Nicholson et al. 2007; Williams et al. 2007; Komandur et al. 2018). This is an area for further research, as currently the evidence has focussed on psychological therapy as a standalone and not adjunctive or integrative approach with Botox in CM (Turk et al. 2008; Sharpe et al. 2019).

Interestingly the MSQ2.1 outcomes (section 5.4.2) supported the view that role restriction (avoidant behaviour) and emotional freedom were improved in Group M compared to Group C, suggesting a potential effect from MT on psychological behaviours that may have influenced the F-A process (Williams. 2007; Sung et al. 2014). This relationship was given some added support as the role of behavioural disengagement (giving up on trying to solve the issue) had a negative effect on PGIC outcomes, consistent with other studies of pain and migraine (Esteve et al. 2007; Radat et al. 2008; Weiser 2012; Stanisławski 2019). However, it was also the only coping behaviour that reduced statistically over the 12 weeks and only in Group M. This may tentatively suggest a mediating role for behavioural disengagement in PGIC outcomes when using MT with Botox, in the same manner as ruminating (avoidant) behaviour has been shown to be a potential mediator between psychological distress and migraine severity (Kokonyei et al. 2016). It is possible that, by undertaking a more active role in treatment, Group M were challenging negative behaviours in the F-A model (Cosio & Lin. 2018). This remains an area for further research and possibly development of a more active/engaged approach to management.

5.6.3. Stress

In this study stress was measured using the PSS10 and HADS instruments. The mean PSS scores in groups M and C were consistent with other CM studies: higher than a healthy population control (norm) and substantially higher than the norm for females (Moon et al. 2017; An et al. 2019). The proportions of depression and anxiety in both groups were also consistent with other CM studies, with participants having more than twice the anxiety and three times the level of depression expected in the general UK population (Zigmond & Snaith. 1983; Crawford 2001, Buse et al. 2011; Yavuz 2013; Breeman et al. 2015). The HADS_Total score was used as a measure of overall emotional (psychological) distress and was abnormal in three-quarters of cases. These figures were not surprising in a group of long-term CM patients, and confirmed the well-established relationship between increased psychological comorbidities and poor outcomes in CM (Breslau et al. 2003; Antonaci et al. 2011; Ashina et al. 2012; Buse et al. 2013; Lampl et al. 2016; Seng et al. 2017). It nevertheless supported the view that the participants in this study were a highly refractory treatment group and any changes in treatment response were most likely the result of the treatment effect.

In this current study, HADS_Total (emotional/psychological distress) was a large contributor to the 40% variation in Group C HIT6 change but did not contribute to variation in Group M. This suggested that HADS_Total may have moderated the effects of Botox on outcomes in Group C (Figure 5.3). The reason for apparent lack of effect on Group M is unclear, although one possibility is that the effect of the MT component in Group M on the HIT6 outcome was mediated directly or via an intervening variable, perhaps substance use or coping behaviours. Alternatively, the effect on outcomes of the MT component in Group M may have been moderated differently by HADS_Total. This points towards a possible role for MT in the management of CM via an influence on psychosocial factors as suggested by other studies (Williams et al. 2007; Saracutu et al. 2015; Wirth et al. 2016; Courtney et al. 2017; Seng et al.2017). A similar response was reported by Holroyd et al. (2009), whereby the treatment effects of stress management (SM) and antidepressants were different, based on the absence or presence of mood and anxiety disorders, when comparing each of the individual components to the adjunctive antidepressant and SM group. Although a detailed modelling of this was beyond the scope of this study, it remains an area for future investigation with a much larger sample.

5.6.4. Manual therapy

Being in Group M was a large contributory factor to being a HIT6 and PGIC responder and conversely the chances of being a HIT6 or a PGIC responder were decreased significantly by being in Group C. The results also suggested that by being in Group M there was a significantly greater chance of being in the PGIC ‘much change’ category than the ‘no change’.

To date, the mechanism of action of Botox in CM is still unclear although it has been suggested that it acts by reducing peripheral nociception from extra and intercranial structures, including upper cervical structures and via the trigeminocervical complex (TCC) (Jakubowski et al. 2006; Burstein et al. 2014; Do et al. 2018; Melo-Carrillo et al. 2019). Similarly, studies have indicated that MT leads to a reduction in the peripheral nociception from extra and linked intercranial structures in the cervical spine and via the TCC leading to diminished central sensitisation (Bartsch et al. 2003; Scheuler et al. 2013; Courtney et al. 2017).

The reduction in peripheral nociception via both MT and Botox has been explained by a reduction of sensitisation in the mechanoreceptors with inhibition of C fibres, decreasing activation of muscle spindles along with the reduction in, and mediation of, inflammatory neurotransmitter actions. Whilst the neurotransmitters involved in

Botox and MT are not the same, there is considerable overlap, including substance P, dopamine, serotonin and acetylcholine (Vigotsky & Bruhns. 2015; Do et al. 2018) which may provide another explanation for the study outcomes. It has also been proposed that the actions of both Botox and MT are not just at the neuromuscular junction but also the spinal and supraspinal levels. This provokes an (indirect) effect on the CNS via plastic changes resulting, in part, from modulation of the peripheral sensitisation (Aoki et al. 2003; Schmidt et al. 2008; Bialosky et al. 2009; Ramachandran & Yaksh. 2014; Escher et al. 2017; Matak et al. 2019; Martinelli et al. 2020). Subsequently, these nociceptive changes can interact in the higher brain (e.g. thalamus, cortex) with inputs from the sensory pathways (psychological including emotions, beliefs and environmental challenges) being modulated by the descending analgesic system (Shacklock 1999; Dodick et al. 2019; Crettaz et al. 2012; Jaime Kalach-Mussali & Algazi. 2018; Weise et al. 2019; Kumar 2018).

It has also been shown that different types of MT act via different mechanisms within similar pathways e.g. SMT on cervical and thoracic spine produces hypoalgesia via mechanisms different from cold stretch for trigger point techniques (Bialosky et al. 2009; Vigotsky & Bruhns. 2015). Therefore, a combined MT approach is likely to provide a greater response than a single one, as is a combination of Botox and MT. The differences in response to Botox in some individuals compared to others may be a result of individual differences in pathophysiology at the cellular level (Durham & Cady. 2011) and therefore the best responders to Botox might gain benefit through more than one pathway, whereas the more refractory group may be reliant on a more restricted number of mechanisms.

In conclusion, the findings of this study are consistent with the proposed mechanisms of MT and Botox having worked in synergy to reduce peripheral nociception and consequently central sensitisation via similar pathways but not necessarily the same cellular processes. MT may have also impacted disability measures through an effect on both physical and psychological factors, consistent with components of both the allostatic and neurobiological models that formed a basis for this study (Figure 5.4).

Images redacted. Figure 1 page 3. Su, M. and Yu, S., 2018. Chronic migraine: A process of dysmodulation and sensitization. Molecular Pain, 14, 174480691876769

Figure 6 page 228. Borsook, D., Maleki, N., Becerra, L. and McEwen, B., 2012. Understanding Migraine through the Lens of Maladaptive Stress Responses: A Model Disease of Allostatic Load. Neuron, 73 (2), 219-234

Figure 5-4. Integrated model of chronic migraine care ;combining allostatic and neurobiological models (adapted from Su & Yu. 2018; Borsook et al. 2012)

5.7. Clinical implications

CM patients represent a high caseload in tertiary neurology clinics, one estimate being that approximately 50% of patients attending a tertiary headache clinic have CM (Kainth et al. 2018; Peres at al. 2019). They present a challenge, as they have tried many other interventions and commonly have comorbid psychological conditions such as depression and anxiety and are heavy users of acute medications (Breslau et al. 2003; Bigel et al. 2008; Lampl et al. 2016; Davies et al. 2018). CM is a pain driven neurological condition in which the mechanisms are not fully understood and for which there were no specifically developed treatment options until Botox (May & Schulte. 2016; Dussor. 2019; Andreou & Edvinsson. 2019). However, none of the available pharmacological interventions are successful in all cases and often yield limited results in many (Carod et al. 2014; Weatherall. 2015; Agostini et al 2019). It is estimated that even after four or five rounds of Botox 30% of patients are still classed as severely disabled (Cernuda-Morollón et al. 2014; Matharu et al. 2017; Parrales Bravo et al. 2018). Consequently, in light of multiple potential drivers and the less than satisfactory outcomes in the gold standard mono-therapy, it is evident that a multi-modal approach to treatment may be more appropriate (Gaul et al. 2011; Wallasch et al. 2012; Grazzi 2013; Burstein et al. 2015; Gaul et al. 2016; Grazzi & D'Amico, 2019).

Hence, this study set out to establish if adjunctive MT affected the treatment outcomes in those with CM already using Botox. The results suggested that MT was a suitable adjunctive capable of achieving clinically and statistically significant beneficial outcomes in a group of female CM patients who had used Botox for a significant period.

There are a several clinical implications from this study. Firstly, the findings concur with the view that not all CM patients benefit from Botox in the same way over time, and a significant proportion remain severely disabled. Early identification of the most refractory group of patients would enable quicker implementation of a multi-modal management approach to improve their outcomes. This study suggests that identifying and addressing medication overuse/high levels of substance use early in treatment would improve results as it was the only baseline factor that reduced the chance of being a responder in both groups.

There should be encouragement for the use of validated electronic diaries/apps tracking a number of factors in real-time over time, rather than relying on the patients completing a single form and or historic diary at the time of their next appointment. This would reduce bias and enable better evaluation of patients' outcomes and progression, providing opportunities for earlier intervention.

Although the characteristics of the subgroup of patients who gained the greatest benefit from the combination of MT and Botox could not be accurately ascertained in this study, as it was not designed to do so, it provided a starting point for future development. The analyses suggested those with higher levels of cutaneous allodynia, maladaptive coping and psychological distress would gain greater benefit from a combined MT/Botox intervention than Botox alone. An initial evaluation of these factors prior to treatment could be a useful method to identify those who might be offered MT.

The results from this study also suggest that future CM studies, involving refractory patients, may require a distinct set of guidelines on outcome measures that more accurately reflect the patient experience. The majority of studies use traditional comparison of active and /or placebo RCT trials with naïve patients, who are the most likely to respond according to the traditional instruments such as HIT6 and MSQ2.1. However, many, like those in this study, still have high level of disability, measured using HIT6 and other validated instruments, after treatment for long periods of time. It may therefore be of benefit to use the PGIC in clinics to gauge treatment outcome (Dworking et al. 2008, 2009).

The findings of this study suggest that continuing long-term use of Botox in the most refractory patients may reinforce the fear-avoidance patterns and encourage poor coping skills rather than helping patients access more appropriate / beneficial interventions. Therefore, there may be a benefit from a detailed screening, including a psychological review, after four or five rounds of Botox to ascertain the progress of a patient and consider alternative/adjunctive interventions if they are exhibiting characteristics of a refractory patient (Aydinlar et al. 2017).

Finally, the evidence presented is consistent with an integrated mechanism of action that combines the neurobiological and allostatic models of pain and migraine. Consequently, it supports the view that a tailored multi-modal approach to the

management of CM, based on patient characteristics, may provide greater benefits to a wider range of patients rather than the continued use of a mono-pharmacological therapy (Gaul et al. 2011; Wallasch et al. 2012; Grazzi 2013; Burstein et al 2015; Gaul et al. 2016; Grazzi & D'Amico, 2019; Borsook et al. 2019).

5.8. Challenges

Undertaking a clinically-based RCT in a busy NHS site, as part of a doctoral study, provided several challenges. As an NHS non-CTIMP randomised control trial, the normal Regional Ethics Committee (REC) involvement inevitably adds time, over and above University ethics, before the recruitment process can begin. The first challenge was therefore the requirement to resubmit the REC application due to a conflict with University policies. This required the original study design, involving two tertiary headache centres with 100 participants, to be restructured. The major centre was removed which meant having to renegotiate an increase in the number of participants at the smaller site. This added a delay of several months to the study and, to ensure the project was completed on time, required good project management, relationship building and communication skills.

Working with the NHS also presented specific challenges in terms of the complexity and time needed to manage multiple interactions with participants, NHS research department, clinical and administrative staff as well as the administrative requirements of an RCT with the University and the Health Research Authority. One of the biggest challenges was ensuring a room was always available in a busy major hospital for participant interactions over the duration of the project. This was managed by ensuring a good relationship and regular contact with the decision-makers.

Recruitment clinics were also cancelled due to staff availability, disrupting recruitment and requiring ongoing changes to the 12-week recruitment schedule. Whilst this is all part of normal NHS life, and as such part of a pragmatic study, it did affect the recruitment time and data collection which required the author to be adaptable to changes, often at short notice, and to maintain a live project management system. A small extension to the original end date was agreed with the NHS and the REC to manage the impact of clinic closures on the recruitment schedule.

A major challenge over the period of the study was the need for recruitment, data collection and treatment phases to run concurrently, requiring a complex approach to communication and implementation. Small groups of participants had to be managed in different phases of the study concurrently, including weekly contact with small numbers of participants for diary updates via text and emails as they progressed through the study, organising treatment schedules at three locations and arranging the follow up and end of study meetings. A detailed project plan and time management system was designed and actively managed to cope with the sometimes rapid and unexpected changes.

5.9. Strengths and limitations of study

5.9.1. Strengths

This PhD study had a number of strengths. It included narrative and systematic reviews that identified a lack of research investigating CM and MT and highlighted issues surrounding the design and quality in headache studies. Consequently, the strength of the study was founded on the pragmatic RCT design, close adherence to CONSORT and IHS guidelines and, by dint of being an NHS non-CTIMP RCT study, the design had to satisfy the REC and HRA procedures as well as the University.

The study was unique in that no other pragmatic RCT trial study involving MT and chronic migraine had taken place in a UK, let alone in an NHS tertiary headache clinic, with all participants diagnosed by experienced headache neurologist. Although previous studies have investigated MT as a standalone intervention for CM, as far as the researcher was aware, none have addressed it as an adjunctive therapy in comparison to the gold standard ‘care as usual’ (Botox) pharmacological intervention in a working clinic. The study was also unique as it demonstrated for the first time that undertaking a MT-RCT alongside standard interventions in an UK NHS setting is possible without disrupting the running of the organisation and that many people with CM are open to being involved. The study had data collection instruments (questionnaires and diary) professionally created and produced; designed to shape participant perception of the documents’ value and importance and encourage the completion and return of the information. This appeared to work well, with a 100% return and completion rate in questionnaires and 85% in diaries.

The design of the booklets intentionally delivered the validated instruments as a series of questions in sections. This was intended to mitigate confirmation bias, by preventing experienced migraineurs from recognising commonly used instruments such as the HIT6 and adjusting their answers out of concern that they may lose access to their Botox intervention (Pannucci & Wilkins. 2010; Althubaiti 2016).

To balance the 'contact' difference between the groups, reduce recall bias and maintain compliance, weekly text messages/emails were sent as reminders to complete the diary (Lin & Wu. 2016). This strategy worked well and gave the ‘care as usual’ group a stronger ‘buy–in’ to the study, evidenced by acknowledgement contact back from many of this group.

At the time of the literature review, design and data collection, this study was the first Botox study to use the Patient Global Impression of Change (PGIC) in an RCT involving chronic migraine despite it being a recommended measure in the IHS guidelines (Tassorelli et al. 2018). Although in a subsequent update to the literature search, a recent trial of a new calcitonin gene–related peptide (CGRP) for CM was found to have used it (Lipton et al. 2019) which bodes well for the future.

5.9.1.1. Internal and external validity

As a pragmatic rather than explanatory design, one of the methodological objectives of this study was the preservation of high external validity to enable the application of the findings to clinical practice, rather than maximising internal validity by strict control of variables (Godwin et al. 2003, Louden et al. 2015).

Nevertheless, a number of factors has been proposed that may affect external validity, including: the setting; selection of participants; characteristics of randomised participants; difference between the trial process and routine clinical practice, and relevance of outcome measures (Rothwell 2006). In this study, these factors were mitigated to increase external validity: The setting was a routine tertiary clinic in the Outpatients department, with MT treatment in similar therapy room settings. Recruitment involved only female participants identified from ongoing clinical list, having had more than 2 cycles of Botox and therefore in a clinical stable situation. There was little difference between the groups after randomisation and the trial process was embedded in routine clinical practice with outcome measures as recommended by the IHS including patient centred outcomes. That said, whilst the study exhibited good external validity (Sedgwick 2014), this would have been

augmented by being extended to the multiple tertiary centres as originally planned. The findings of this study have potential benefit for females with CM attending a tertiary clinic being treated with Botox on a 12-week cycle.

However, it may also be possible that these findings are applicable to primary care since all other factors, apart from the tertiary care clinic setting for Botox injections, would be similar for any female being treated with Botox. One of the main caveats to this argument may be that as this study most likely involved refractory migraineurs they may not represent first time attendees in either tertiary or primary care clinics. However, it is well reported that people with CM are under/mis diagnosed in primary care and often experience a prolonged period of mismanagement. Thus, the participants in this study are likely to reflect those in primary care with a longstanding history classed as simply ‘migraine or chronic headache’ who are not fortunate enough to get to tertiary care. (Al-Hashel et al. 2013; Dodick et al. 2016). In part this may be because CM, like many other chronic pain conditions, currently lacks identifiers for best outcomes (treatable characteristics) with inclusion for appropriate treatment based on diagnostic labelling that is often very subjective. (Shrimanker et al. 2018).

This study tried to maximise the internal validity through the application of the RCT process and the CONSORT guidelines (MacPherson 2004; Zwarenstein et al. 2008, 2010). To ensure high internal validity, ideally there would be randomising of participants together with blinding of those handling data at any stage of the process. However, as part of a doctoral programme the lack of resource meant it was not possible to blind data collection, which should be seen as a limitation, although patients were successfully randomised and the data were re-coded by a supervisor prior to analysis.

5.9.2. Limitations

All research has its limitations. This study was no exception; the usual limitations on time and resources encountered by the majority of doctoral candidates were primary factors.

Despite the impact of CM on the individuals and society, it is a relatively newly defined condition; this, together with the combination of CM with MT, resulted in a limited research base against which to evaluate the outcomes of this study. Conversely this provides an opportunity for significant development of

understanding. Therefore, the lack of comparative studies found in the systematic literature review against which to evaluate the outcomes may be considered a limitation. The researcher's reliance on existing nursing staff in the NHS tertiary clinic supporting recruitment on a voluntary basis acted to some degree as a limitation in some of areas of the study process. Elements of miscommunication in the recruitment process may have contributed in part to the lower than anticipated conversion rate. For example, potential participants were initially advised by NHS staff that they would have to attend the hospital for treatment if randomised to Group M. Consequently, they declined to progress in the recruitment process as travelling to and parking at the hospital is difficult. In fact, there were three treatment locations, awareness of which might have influenced the participation decision. Short notice changes to the planned 12 weeks follow up appointments also compromised researcher availability to attend on every occasion which sometimes meant rescheduling data collection, particularly in Group C.

With hindsight, a limitation was the paper diary approach. Although it is recommended by the IHS (Tassorelli et al. 2018) and had a high compliance in this study, the design was not optimal and led to some limitations in analysis. For example, it would have been better to collect migraine attack data and non-migraine headache data separately rather than just headache data, and to use a four-point categorical scale for better comparison with existing studies. The use of mobile electronic diaries and migraine Apps was investigated during the design phase to help reduce recall bias inherent in paper (Althubiati 2016); a suitable option was not available and, although an online diary was made available, only three participants chose to use it. It is also the case that many current electronic diaries require high levels of IT and administrative support (Hanson 2016), which was not available in this study. Ease of use, security and quality of data are essential in diary data collection and future studies may benefit from the development of secure app data collection systems that are pre-validated by official research organisations such as universities. It was also evident from the initial randomisation meetings that MT was an attractive option for many participants, with disappointment resulting from an allocation to Group C. For this reason, collecting the participants' expectations of likely outcome prior to treatment may have been an improvement; enabling an exploration of any possible association between initial beliefs and experienced outcomes, which has been shown to be a factor in other studies (Autret et al. 2012; Benedetti 2014; Frisaldi et al. 2017).

The nature of the study prevented the implementation of a double-blind RCT as is always the case in studies involving MT. Whilst single blinding and the use of some form of placebo or sham group would have improved the strength of the findings, the resource limitations inherent in being part of a doctoral programme meant it was difficult to add an extra group. The issue of time resource in a doctoral study also prevented the inclusion of a follow-up period, as recommended by the IHS. An important limitation was the lack of knowledge of psychological comorbidities for which participants may or may not have been treated. The randomisation process equalised the balance of any co-morbidities between groups but the individual degree of co-morbidity may have influenced the final outcomes.

The use of a single site in Salford could be viewed as a limitation. It is likely to have reduced the generalisability of the findings on a socioeconomic basis as Salford was the 22nd most deprived local authority area out of 326 in the UK (CQC, 2016). However, as the majority of the participants were from outside the Salford area (Figure 4.6) and comprised a wide range of socioeconomic status, generalisability is considered less of an issue. Although the sample size was consistent with other RCTs studies involving MT, migraine, CM, it was still a relatively small trial and should be seen as a limitation with regard to the power calculations. This made the results of some of the more data intensive (e.g. regression) statistics more prone to uncertainty and they should be viewed as an exploratory step in developing models to identify those patients who may benefit from the combination of MT and Botox in the treatment of CM.

5.10. Summary

This chapter began with the background and rationale for this study. It then gave a reminder of the research questions, followed by a discussion the findings in relation to these questions and the relevant literature and theories underpinning the study. The characteristics of the two randomised groups were considered before discussing the similarities and differences between the primary and secondary outcome measures in research question one and the effect of baseline characteristics in research question two. A summary of clinical implications of the findings was then presented followed by the study strengths and limitations. The next chapter completes this body of work by providing a summary of conclusions that can be drawn from the findings, followed by the key contributions to knowledge and concludes with suggestions for areas of future research.

CHAPTER 6 CONCLUSIONS

6.1. Introduction

At the time of undertaking this PhD, the gold standard for CM treatment in tertiary clinics was the mono-therapy of Botox. Whilst this benefits many patients, often the effects are only partial, resulting in a substantial proportion of individuals still severely affected even after years of intervention. Consequently, there is potential for new approaches to be examined (Silberstein et al. 2014; Ahmed & Gooriah. 2015; Sarchielli et al. 2017).

A narrative review of literature was undertaken that concluded CM was a condition with multiple possible drivers and likely to benefit from a multi-modal approach to treatment including physical therapy, psychotherapy and pharmacological (Diener et al. 2015, Gaul et al. 2016). It highlighted two theories that suggested MT was a potential adjunctive intervention. The first was a neurophysiological-pain model, the second the allostatic model, incorporating a wider range of biopsychosocial considerations (Borsook et al. 2012; May & Schulte. 2016; Bonivita et al. 2018). This was followed by a systematic literature review that confirmed gaps in research, with only two studies of MT as an adjunctive to 'care as usual' CM treatment (Botox) identified. These findings established the overall need for, and aim of the study, which was to evaluate the effect of MT as an adjunctive approach to treatment of CM. There were two main research questions. The first considered what effect adjunctive MT had on treatment outcomes in CM and comprised the primary outcome with additional secondary related outcomes. The second considered the effect of participant baseline characteristics on outcomes.

6.2. Research question one

The results of the primary outcome and secondary outcome measures showed improvements in both disability and quality of life measures when adding MT to Botox over and above Botox alone. Previous studies into the role of MT in primary headaches were often criticised for their low quality and heterogeneity of approach (Fernadez-de-las-Penas 2006; Gonzales 2018). To address this criticism the decision was made to design a pragmatic RCT in a tertiary CM clinic that followed International Headache Society and CONSORT guidelines (Boutron et al. 2017; Tassorelli et al.2018). However, significant variations in the results were found

between this study and that of the main comparative study (Cerritelli et al. 2015) that were most likely the result of differences in design and recording of outcomes (particularly participant selection criteria). For example, compared to this study and larger CM studies, the participants in Cerritelli et al. (2015) had a lower severity in baseline headaches; participants were also excluded if they had common co-morbidities. The proportion of male participants varied significantly between the intervention groups within the Cerritelli et al (2015) study and was much greater than in the majority of CM studies (Popescu et al. 2010; Buse et al. 2013; Scher et al. 2018; Sorge & Strath. 2018). As a result, it was concluded from this current study that heterogeneity in study design for CM was still an issue particularly affecting comparisons of efficacy. It was also concluded that naïve Botox users benefitted from early intervention gains in the first two cycles of treatment followed by reducing returns and a stabilisation after approximately four cycles (Guerzoni et al. 2017; Vernieri et al. 2019; Pijpers et al. 2019). Thus, outcomes in long-term users of Botox, who are still severely disabled, are unlikely to be comparable to naïve users.

In summary, MT as an adjunctive to Botox provides a beneficial effect to females with CM in this study. However, the boundaries of this conclusion may be limited by the CM patient group, which in this study are females who are still severely disabled after more than 4 cycles of Botox and by default most likely in need of an alternative, multi-modal approach to treatment.

6.2.1. Responder rates

This study reported HIT6 responder rates and was the first CM study to report the PGIC responder rates. The results were significantly in favour of adjunctive MT, concluding that MT is useful adjunctive to Botox. Nevertheless, the PGIC results were more significant than the difference in the primary outcome measure (HIT6) would have suggested. This could be seen to corroborate the conclusions of the IMMPACT group (Dworkin et al. 2008, 2009) in that the responder rates provide a broader overview of therapeutic benefit associated with treatment compared to group mean change scores. In contrast, there was no statistical difference in each group, or between groups, over 12 weeks in the responder rates for moderate to severe headache frequency; greater than 30% or 50% reduction (Tassorelli et al. 2018). There was however a high number of participants with a 50% reduction in mild to moderate headache. This outcome was difficult to compare to similar studies as the definitions of a responder, in terms of the percentage reduction in frequency, and the quantification of severity of headaches, e.g. mild/moderate, varied.

A further conclusion from this PhD study, consistent with long-term responder Botox studies, is that the definition of responders in CM studies is an area for further development to enable useful comparison of responder outcomes (Vernieri et al. 2019).

This was the first MT-CM study to use the ASC and presented new data on the reduction in levels (e.g. mild, moderate, etc) of CA. The results suggested that a higher proportion of those in Group M reduced their level of allodynia compared to Group C. From this, it was concluded that this may be a result of the adjunctive benefit of MT reducing central sensitisation and for which a mechanism of action was proposed. However, it was also concluded that using the ASC cut off score (≥2) as a binary measure of CA may mask important underlying clinical changes. At the time of writing and as far as the author is aware, the information presented on ASC outcomes in this study is novel and the first time it has been addressed in CM.

In addressing research question one, both the primary and secondary outcome measures support the view that MT is an effective adjunct to Botox in CM for this group (severely affected female, long-term users of Botox).

6.3. Research question two

This section addresses research question two with regard to the baseline characteristics of participants that influence the outcomes, and that help to identify those patients who might benefit most from MT as an adjunctive treatment. This study was the first to explore the role of potential moderators in MT and CM and put forward initial suggestions on baseline participant characteristics, including biopsychosocial factors, that might be used to determine levels of response. It is important to acknowledge that, although the findings were consistent with other Botox studies (Probyn et al. 2017; Bottiroli et al. 2018), the analyses were made rooted in a small sample size. The results should therefore be seen as a basis for development and provide support for larger studies in the future. The study highlighted four factors of interest in the models; central sensitisation (allodynia), stress related (depression/anxiety), coping behaviour and the relative role of the intervention (MT).

6.3.1. Central sensitisation

The higher allodynia scores appeared to be associated with negative changes for HIT6 outcomes and positive ones for PGIC outcomes. This supports the conclusion that allodynia may be mediated or moderated by factors, not considered in this study but have been in others (Sandkuller et al. 2009; Crettaz et al. 2012; Dodick et al. 2019). It also highlighted how the differences in construct validity of PROMS can produce seemingly contradictory results and reinforced the importance of selecting appropriate measurement instruments for the study design (Scott & McCraken. 2015).

6.3.2. Stress

In this study the stressors identified were consistent with previous studies and included higher than normal levels of depression, anxiety and stress (PSS) and the presence of medication overuse in a high percentage of participants. It concluded that these factors are associated with a more refectory group of CM patients and poorer outcomes. Consequently, giving appropriate consideration to these comorbidities should be an essential part of a multi-modal intervention approach (Buse et al. 2011; Yavuz 2013; Breeman et al. 2015; Lampl et al. 2016; Probyn et al. 2017 Seng et al. 2017).

6.3.3. Coping behaviours

A significant and unexpected finding was the use of maladaptive coping behaviours in positive outcomes. This has been discussed in studies of the ‘fear-avoidance’ model in chronic pain and headaches. These suggest short term maladaptive coping can be useful, particularly in cases where patients believe there is no solution to their problem (Philips 1987; Gunnel & Akkaya. 2008; Turk & Wilson. 2010; Biagianti et al. 2014; Garcia et al. 2018). An important conclusion therefore is that the long-term use of Botox in some patients may be enabling maladaptive avoidance coping, which provides a short-term fix, but could result in long term disability. This disability may then be reflected in, and affected by, a two-way relationship with stressors such as depression and musculoskeletal pain. This would support the chronification process for CM proposed in the allostatic model (Borsook et al. 2012).

6.3.4. Medication use

Although substance or medication use is a coping behaviour, it is important to highlight its negative influence at almost every stage of analysis in this study. Medication overuse was also the only factor that reduced the probability of being a HIT6 responder in both groups. This finding corroborates previous work into the negative influence of increased substance use i.e. medication overuse on treatment outcomes in CM (May & Schulte. 2016; Vandenbussche et al. 2018).

6.3.5. Manual therapy, mediation and moderation

The pragmatic conclusion in this study is that MT, as an adjunctive to Botox, improved the outcomes for Group M compared to Group C. However, conclusions on the potential roles of MT, outlined below, are areas for further development. The study indicated that the baseline HADS_Total may have moderated the effect of Botox in Group C whilst other, possibly different, unidentified mechanisms, reduced its effect on the combined MT and Botox in Group M. In addition, behavioural disengagement was the only coping factor that showed a significant reduction over the 12 weeks, in favour of Group M. From this, a tentative conclusion is that it may have a mediating role on Group M. These findings suggest a possible role for MT in the management of CM via an influence on psychosocial factors (Williams et al. 2007; Wirth et al. 2016; Courtney et al. 2017; Seng et al.2017).

Based on the changes seen in the ASC outcomes for CA in Group M, it might be concluded that if both Botox and MT reduce peripheral nociception (Scheuler et al. 2013; Burstein et al. 2014; Courtney et al. 2017; Do et al. 2018; Melo-Carrillo et al. 2019;) then there was an additive effect from MT which helped reduce nociceptive input compared to Botox alone. Consequently, these nociceptive changes could have interacted in the higher brain (e.g. thalamus, cortex) with inputs from the sensory (psychological including emotions, beliefs and environmental challenges) which are then modulated by the descending analgesic system (Shacklock 1999; Crettaz et al. 2012; Kumar 2018; Dodick et al. 2019). Therefore, this study's outcomes suggest an involvement with MT on both pain and psychological mechanisms of migraine as suggested in the allostatic and neurobiological models of migraine used to underpin the rationale for the study (Borsook et al. 2012; Schwedt 2014; May& Schulte. 2016; Bonivita et al. 2018; Borsook et al. 2019). It was concluded that adjunctive MT provides a better response in HIT6 and PGIC responder outcomes than Botox alone in those patients who have maladaptive coping behaviours and higher levels of allodynia.

6.4. Summary

This PhD study supports the view that severely affected female CM patients may be better helped by embracing a multi-modal model of treatment that addresses factors proposed in both the neurophysiological and allostatic models of CM (Figure 5.4) rather than a mono-therapeutic approach. A combination of Botox and MT is one such option.

6.5. Contributions to knowledge

The findings built on the work of Cerritelli et al. (2015) and Gandolfi et al (2017) adding new evidence for the role of MT as an adjunctive intervention for CM and built support for evidence-based multi-modal intervention options for those with CM. The study also identified a lack of consistency in the selection of participants, reporting of outcome measures and the measurement tools used in the two previous studies involving CM and MT. This represented an important finding as it highlighted the difficulties with comparing outcomes between studies and reinforced the drive for improvements in headache-MT study guidelines.

At the time of writing this was the first CM study to use the PGIC outcomes to evaluate the difference in responder rates between two interventions and found a significantly higher responder rate for the adjunctive MT therapy over Botox alone. This outcome supported the view of the IMMPACT trial that a broader measure of treatment response (e.g. PGIC) may be required over and above just measures of power and differences in group mean change scores. The study also contributes new information by identifying baseline participant factors that might identify those females with long standing CM most likely to respond to MT as an adjunctive to Botox. These are: central sensitisation, stress related (depression/anxiety) and coping behaviour. Although individually these have been linked to migraine and chronic migraine, no previous study has brought them together. The movement between categories in allodynia, measured by the ASC, also suggested that examining these changes may be a better indication of treatment effect on central sensitisation rather than using the current dichotomous cut-off score. The analysis also provided both new and unexpected information on the use of maladaptive coping with denial and self-distraction both increasing the likelihood of being a responder in PGIC and HIT6, rather than the expected reduction. One interpretation of this finding is that, in this group of patients, the long-term use of Botox may be encouraging dependency and a failure to try potentially more useful coping strategies, which aligned with findings from studies of the fear-avoidance model in

chronic conditions and has significant clinical implications. This was also the first study to explore the potential effect of moderating factors in MT and Botox in CM on outcomes. As a result, the HADS_Total was found to affect the HIT6 outcomes in the Botox group but not the adjunctive MT group, which suggests that psychological stress (HADS_Total) might moderate the action of Botox and could be an important consideration in multi-modal treatment. All of the above analyses were made acknowledging the small sample size and propose that this study should be seen as a starting point for larger studies.

6.6. Publications

Published:

Odell et al. (2019). Manual therapy for chronic migraine: a pragmatic randomised controlled trial study protocol. Chiropractic and manual therapies. doi.org/10.1186/s12998-019-0232-4

Planned:

1. Manual therapy as an adjunctive to Botox in females with chronic migraine: a pragmatic randomised controlled trial. Target journal: Chiropractic and Manual Therapies
2. Coping strategies in long term users of Botox for chronic migraine. Target journal: The Journal of Head and Face Pain
3. Manual therapy and allodynia in chronic migraine using the allodynia score checklist. Target journal: Musculoskeletal Science and Practice

Presentations:

Royal College of Chiropractors Conference. Headache Guidelines. Jan 2020

6.7. Suggestions for future research

This study, as with others of MT in CM, had a relatively small sample size. There is a need for larger studies to build upon the findings of the few existing studies in the field. To achieve this, it would be useful to have multisite studies encompassing different geographic regions, as was originally planned for this PhD study. Such studies would also enable the impact of differences in day-to-day clinical practice on outcomes to be examined. Consistent with a larger and multisite study the use of a ‘sham’ placebo group combined with ‘care as usual’ (and perhaps wait list groups)

should also be encouraged. This would make outcomes more readily comparable to non-MT studies, and would also strengthen the external validity of the studies. However, because a true adjunctive sham MT intervention is difficult to create (as it is argued that any form of MT can create a potential effect) a different approach and reasoning for the sham might need considering. The question often raised is the level of placebo effect from MT, over and above the 'gold standard treatment' in an adjunctive study. Since two factors, expectancy and conditioning (social interaction with clinician), are the most cited, then it may be possible to use an inert 'pill/medication' as an adjunctive placebo. The participants receiving 'care as usual' and the placebo could attend on the same basis as the MT sessions, during which similar measurements could be taken. This would have the effect of replicating the theorised placebo effect gained from the increased contact participants have with MT, without the application of any MT. However, since the undefined psychosocial component of headache interventions is considered to add to the placebo effect, future research should focus on quantifying the differences that factors such as expectancy and time spent with the clinician make to outcomes.

With the advent of more expensive pharmacological interventions such as the latest CGRP medications and the continuation of existing ones, the importance of identifying sub-groups of responders to treatment is paramount for both for the patients and also health care providers. Future adjunctive studies should be used to identify these subgroups from their baseline characteristics, which can only be achieved with appropriate study design. The evidence from existing studies shows there is a difference between outcomes in long term users of Botox and naive users, with most pharmacological studies involving a high proportion of naive users. This PhD study involved long term users of Botox, which most likely reduced the effect of Botox on the one hand but made the group as a whole more refractory to treatment. To make suitable clinical comparisons of treatment effect, future studies should consider comparative studies involving naive and long-term users to gauge the effect of MT alone, and as an adjunctive to Botox in CM.

My PhD study also found that there is still limited understanding of the mechanisms of action of MT in CM. This needs to be addressed with clinical research, in order to help validate or modify existing models. This study suggested that MT helps reduce central sensitisation by adding to the reduction in nociception achieved with Botox. However other studies suggest MT may also have an effect on other neurotransmitters (including inflammatory neurotransmitters) associated with

reductions in central sensitisation and CM outcomes. Future research into biochemical changes in CM, or chronic pain, that result from MT should be considered. Following on from this, since the development of central sensitisation and allodynia is an important step in CM and other chronic pain conditions. In this study, the ASC outcomes seemed to show that MT added to the effect of botox in reducing allodynia. Future research into the benefits of MT in CM or other chronic pain conditions using objective measures (rather than PROMs) of allodynia/central sensitisation would be valuable in the development of new approaches to management.

One of the unexpected findings in this study was the influence that negative, avoidant behaviours appeared to play in positive outcomes which showed strong resonance with the FA models of pain behaviours. Thus, whilst many studies have identified an association between psychological factors and both treatment response and chronification in CM, no studies to date have explored the mediators or moderators in treatment response involving MT (or any other intervention). The sample size in this PhD study was designed to address the study's primary objective and was unable to provide anything other than an indication of potential in the area of moderation and mediation. However, the results were consistent with studies for similar conditions such as fibromyalgia, chronic pain and tension headaches, in suggesting that certain psychological factors may mediate or moderate treatment outcomes. Support was also given to existing studies that MT may create effect through / on psychological factors. As many CM patients have similar psychological co-morbidities in common, fruitful areas for study could include:

(1) exploring the effect of MT as an adjunctive to psychological therapy for CM and EM, with a view to identifying those factors that lead to chronification and the role of the fear avoidance model.

(2) developing more substantive predictive models, using baseline psychological factors to identify those most likely to respond to Botox (or other intervention).

All headache studies, including CM, rely on patient reported outcomes (PRO), in the absence of objective clinical measures. This has led to treatment outcomes focussed on change between group means measures and *p* values. However, for many of the PRO used there is no agreed MCID for CM (or other headaches) and the ensuing calculated clinical change may often not be seen as a beneficial or substantive change to the individual patients. This is especially true for CM patients

when many are still classed as severely disabled by the HIT6 scoring after long term use of interventions such as Botox. A similar pattern is also seen in many clinical trials where, despite a statistically significant difference in group mean change scores using the HIT6 outcome, many participants are still classed as severely affected. An example from this PhD study is the seemingly disproportionate PGIC responder outcomes when compared to the difference in the HIT6 between group mean change score outcomes. This suggests the PGIC is measuring other attributes of treatment outcome that may have importance to the participants. For patients receiving long term intervention, but who remain severely disabled, future research should look to develop measurement instruments that can be used in clinical trials and clinical practice to better evaluate beneficial change at both individual and group levels.

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CHAPTER 8 APPENDICES

Appendix 1. Systematic reviews explored

Table of systematic reviews assessed for studies to include.	
Bronfort G. 2001	Efficacy of spinal manipulation for chronic headache: A systematic review, Journal of Manipulative and Physiological Therapeutics
Astin, J. A. 2002	The effectiveness of spinal manipulation for the treatment of headache disorders: A systematic review of randomized clinical trials Cephalalgia
Bronfort G. 2010	Effectiveness of manual therapies: The UK evidence report Chiropractic and Osteopathy
Chaibi, A. 2011	Manual therapies for migraine: A systematic review Journal of Headache and Pain
Posadzki P. 2011	Systematic reviews of spinal manipulations for headaches: An attempt to clear up the confusion. Headache
Chaibi A. 2014	Manual therapies for primary chronic headaches: a systematic review of randomized controlled trials Journal of Headache and Pain
Clar C. 2014	Clinical effectiveness of manual therapy for the management of musculoskeletal and non-musculoskeletal conditions: Systematic review and update of UK evidence report
Lopez L 2014	Efficacy of manual therapy in the treatment of tension-type headache. A systematic review from 2000 to 2013
Wanderley D. 2014	Manual therapies for pain relief in patients with headache: A systematic review Revista Neurociencias
Updated at end of Jan 2019 and Jan 2020	
Falsiroli Maistrello L 2018	Effectiveness of trigger point manual therapy on the frequency, intensity and duration of attacks in primary headaches: A systematic review and meta analysis of randomized controlled trials. Frontiers in Neurology
Falsiroli Maistrello L 2019	Falsiroli Maistrello, L., Rafanelli, M. and Turolla, A., 2019. Manual Therapy and Quality of Life in People with Headache: Systematic Review and Meta-analysis of Randomized Controlled Trials. Current Pain and Headache Reports, 23 (10).
Rist P M 2019	Rist, P., Hernandez, A., Bernstein, C., Kowalski, M., Osypiuk, K., Vining, R., Long, C., Goertz, C., Song, R. and Wayne, P., 2019. The Impact of Spinal Manipulation on Migraine Pain and Disability: A Systematic Review and Meta-Analysis. Headache: The Journal of Head and Face Pain, 59 (4), 532-542.

Appendix 2. Literature search results

Database	Results search	Imported to endnote following title search	Remove duplicates	First filter Title, case studies, systematic reviews, Non studies, articles etc	2nd filter Title, Abstract	Final full text search	Included in study
Web of Science	574	90					
CinAhl	898	77					
Embase	1536	244					
Medline (pubmed)	468	125					
PsychInfo	90	88					
Cochrane	23	23					
Science Direct	893	221					
Scopus	1276	75					
AMED	194	38					
Other sources		1					
Total left	5952	982	753	123	66	27	2

Appendix 3. De las Penas headache quality checklist proforma

1. Study population (30 points)	
A. Description of inclusion and exclusion criteria (1 point). Restriction to a homogeneous study population (1 point) -	
B. Comparability of relevant baseline characteristics: duration of complaint (1 point), value of outcome measures (1 point), age (1 point), recurrences (1 point), and radiating complaints/associated symptoms (1 point)	
C. Description of the randomization procedure (2 points). Randomization procedure which excluded bias, ie, random numbers table (2 points)	
D. Description of dropout for each group and reason (3 points)	
E. Loss to follow up: < 20% (2points) OR < 10% (4 points)	
F. Sample size: greater than 50 subjects in the smallest group after randomization (6 points), OR greater than 100 subjects in the smallest group after randomization (12 points)	
2. Interventions (30 points)	
G. Correct description of the manipulative intervention (5 points). All interventions described (5 points)	
H. Pragmatic study: comparison with an existing treatment modality (5 points)	
I. Co-interventions avoided in the design of the study (5 points)	
J. Comparison with a placebo control group (5 points)	
K. Mention of the experience of the manipulative therapist (5 points)	
3. Measurement of effect (30 points)	
L. Placebo controlled studies: patients blinded (3 points), blinding evaluated and fully successful (2 points)	
OR	
Pragmatic studies: patients fully naive, evaluated and fully successful (3 points), time restriction of no manipulative treatment for at least 1 year (2 points)	
M. Outcome measures: pain assessment (2 points), global measure of improvement (2 points), functional status (2 points), spinal mobility (2 points), medical consumption (2 points)	
N. Each blinded outcome measure mentioned under item L earns 2 points	
O. Analysis of post-treatment data (3 points), inclusion of a follow-up period longer than 6 months (2 points)	
4. Data presentation and analysis (10 points)	
P. Intention-to-treat analysis when loss to follow-up is less than 10% OR intention-to-treat analysis as well as worst-case analysis for missing values when loss to follow-up is greater than 10% (5 points)	
Q. Corrected presentation of the data: mean or median with a standard deviation or percentiles for continuous variables 5 points	
Total Score/100	
Methodological Quality > 50 = Good	

Appendix 4. Studies excluded from final screening

Studies excluded from final eligibility screen (CM = chronic migraine)		
Author	Title	Brief description and reason for removal
Adragn et al. 2015	Migraine without aura and osteopathic medicine, a non-pharmacological approach to pain and quality of life: open pilot study	A small (n=8) migraine only study. Single treatment. Not CM.
Akbayrak et al. 2001	Manual therapy and pain changes in patients with migraine - an open pilot study	A female only (n=30) study of migraine and connective tissue massage. Included physical therapy of a hot pack. Not CM
Bevilaqua-Grossi et al. 2016	Additional Effects of a Physical Therapy Protocol on Headache Frequency, Pressure Pain Threshold, and Improvement Perception in Patients With Migraine and Associated Neck Pain: A Randomized Controlled Trial	A migraine study, plus neck pain . no CM included (n=50) this was an adjunctive study
Boline, et al,1995	Spinal Manipulation vs Amitriptyline for the treatment of Chronic Tension Type Headaches -An RCT	Large (n=150) study. All chronic tension-type. Not CM.
Calandre et al. 2003	Effectiveness of prophylactic trigger points inactivation in chronic migraine and chronic daily headache with migraine features	This is not manual therapy but injections using ropivacaine.
Chaibi et al. 2017	Chiropractic spinal manipulative therapy for migraine: a three-armed, single-blinded, placebo, randomized controlled trial	A migraine study,(n= 105). not CM.
Chatchawan et al. 2014	Effects of Thai traditional massage on pressure pain threshold and headache intensity in patients with chronic tension-type and migraine headaches	The group is described at chronic tension-type headache and migraine. No separate analysis of each is made and no mention of CM (n=72)
Espí-López, et al. 2016	The effect of manipulation plus massage therapy *versus* massage therapy alone in people with tension-type headache. A randomized controlled clinical trial	Tension type headache only. (n=105) compared SMT and massage versus massage
Espí-López et al. 2017	Manual therapy as a proposed treatment for CM	A position paper
Ferracini et al. 2017	Myofascial Trigger Points and Migraine-related Disability in Women With Episodic and Chronic Migraine	A study of characteristics not treatment. Did include CM (n=55) but no stratification of results
Ferragut-Garcıas et al. 2016	Effectiveness of a Treatment Involving Soft Tissue Techniques and/or Neural Mobilization Techniques in the Management of Tension-Type Headache: A Randomized Controlled Trial	Tension type only. (n=97).
Ghanbari et al. 2015	Migraine responds better to a combination of medical therapy and trigger point management than routine medical therapy alone	An adjunctive study on migraine (n=22). Not CM.
Happe et al. 2016	The efficacy of lymphatic drainage and traditional massage in the prophylaxis of migraine: a randomized, controlled parallel group study	Migraine only, No CM. (n=64)
Lawler &	A randomized, controlled trial of massage therapy as a	An RCT migraine study (n=48). No

Cameron,2006	treatment for migraine	CM included.
Nelson et al.1998	The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache	Migraine study.CM people were included but had concomitant TTH and no stratified results were produced.
Noudeh et al. 2012	Reduction of current migraine headache pain following neck massage and spinal manipulation	Acute migraine males only (n=10) No CM.
Parker, Tupling & Pryor, 1978	A controlled trial of cervical manipulation of migraine	Number of migraine days per month in subjects do not qualify as CM (n=99).
Rolle et al. 2014	Pilot Trial of Osteopathic Manipulative Therapy for Patients With Frequent Episodic Tension-Type Headache	This is episodic tension-type headache (n=40)
Schnider et al. 2002	Physical therapy and adjunctive botulinum toxin type A in the treatment of cervical headache: A double-blind, randomised, placebo-controlled study	This is cervicogenic headaches (n=33) and used his criteria. Not primary headache or CM.
Tuchin, Pollard & Bonello et al. 2000	A randomized controlled trial of chiropractic spinal manipulative therapy for migraine	The term CM didn't exist but figures supplied show that average frequency of attacks was only 7 pm which does not qualify as CM (n=127).
Voight et al. 2011	Efficacy of Osteopathic Manipulative Treatment of Female Patients with Migraine: Results of a Randomized Controlled Trial	This was migraine only (n=42). It was not compared against active intervention.
Following studies were not included as details could not be obtained.		
Xu Ji-Hua et al. 2017	A randomized controlled trial of acupressure as an adjunctive therapy to sodium valproate on the prevention of chronic migraine with aura	Study states CM in title but migraine in text and episodes per month average only 2 which is not CM (n=89). Author contacted
Granato A, et al.2017	Efficacy of onabotulinumtoxin A and physical therapy combined in treatment of chronic migraine	Used CM although included exercises and no details on stratified results. (n=25). Author contacted
Stodolny & Chmielewski, 1989	Manual therapy in the treatment of patients with cervical migraine	Abstract indicates migraine. Full text requested although CM was not a common term in 1989 and text may indicate CM.
Forbes et al. 2015	Use of physiotherapy by 83 people with chronic migraine undergoing treatment with botulinum toxin Type A (BTX-A)	This was a physiotherapy not manual therapy study into CM. The author was contacted and sent details but it was not peer reviewed and not available in complete form so was excluded at this stage (n=83)

Appendix 5. Cerritelli et al. Study Quality by Score

CERRITELLI ET AL ET AL. (2015) CLINICAL EFFECTIVENESS OF OSTEOPATHIC TREATMENT IN CHRONIC MIGRAINE: 3-ARMED RANDOMISED CONTROLLED TRIAL.	
1. Study population (30 points)	
A. Description of inclusion and exclusion criteria (1 point). Restriction to a homogeneous study population (1 point) - **ICHD criteria for CM confirmed by neurologist** **- Inclusion and exclusion**	2
B. Comparability of relevant baseline characteristics: duration of complaint (1 point), value of outcome measures (1 point), age (1 point), recurrences (1 point), and radiating complaints/associated symptoms (1 point) **- no difference between groups - HIT 6 (-2.3diff)**	3
C. Description of the randomization procedure (2 points). Randomization procedure which excluded bias, ie, random numbers table (2 points)	4
D. Description of dropout for each group and reason (3 points)	3
E. Loss to follow up: < 20%(2points) OR < 10% (4 points)	4
F. Sample size: greater than 50 subjects in the smallest group after randomization (6 points), OR greater than 100 subjects in the smallest group after randomization (12 points)	0
2. Interventions (30 points)	
G. Correct description of the manipulative intervention (5 points). All interventions described (5 points)	10
H. Pragmatic study: comparison with an existing treatment modality (5 points)	5
I. Co-interventions avoided in the design of the study (5 points) - **not mentioned**	0
J. Comparison with a placebo control group (5 points) - **used sham**	5
K. Mention of the experience of the manipulative therapist (5 points)	5
3. Measurement of effect (30 points)	
L. Placebo controlled studies: patients blinded (3 points), blinding evaluated and fully successful (2 points)	5
OR	
Pragmatic studies: patients fully naive, evaluated and fully successful (3 points), time restriction of no manipulative treatment for at least 1 year (2 points)	0
M. Outcome measures: **pain assessment (2 points**), **global measure of improvement** (**2 points), functional status (2 points**), spinal mobility - (2 points), **medical consumption (**2 points)	8
N. Each blinded outcome measure mentioned under item L earns 2 points (not clear what was)	2
O. Analysis of post-treatment data (3 points), inclusion of a follow-up period longer than 6 months (2 points)	3
4. Data presentation and analysis (10 points)	
P. Intention-to-treat analysis when loss to follow-up is less than 10% OR intention-to-treat analysis as well as worst-case analysis for missing values when loss to follow-up is greater than 10% (5 points)	5
Q. Corrected presentation of the data: mean or median with a standard deviation or percentiles for continuous variables 5 points	5
Total Score/100	69
Methodological Quality > 50 = Good	Very Good

Appendix 5a. Gandolfi et al. Quality by Score

Gandolfi et al. (2017) - Does myofascial and trigger point treatment reduce pain and analgesic intake in patients undergoing OnabotulinumA injection due to chronic intractable migraine? - Pilot single blind RCT	
1. Study population (30 points)	
A. Description of inclusion and exclusion criteria (1 point). Restriction to a homogeneous study population (1 point)	2
B. Comparability of relevant baseline characteristics: duration of complaint (1 point**), value of outcome measures (1 point),** age (1 point**),** recurrences (1 point), and radiating complaints/associated symptoms (1 point)	3
C. Description of the randomization procedure (2 points). Randomization procedure which excluded bias, ie, random numbers table (2 points)	2
D. Description of dropout for each group and reason (3 points**) - none**	3
E. Loss to follow up: < 20%(2points) OR < 10% (4 points)	0
F. Sample size: greater than 50 subjects in the smallest group after randomization (6 points), OR greater than 100 subjects in the smallest group after randomization (12 points)	0
2. Interventions (30 points)	
G. Correct description of the manipulative intervention (5 points). All interventions described (5 points)	10
H. Pragmatic study: comparison with an existing treatment modality (5 points)	0
I. Cointerventions avoided in the design of the study (5 points) **(tricky)**	3
J. Comparison with a placebo control group (5 points) - **TENs - not really placebo**	3
K. Mention of the experience of the manipulative therapist (5 points) -	0
3. Measurement of effect (30 points)	
L. Placebo controlled studies: patients blinded (3 points), blinding evaluated and fully successful (2 points)	5
OR	0
Pragmatic studies: patients fully naive, evaluated and fully successful (3 points), time restriction of no manipulative treatment for at least 1 year (2 points)	0
M. Outcome measures: **pain assessment (2 points), global measure of improvement (2 points), functional status (2 points), spinal mobility - (2 points), medical consumption (2 points) -**	10
N. Each blinded outcome measure mentioned under item L earns 2 points	2
O. Analysis of post-treatment data (3 points), inclusion of a follow-up period longer than 6 months (2 points)	3
4. Data presentation and analysis (10 points)	
P. Intention-to-treat analysis when loss to follow-up is less than 10% OR intention-to-treat analysis as well as worst-case analysis for missing values when loss to follow-up is greater than 10% (5 points)	0
Q. Corrected presentation of the data: mean or median with a standard deviation or percentiles for continuous variables 5 points	5
Total Score/100	51
Methodological Quality > 50 = Good. NB this was a pilot study	Good

Appendix 6. OCEBM – Levels of Evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

Appendix 7. TiDier Checklist - Cerritelli et al. (2015)

Provide the name or a phrase that describes the intervention.	Page
1a. Osteopathic Manipulative Treatment versus 1b. Sham Therapy (light manual contact) plus medication (triptans) and 1c. Medication (triptans)	150,151
WHY	
2. Describe any rationale, theory, or goal of the elements essential to the intervention.	150
Migraine aetiology is thought to be the result of multifactorial epigenetic mechanisms. There is accumulating evidence to support that the central sensitization plays a critical role in migraine pathogenesis. This creates a functional alteration of key centers in the central nervous system (CNS), in particular the trigeminovascular nuclei. Neurogenic inflammation of meninges is considered to activate specific neural pathways transmitting pain signals to the trigeminovascular system and vegetative nervous system (VNS) nuclei. This condition may predispose to VNS dysfunctions which have been suggested to be one of the causes of headache. Therefore, dysfunctional nervous structures, inflammatory condition and functional alteration of the VNS may be responsible for the pain and contribute to migraine pathophysiology. Recent studies provided information about the possible association between manual therapies in particular osteopathic manipulative treatment (OMT) and its effects on migraine. Voigt et al. carried out an RCT showing the effects of OMT on migraineurs' quality of life. The author claimed a significant improvement in the quality of life parameters as well as a reduction of pain. Another piece of research evaluated the effects of OMT in patients with headaches. Patients who received 8—12 osteopathic sessions showed a significant reduction of pain and frequency of attacks. In 2006 Anderson and Seniscal compared the effects of OMT to progressive muscular relaxation exercises on patients with tension-type headache. Subjects who under-went both treatments, showed significant improvement on joint and myofascial stiffness and reduction of pain com-pared to exercise only.	
WHAT	
3 N/A	
4a. Osteopathic manipulative treatment (OMT) based on an individual structural evaluation and an indirect technique treatment.	151, 152 (Table 1)
Myofascial release & BLT: A system of soft manual treatment directed to the muscles and fascia which engages the detection of restriction of motion and continual palpatory feedback to achieve release of myofascial tissues A complex of light manual movements that allows the practitioner to test the tension of ligaments, disengage the area with SD, find the point of balance and treat the area according to the existing range of motion	
BMT : Same as BLT but applied to the cranial field	
Cranial-sacrum : An approach that uses soft touch to explore the primary respiratory mechanism and treat any imbalance between sacrum (pelvis) and cranial bones motility	
4b. SHAM	
Sham treatment used light manual contact to ''treat'' the subject and was administered with subject lying supine on the treatment table.	
4c. Medication Care as Usual. Triptans	
4d. Secondary outcome measures were taken from the migraine diary.	
WHO PROVIDED	
5a. OMT and Sham provided by 6 osteopaths, ROI certified.	151
5b. Care as Usual medication provided by neurologist.	
WHERE	
7a. Recruitment and medication undertaken in Department of Neurology of Ancona's United Hospitals. Actual OMT and SHAM treatment location is unclear.	150
WHEN and HOW MUCH	
8a. OMT and sham therapy sessions were face to face and lasted 30 min. They were scheduled weekly for the first two sessions, biweekly for the subsequent two, then monthly for the remained four sessions	151
8b. Medication was On-going.	
TAILORING	
9a. OMT: A need-based patient treatment approach based on findings derived from the osteopathic evaluation and not based on a pre-determined protocol, was applied to the study group. Criteria considered for osteopathic evaluation and treatment were tissue alteration, asymmetry, range of motion and tenderness parameters.	151
9b. Sham: The anatomical areas contacted were different across sessions and were based on the personal choice of the operator. There was no standardized protocol in terms of number, duration and typology of touching regarding the manual bodily contacts.	
MODIFICATIONS	
10a. Both OMT and Sham groups required to maintain stable medication regimens but could alter acute medication	151
10b. Care as usual group (medication) were able to adjust, change and optimize medication regimens as directed by the physician	
HOW WELL	
Clinical evaluations were performed at entry (T0) and after 24 weeks (T1) by the same neurologist who was blinded to the patient's allocation and outcomes.	150, 151
No planned assessment of adherence identified upfront.	
No final intervention assessment reported although figures suggest all randomised participants completed the study.	

Appendix 7a. TiDier Checklist - Gandolfi et al. (2017)

Provide the name or a phrase that describes the intervention.	Page number
1a. Manipulative techniques plus OnabotulinumA 1b. Transcutaneous Electrical Stimulation (TENS) plus Onabotulinum	
WHY	
2a. Although Chronic migraine can be very disabling its pathophysiological mechanisms are not entirely understood, it involves dysfunctions in the pain-modulating network due to altered regulation of excitatory-inhibitory balance results in sensitization of the trigeminocervical caudalis nucleus that, in turn, lowers the threshold for developing new attacks. Factors besides neurovascular dysfunction that can contribute to migraine are myofascial trigger points which increase tension of the taut muscular bands and the facilitation of motor activity contribute to the development or maintenance of sensitization mechanisms by excitation of muscle nociceptors. During these sensitization phenomena, the dorsal horn neurons may become hyperexcitable with the presence of multiple (spatial summation) and active trigger points (temporal summation) provoking a continued nociceptive afferent barrage into the central nervous system. Patients with migraine exhibit active myofascial trigger points in the splenius capital, upper trapezius, and sternocleidomastoid muscles, which reproduce their migraine. Standard preventive treatments include betablockers, topiramate or valproate though their tolerability and adverse effects often limit their use. Epidemiological studies have indicated that more than one in four migraineurs need prophylactic therapy, but only 33% of these patients receive it. In 2010, onabotulinumtoxinA injection was approved by the U.S. Food and Drug Administration for the preventive treatment of chronic migraine. Rehabilitation procedures (e.g., transcutaneous electrical nerve stimulation [TENS], physical therapy) play a key role in treatment programs addressed to mitigate neuromuscular dysfunction in headache patients. Manual therapies focus on soft tissue work, stretching, active and passive mobilization and manipulation techniques to treat musculoskeletal dysfunction. The effectiveness of manipulative treatment as an adjuvant therapy in the management of patients with neurological diseases has been recently reviewed. Results showed that studies on the efficacy and/or effectiveness of manipulative treatment are scarce.	2,3
2b. The aim of this study was to evaluate the feasibility of myofascial and trigger point treatment in chronic migraine patients receiving prophylactic treatment with onabotulinumtoxinA. To evaluate the treatment effects on headache frequency and intensity, analgesic consumption, cervical range of motion, trigger point pressure pain threshold, quality of life, and disability	4,5
WHAT	
3 N/A	
4a. Manipulative treatment	4,5
Each session consisted of two steps: myofascial release and manipulative articulatory technique. The manipulative techniques were aimed at improving cervical and thoracic spine joint mobility and reducing soft tissue stiffness of the cervicothoracic spine. Cervical manipulative articulatory technique in side bending. Occipito-Atlant manipulative articulatory technique in side bending. Thoracic technique (Full details of all intervention are provided in paper)	
4b. TENS	
Delivered with a portable device (Master 932, Elettronica Pagani SRL , Milan, Italy) that generates symmetric, bi-phasic rectangular pulses 140 μs in duration. Current frequency was set at 150 Hz and intensity was increased up to the patient's perception of paresthesia. The negative electrode was placed on the active trigger point of the upper trapezius muscle and the positive electrode on the insertion of the acromial tendon. Treatment frequency and duration were the same as described for the experimental group (EG) treatment (1 session/week for 4 weeks).	
4c. OnabotulinumA administered by injection for all treatments	
4d. Secondary outcome measures were taken from the migraine diary.	
WHO PROVIDED	
5a. Manual Therapy and TENS sessions were performed by one experienced physical therapist per group	4
5b. OnabotulimumA injected by neurologist.	
WHERE	
7a. All treatment in Neurorehabilitation Unit of AOUI of Verona (Italy).	3
WHEN and HOW MUCH	
8a. Treatment consisted of 4 sessions (30 min/session, 1 session/week for 4 weeks).	4
TAILORING	
9a. Manipulation plus Botox: The treatment processes were specific but the application was on an individual basis.	4
9b. TENs plus botox : not tailored	
MODIFICATIONS	
10a. none	
HOW WELL	
11a. The planned assessment of adherence was identified up front.	4,5
11b. Final intervention assessment was fully reported.	6,7

Appendix 8. PRECIS – 2. Study Analysis

DOMAIN	SCORE	RATIONALE
Eligibility Criteria	5	Females over 18 diagnosed with chronic migraine and without other neurological conditions. Not having had manual therapy in last 6 weeks. All having had at least 1 round of botox to minimize risk of medication over use.
Recruitment Path	5	From consultant list. Everyone with chronic migraine attending for treatment
Setting	5	In the neurology clinic with manual therapy at set clinics as intervention would normally be applied
Organisation intervention	4	a trained manual therapist with relevant skills
Flex of experimental intervention – Delivery	5	The therapist has an open protocol for the intervention approach only subject to treating the upper body, head neck with manual therapy
Flex of experimental intervention – Adherence	3	Text messages are sent weekly to remind participants to complete diary and they are contacted when final information/examination is required. The Manual therapy group have set appointments which they attend. No specific methods to adhere are made
Follow up	4	All participants complete a diary, a start and end questionnaire - very similar to their normal approach but including more data
Outcome	5	The primary outcome is a change in their disability measure HIT6 with other patient reported outcomes used.
Analysis	3	Participants who become excluded after the randomisation will not be included nor will the data from those who drop out. Partial data will be included with analysis altered to the situation

Appendix 9. Letter of Invitation

V17.0 24/06/18

Addressed from Salford Royal NHS Trust

Dear Ms XYZ

Help with Research into Chronic Migraine

I would like to ask you to consider taking part in a study into manual therapy and its effect on your chronic migraine. There will be two groups and you have a one in two chance of being allocated to the group that does not receive manual therapy. In this case you will still receive your usual care for migraines.

If you think you might be interested in taking part after reading the enclosed Participant Information Sheet please bring this letter to your next appointment with Dr Zermansky/Nurse Jones.

Alternatively if you would like to register your interest prior to your next appointment or have any questions to help you make a decision about taking part, please do not hesitate to contact Mr Odell on 07413 833690 or via email on JOdell@Bournemouth.ac.uk.

Yours Sincerely,

Dr Zermanksy

You will be given a Personal Reference which will be confirmed if you decide to take part. It is the combination of your month of birth, the first letter of your surname and the first name of your favourite singer or actor. For example if you were born in August and your surname is Smith and you like Elvis Presley your PR would be 8SELVIS.

Appendix 10. Participant Information Sheet

Participant Information Sheet

A STUDY INTO MANUAL THERAPY AS AN ADDITION TO CARE AS USUAL FOR CHRONIC MIGRAINE

I would like to invite you to take part in my research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information.

Why have I been invited to take part in the study?

You have been invited as you are a woman, over 18 years of age, diagnosed with chronic migraine and currently undergoing treatment from a neurologist.

What is the purpose of the study?

The purpose of the study is to see what effect manual therapy (massage and manipulation to the muscles and joints of the neck, shoulders and upper back) has when given alongside care as usual in the treatment of chronic migraine.

Do I have to take part?

It is completely your decision to take part in this study. If you would like to take part you will be asked to sign a consent form. You are free to withdraw at any point from the study without explanation and this will not alter the care you receive.

What will happen to me if I take part?

You will sign a consent form and then you will be allocated randomly by computer (a bit like tossing a coin) to either, a “Care as Usual" group where you will continue with your normal treatment by your neurologist, or to a "Care as Usual **plus** Manual Therapy" group.
You will not know which group you are in before consenting to take part in the study and have an equal chance of being in either the Care as usual group or the Care as usual plus Manual therapy group.

Both groups will be asked to complete questionnaires at the start and end of the study (approximately 20 minutes each) and to complete a paper or online diary (few minutes) once per week concerning your headaches, stresses and sleep. You will also have an initial meeting with the researcher at the start and end of the study (15 minutes each time) to take some measurements relating to pain threshold.

Participants in the Manual Therapy group will be expected to attend five 30 minute sessions over 12 weeks. They will take place at a Salford Royal (SRFT) NHS site .The sessions will involve massage and/or manipulation of the muscles around the neck and shoulders performed by the researcher who is an experienced chiropractor and runs a clinic for SRFT.

What are the risks of taking part?

If you are randomised to the“Care as Usual” group you will continue to see your neurologist as normal. You will not receive manual therapy. If you are randomised to the “Manual Therapy” group you will also receive massage and/or manipulation of the muscles and joints of the neck, shoulders and upper back. About 50% of people treated with any manual therapy can expect mainly minor to moderate temporary increased discomfort after treatment. A possible link between spinal manipulations of the neck with one rare type of stroke has been investigated and the conclusion is that there is no evidence of spinal manipulation causing this. The link is thought to be that patients with this rare disorder may seek care from a chiropractor or GP for relief of neck symptoms that result from the undetected stroke.

What are the benefits of taking part?

Manual therapy to the head/neck and upper back, alongside neurologist care, might be an effective treatment for chronic migraine. Although you may not gain benefit from taking part in the study, the findings could still contribute to improving the treatment of this condition.

What if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens this will be discussed with you and you can decide whether or not you wish to continue with the study.

What happens when the study ends?

If you require or would like manual therapy treatmer after the study period you may be able to obtain further treatment via the NHS (depending on where you live) or alternatively by making private arrangements for which you will have to pay. The "Care as Usual" with your neurologist will continue as prescribed by your neurologist.

What if there is a problem or I have a complaint'

If you have any concerns or complaints about the study, please contact me and I will do my best to address your concerns. If you are still unhappy, you can contact Professor Stephen Tee as the Dean of

the Faculty of Health and Social Sciences at Bournemouth University. If you are harmed during the study as a result of negligence, you may have grounds for compensation against Bournemouth University; however, you may have to pay your own legal costs. The National Health Service complaints service will be available to you. You will also be able to contact the Patient Advice and Liaison Service (PALS).

Will my taking part in this study be kept confidential?

Your information will be kept confidential as you would expect in all of your healthcare encounters. The questionnaires and diaries will not have your personal details attached, only an individual reference number. All information will be used for this research only and kept securely on password protected computers and only accessible by members of the research team. Any data that can identify a participant will be destroyed within 3 months of final data collection. Anonymous data may be kept for up to 5 years on a secure university computer.

Bournemouth University (BU) is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly.

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting researchgovernance@bournemouth.ac.uk, or for more general queries DPO@bournemouth.ac.uk.

Salford Royal will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from BU and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Salford Royal will pass these details to BU along with the information collected from you The only people in BU who will have access to information that identifies you will be people who need to contact you in the event of major changes t the study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

What will happen to the results of the research study?

The results of the study will be presented in my PhD thesis and submitted to Bournemouth University. They will also be presented at academic conferences and submitted for publication in international journals. Summaries of the findings wil also be made available to migraine charities. If you would like a copy of the summary findings please contact me.

Who is organising and funding the research?

The study is being funded by a research grant from Bournemouth University, The McTimoney College o Chiropractic and the Royal College of Chiropractors

Who has reviewed the study?

The study has been reviewed by my supervisors Dr Carol Clark, Dr Jonny Branney and Dr Osman Ahmed. It has also been given a favourable opinion by the Research Ethics Committee.

Further information and contact details:

Mr Jim Odell
Research Fellow Bournemouth University
Tel 07413833690
Email: JOdell@bournemouth.ac.uk

Dr Carol Clark
Supervisor, Associate Professor
Head of Department Human Sciences and Public Health, R 612
Tel 01202 963022
Email: cclark@bournemouth.ac.uk

Dr Jonny Branney
Supervisor, Lecturer in Adult Nursing
Faculty of Health and Social Sciences
Bournemouth University, B211
Tel 01202 967282
Email: jbranney@bournemouth.ac.uk

Dr Osman Ahmed
Supervisor, Lecturer in Physiotherapy
Faculty of Health and Social Sciences, R601
Tel: 01202 968147

Appendix 11. Informed Consent

Bournemouth University

INFORMED CONSENT

Title of Project

TERTIARY CARE WITH OR WITHOUT MANUAL THERAPY FOR CHRONIC MIGRAINE

Name of Researcher: Jim Odell

Office use only.
Participant Reference (PR):

Please Tick Box

I confirm that I have read and understand the Participant Information Sheet, V15.0.22/05/18 for the above study and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that sections of my medical notes relating to my taking part in the study may be looked at by an independent nurse/researcher directly involved in the study. I give permission for these individuals to have access to my records, if necessary.	☐
I agree to my GP being informed of my participation in this study.	☐
I understand I will be randomly allocated to either: - The Manual Therapy Group - Care as Usual Group	☐
I have been shown the diary and agree to complete it as explained.	☐
I agree to take part in the above study.	☐

Name of Subject (BLOCK CAPITALS)	Date	Signature
Name of person taking consent	Date	Signature

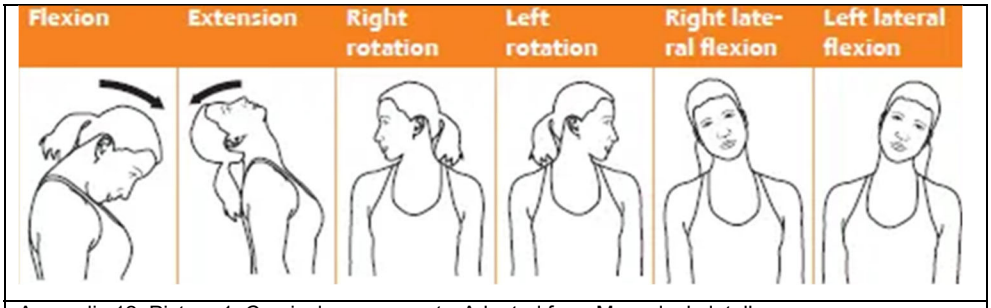
Appendix 12. Assessment and Treatment

1. Assess upper body[a] posture in sitting

The aim is to identify which areas should be focussed on for treatment: Examples of observations include: anterior head carriage, tilt/rotation of head, protracted scapulae, glenohumeral joint internally rotated; increased/decreased thoracic curve, scoliosis; rotation of upper body).

2. Assess active and passive neck range of motion (RoM)

See picture below for active. Passive completed by therapist. Aim is to identify RoM restrictions comparing left to right and both to normal expected RoM and to identify any pain with movement. Muscles assessed include: upper cervicals, scaleni, sternocleiodomastoids, Cervical joints palpation: static and motion



Appendix 12. Picture 1. Cervical assessment. Adapted from Musculoskeletalkey.com

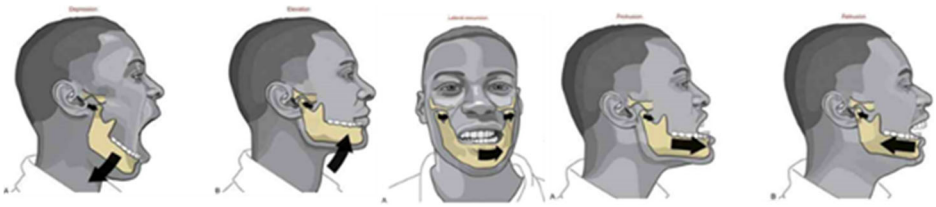
Appendix 12. Picture 2. Shoulder and Thoracic Assessment

3. Assess shoulder girdle range of motion by active and passive raising of each arm sideways (individually and together) from side of body up to ear (Pictures 10.2)

Assessment points: Observe range of motion with raising of arms; singularly and then together. Note any compensations (e.g. shoulder hiking) to achieve movements and any pain with movement. Muscles assessed include latissimus dorsi, serratus, trapezius, levator scapula, pectoral

Appendix 12 (contd). Assessment and Treatment

4. Assess the temporomandibular joint
   Check movements of jaw for deviations, pain or limitations.Palpate muscles including masseter, temporalis, pterygoids, mylohyoid



Appendix 12. Picture 3 TMJ Assessment

5. Identify areas to treat in sitting position.
   Examples include: cervical spine, trapezius muscles, rhomboids, levator scapula, thoracic spine down to T12 including obliques around thoracolumbar fascia
6. Administer MT using mobilisation, manipulation and soft tissue release in sitting position
7. Assess patient shoulder girdle, neck and head supine and prone (note: supine is assessed and treated then prone assessed and treated). Examples of approach include
   Static and motion palpation of cervical joints, thoracic spine and ribcage. Palpation of anterior neck, pectoral muscles and thoracic musculature.
8. Administer MT in supine and prone position
   Comprises appropriate soft tissue release, mobilisation and manipulation as required. Chiropractic adjustments include HVLA (McTimoney) if appropriate.
9. Following each session an outline of the MT used will be recorded. A total of 30 minutes will be allocated for each participant at these consultations

[a] Upper body defined as from thoraco-lumbar junction upwards

Appendix 12a. PREEMPT Protocol

PREEMPT Paradigm overview

The PREEMPT Paradigm is based on 10 years of study to assess patient type, muscle selection, dose, and treatment interval.[9-17]

155 UNITS

PROVEN DOSE
155 Units[1]

12 WEEKS

PROVEN SCHEDULE
Trial of 2 treatments, 12 weeks apart, with further re-treatment every 12 weeks[1,*]

31 SITES

PROVEN SITES
31 sites across 7 specific head and neck muscle areas[1]

Summary of dose by area[1]

MUSCLE AREA	RECOMMENDED DOSE/NUMBER OF SITES
Corrugator	10 Units divided between 2 sites
Procerus	5 Units in 1 site
Frontalis	20 Units divided between 4 sites
Temporalis	40 Units divided between 8 sites
Occipitalis	30 Units divided between 6 sites
Cervical paraspinal	20 Units divided between 4 sites
Trapezius	30 Units divided between 6 sites
TOTAL DOSE	155 Units† divided between 31 sites

*Re-treatment after 24 weeks should be determined per clinician's discretion.
†Document and discard the 45-Unit wastage.

The following section provides a step-by-step overview of the PREEMPT Paradigm for BOTOX®. Departures from the approved paradigm may lead to efficacy results and adverse events different from those seen in the clinical trials.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

Please see additional Important Safety Information about BOTOX® on following pages.

Appendix 12a. PREEMPT Protocol (Contd)

BOTOX® onabotulinumtoxinA injection

General injection considerations

STANDARD METHODS REGARDLESS OF AREA

- For each injection, the **injection volume will be 0.1 mL** (equivalent to 5 Units)[1]
- **Consider injecting** in the most superficial aspect of the muscle
- **Evaluate the anatomy,** including relevant function and the effects of treatment on these muscles (eg, weakening)
- **Recognize unique anatomy,** as no 2 patients are alike; focus on the muscle, not measurements, to adjust for individual anatomical variations
- **Consider location, depth, and angle carefully,** as the site of medication delivery may be different from the needle insertion point
  - Injection sites depicted in diagrams represent delivery point of the medication

BEFORE INJECTION

- **Examine the patient** to identify unique anatomy and any muscle weakness or pain/tenderness
  - Visually **inspect** the muscle
  - Ask the patient to **activate** the muscle
  - **Palpate** the muscle
- **Verify the needle is securely fastened** to the injection syringe
- **Line up the bevel of the needle** with the gradations on the syringe so the bevel is facing upward; this will help you more easily orient the bevel of the needle when injecting

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The following adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see *Boxed Warning*); Serious Adverse Reactions With Unapproved Use (see *Warnings and Precautions*); Hypersensitivity Reactions (see *Contraindications* and *Warnings and Precautions*); Increased Risk of Clinically Significant Effects With Pre-Existing Neuromuscular Disorders (see *Warnings and Precautions*); and Dysphagia and Breathing Difficulties (see *Warnings and Precautions*).

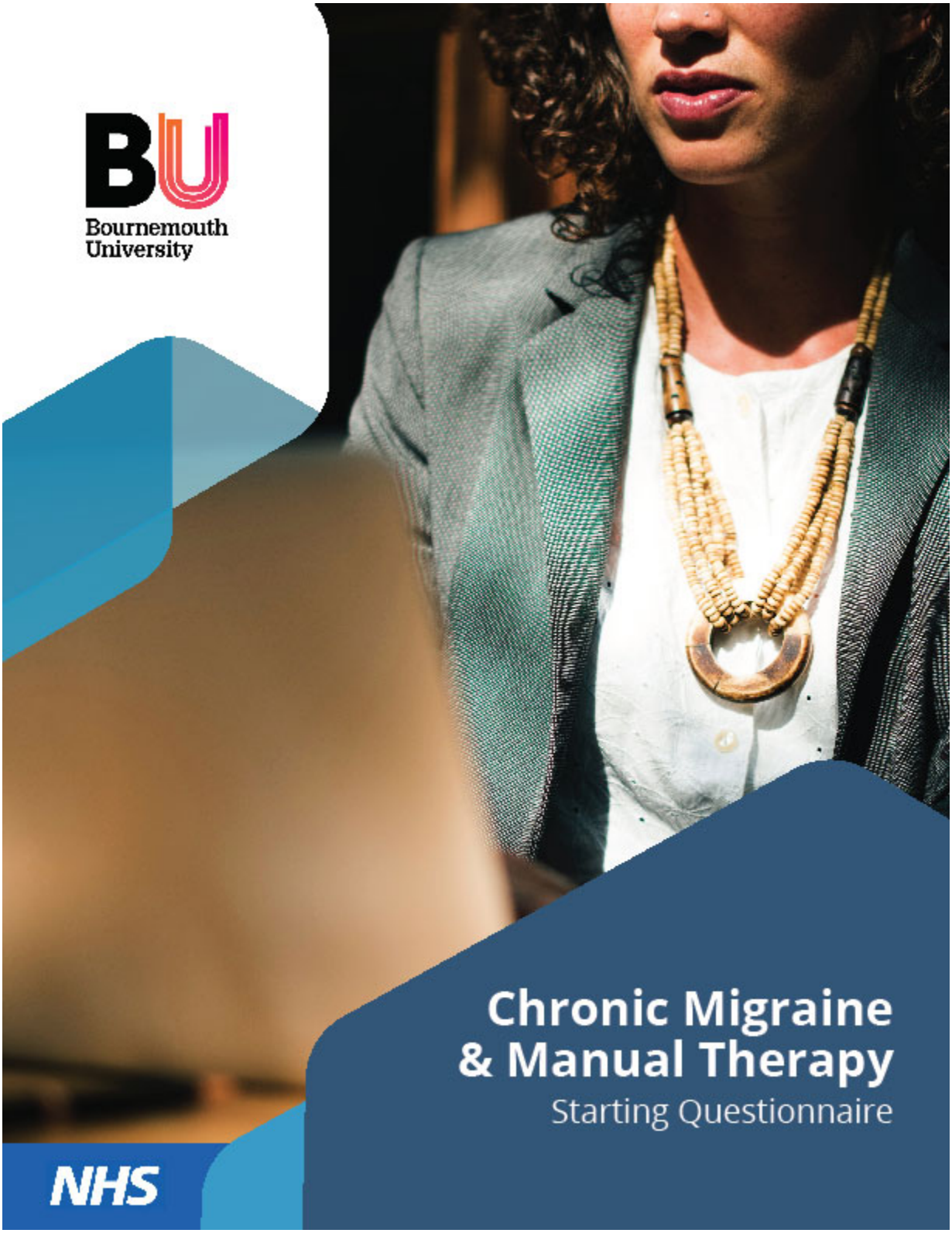
Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX® for chronic migraine vs placebo include, respectively: neck pain (9% vs 3%), headache (5% vs 3%), eyelid ptosis (4% vs < 1%), migraine (4% vs 3%), muscular weakness (4% vs < 1%), musculoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (3% vs 2%), musculoskeletal pain (3% vs 1%), myalgia (3% vs 1%), facial paresis (2% vs 0%), hypertension (2% vs 1%), and muscle spasms (2% vs 1%).

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX® treated patients in study 1 and study 2, usually within the first week after treatment, compared with 0.3% of placebo-treated patients.

8

Appendix 13. Starting Questionnaire



Appendix 14. Weekly Diary

Bournemouth University

Weekly Migraine Diary

Study: Chronic Migraine and Manual Therapy

Please enter your Participant Reference Number

Principal Researcher: Jim Odell

Supervisor: Dr Carol Clark

Date:

NHS

Appendix 15. Final Questionnaire

Appendix 16. Headache Impact Test 6

HIT-6™
(VERSION 1.1)

HEADACHE IMPACT TEST™

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1 When you have headaches, how often is the pain severe?

Never | Rarely | Sometimes | Very Often | Always

2 How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never | Rarely | Sometimes | Very Often | Always

3 When you have a headache, how often do you wish you could lie down?

Never | Rarely | Sometimes | Very Often | Always

4 In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never | Rarely | Sometimes | Very Often | Always

5 In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never | Rarely | Sometimes | Very Often | Always

6 In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never | Rarely | Sometimes | Very Often | Always

COLUMN 1 (6 points each) + COLUMN 2 (8 points each) + COLUMN 3 (10 points each) + COLUMN 4 (11 points each) + COLUMN 5 (13 points each)

To score, add points for answers in each column.
Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36-78.

Appendix 16a. HIT 6 reliability and validity studies

Study	Condition	Reliability	Validity
Pryse-Phillips, 2002	Migraine n=164		The strong correlations (0.51 to 0.87) between HIT6 scores and scale score support the validity of the test as a measure of headache disability
Kosinski et al. 2004	All headaches n=1005	Internal consistency, alternate forms, and test–retest reliability estimates of HIT-6 were 0.89, 0.90, and 0.80,	validity in discriminating across diagnostic and headache severity groups, relative validity (RV) with coefficients of 0.82 and 1.00 Construct validity with SF8 factors between 0.31 and 0.45
Martin et al. 2004	All headaches N=1171 14 countries	The Cronbach α coefficients for 14 languages was above the 0.70 criterion implying HIT-6 is reliable in all languages studied	
Kawata et al. 2005	Speciality headache clinic chronic daily headache n=309	The HIT-6 showed high internal consistency reliability (Cronbach's coefficient α = 0.87).	Construct validity correlating HIT-6 scores with the SF-36 ranged from −0.22 for mental health to −0.57 for social functioning. Strongest correlations between HIT-6 score and the role physical (r = −0.52) and social functioning (r = −0.57)
Yang et al. 2011	Chronic and episodic migraine n=2049	High reliability with internal consistency (time1/time2) of 0.83/0.87 in national survey headache impact and 0.82/0.92 in HIT6-validation study. Intra-class correlation for test-retest reliability was very good at 0.77	Construct validity HIT-6 scores correlated significantly (p<.0001)with total Migraine Disability Assessment Scale scores (r=.56),
Zandifer et al. 2013	Migraine and TTH n=274 (Persian)	Internal consistency calculated Cronbach's as 0.74, 0.82, and 0.86 for the 1st, 2nd, and 3rd visits, respectively Test-Retest reliability was evaluated at visit 2 vs. visit 1the Pearson's correlation coefficient, r=0.50; P<0.001)	Construct validity correlation between HIT6 and SF36 the total scores (range: 0.52–0.77).
Baum et al. 2014	Chronic migraine n=1384	Good reliability was observed across studies with Cronbach's α: 0.75–0.92	Correlations between HIT-6 total scores and scale scores of the MSQ were above the recommended threshold of 0.40 for convergent validity across studies and time points, ranging between −0.86 and −0.59
Smelt et al. 2014	Migraine n=368	HIT-6 showed adequate internal consistency (Cronbach's =80).	Responsiveness individual MCID 2.5-6, Between group 1.5

Appendix 17. Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix 18. Migraine Specific Quality of Life V2.1 (MSQ 2.1)

(Layout altered here for simplicity)

PATIENT INSTRUCTIONS:

Please fill out this questionnaire. It will help us understand the effects of migraine headache on your daily activities.

The questionnaire has been designed so that it can be completed quickly and easily. Please select only one answer for each question. You should answer every question.

Thank you for your time.

While answering the following questions, please think about ***all migraine attacks*** you may have had ***in the past 4 weeks***.

1. In the past 4 weeks, how often have migraines **interfered** with how well you dealt with family, friends and others who are close to you? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

2. In the past 4 weeks, how often have migraines **interfered** with your leisure time activities, such as reading or exercising? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

3. In the past 4 weeks, how often have you had **difficulty** in performing work or daily activities because of migraine symptoms? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

4. In the past 4 weeks, how often have migraines **kept you** from getting as much done at work or at home? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

5. In the past 4 weeks, how often have migraines **limited** your ability to concentrate on work or daily activities? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

6. In the past 4 weeks, how often have migraines **left you too tired** to do work or daily activities? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

Appendix 18. Contd. Migraine Specific Quality of Life V2.1

7. In the past 4 weeks, how often have migraines **limited** the number of days you have felt energetic? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

8. In the past 4 weeks, how often have you had to **cancel** work or daily activities because of your migraines? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

9. In the past 4 weeks, how often did you **need help** in handling routine tasks such as every day household chores, doing necessary business, shopping, or caring for others, because of your migraines? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

10. In the past 4 weeks, how often did you have to **stop** work or daily activities to deal with migraine symptoms? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

11. In the past 4 weeks, how often were you **not able to go** to social activities such as parties, dinner with friends, because of your migraines? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

12. In the past 4 weeks, how often have you **felt** fed up or frustrated because of your migraines? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

13. In the past 4 weeks, how often have you **felt** like you were a burden on others because of your migraines? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

14. In the past 4 weeks, how often have you been **afraid** of letting others down because of your migraines? (Select only **one** response.)

1❑ Never 2❑ Rarely 3❑ Some of the time 4❑ A good bit of the time 5❑ Most of the time 6❑ All of the time

Appendix 19. State and Trait Anxiety Inventory 6 (STAI)

Name ..... Date .....

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. *There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.*

	Not at all	Somewhat	Moderately	Very much
1. I feel calm	1	2	3	4
2. I am tense	1	2	3	4
3. I feel upset	1	2	3	4
4. I am relaxed	1	2	3	4
5. I feel content	1	2	3	4
6. I am worried	1	2	3	4

Please make sure that you have answered *all* the questions.

Appendix 20. Brief Cope

These items deal with ways you've been coping with the stress from your migraine. Ther are many ways to try to deal with problems. These items ask what you've been doing to cope with this one. Obviously, different people deal with things in different ways, but I' interested in how you've tried to deal with it. Each item says something about a particul way of coping. I want to know to what extent you've been doing what the item says. How much or how frequently. Don't answer on the basis of whether it seems to be working or not—just whether or not you're doing it. Use these response choices. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can.

1 = I haven't been doing this at all
2 = I've been doing this a little bit
3 = I've been doing this a medium amount
4 = I've been doing this a lot

1. I've been turning to work or other activities to take my mind off things.
2. I've been concentrating my efforts on doing something about the situation I'm in.
3. I've been saying to myself "this isn't real.".
4. I've been using alcohol or other drugs to make myself feel better.
5. I've been getting emotional support from others.
6. I've been giving up trying to deal with it.
7. I've been taking action to try to make the situation better.
8. I've been refusing to believe that it has happened.
9. I've been saying things to let my unpleasant feelings escape.
10. I've been getting help and advice from other people.
11. I've been using alcohol or other drugs to help me get through it.
12. I've been trying to see it in a different light, to make it seem more positive.
13. I've been criticizing myself.
14. I've been trying to come up with a strategy about what to do.
15. I've been getting comfort and understanding from someone.
16. I've been giving up the attempt to cope.
17. I've been looking for something good in what is happening.
18. I've been making jokes about it.
19. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.
20. I've been accepting the reality of the fact that it has happened.
21. I've been expressing my negative feelings.
22. I've been trying to find comfort in my religion or spiritual beliefs.
23. I've been trying to get advice or help from other people about what to do.
24. I've been learning to live with it.
25. I've been thinking hard about what steps to take.
26. I've been blaming myself for things that happened.
27. I've been praying or meditating.
28. I've been making fun of the situation.

Appendix 21. Perceived Stress Scale – 10 (PSS10)

The questions in this scale ask you about your feelings and thoughts during the last month. **In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.**

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

	0 = Never	**1 = Almost Never**	**2 = Sometimes**	**3 = Fairly Often**	**4 = Very Often**
1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Appendix 22. Allodynia Symptom Checklist -12 (ASC-12)

How often do you experience increased pain or unpleasant sensation on your skin during your worst headaches when you engage in the following?	Does not apply	Never	Rarely	Less Than half time	Half the time or more
	Score 0	Score 0	Score 0	Score 1	Score 2
Combing your hair					
Pulling your hair back					
Shaving your face					
Wearing eyeglasses					
Wearing contact lenses					
Wearing earrings					
Wearing a necklace					
Wearing tight clothing					
Taking a shower					
Resting your face or head on a pillow					
Exposure to cold (e.g washing face with cold water)					
Exposure to heat (cooking hot water on face)					
Total Scores					
Sum of total scores					

Allodynia	ASC Range
None	0-2
Mild	3-5
Moderate	6-8
Severe	9 or more

Appendix 23. Patient Global Impression of Change (PGIC)

Since beginning treatment during this study, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your chronic migraine?

Choose ONE.
___No change (or condition has gotten worse) (1)
___Almost the same, hardly any change at all (2)
___A little better, but no noticeable change (3)
___Somewhat better, but the change has not made any real difference (4)
___Moderately better, and a slight but noticeable change (5)
___Better and a definite improvement that has made a real and worthwhile difference (6)
___A great deal better and a considerable improvement that has made all the difference (7)

Appendix 24. Sample size calculation

Sample size calculations

	HIT6(SD)	Study	N-1	SD*SD	SD	N	
	59.2 (8.2)	Baum et al. 2014	176	67.24	8.2	177	Outliers SD>8
	(66.1 ± 8.	Berra et al. 2015	50	70.56	8.4	51	
			N-1	SD*SD	SD	N	
1	68.9 (4.3)		176	18.49	4.3	177	
2	65.3 (4.4)	Rendas Buam et al	704	19.36	4.4	705	
3	65.6 (4.0)		678	16	4	679	
4	62.5(7.8)	Yang et al. 2010	130	60.84	7.8	131	
5	68.9 (4.3)	Negro et al. 2015	131	18.49	4.3	132	
6	58.5(5.8)		34	33.64	5.8	35	
7	59.9(8.0)		34	64	8	35	
8	58.9(7.0)	Cerriteli etl al. (2017)	34	49	7	35	
9	64.3(4.7)		375	22.09	4.7	376	
10	64.6(4.4)		378	19.36	4.4	379	
11	64.1(4.8)	Siberstein et al. 2017	374	23.04	4.8	375	
12	65.4 (4.3)	Aurora et al. 2014	481	18.49	4.3	482	
13	65.4 (4.0)		511	16	4	512	
14	65.20 (5.08)		59	25.8064	5.08	60	
15	65.73(5.43)		59	29.4849	5.43	60	
16	61.2 (7)	Rojo et al. 2015	175	49	7	176	
17	62.1(6.0)	Suh et al. 2014	51	36	6	52	
						4401	

$$s_{pooled} = \sqrt{\frac{(n_1-1)s_1^{\,2}+(n_2-1)s_2^{\,2}+\ldots+(n_k-1)s_k^{\,2}}{n_1+n_2+\ldots+n_k-k}}$$

	SD Pooled
Without outliers	4.7
With outliers	4.9

$$n = f(\alpha,\beta)\cdot\frac{2s^2}{\delta^2}$$

Sample size figures	α = 0.05	β = 80%
SD	4.7	4.9
Difference	3.3	3.45
Number in each group	32	32

Appendix 25. Ethical approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr James Odell
12 Granville Street
Monton
M30 9PX

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

21 June 2018

Dear Mr Odell

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title: A two-centre pragmatic randomised controlled trial on the **effectiveness of manual therapy as an adjunct to tertiary management of chronic migraine**

IRAS project ID: 228901

REC reference: 18/SC/0069

Sponsor Bournemouth University

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales? You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment. Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal

notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here. How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations.

You should work with your non- NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

Registration of research

Notifying amendments

Notifying the end of the study

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

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?

You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Assoc. Prof C Clark Tel: 01202 963022

Email: cclark@bournemouth.ac.uk

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below. Your IRAS project ID is **228901**. Please quote this on all correspondence.

Yours sincerely

Juliana Araujo Assessor

Email: hra.approval@nhs.net

Copy to: Sponsor Representative: Assoc. Prof C Clark, Bournemouth University Lead NHS R&D Office Representative: Katie Doyle, Salford Royal NHS Foundation Trust & The Pennine Acute Hospitals NHS Trust

Appendix 26. Brief Cope calculations

Brief Cope Pre and Post Means (SD)					Mann-Whitney U Results difference in change scores between groups
	Group M (n=32)	Group C (n=30)	Group M (n=32)	Group C N=(30)	
Variable	Pre (SD)	Pre (SD)	Post(SD)	Post (SD)	Significance
Self-distraction	5.28 (1.73)	4.93 (1.91)	4.59 (1.64)	4.57 (1.65)	P=0.608 U=444, z= -0.513
Denial	3.00 (1.55)	2.77(1.48)	2.63 (1.36)	2.73 (1.39)	P=0.478 U= 434, z=-0.71
Substance use	2.84 (1.48)	2.60(1.22)	2.41(1.19)	2.53(1.01)	P=0.515 U=439 z= -0.65
Behavioural disengagement	3.97(1.99)	3.07(1.55)	3.16 (1.48)	3.53(1.55)	P=0.036 U=333 z=-2.1, η2=0.07
Self-blame	4.50(1.90)	3.77(2.08)	4.16 (2.32)	3.83(2.02)	P=0.685 U=451 z= -0.46
Use of emotional support	5.06 (2.05)	4.30(1.62)	4.03 (1.87)	4.23(1.99)	P=0.202 U= 390 z= -1.27
Use of instrumental support	3.63 (1.21)	3.40(1.28)	3.34(1.29)	2.93(0.98)	P=0.858 U= 492, z= -0.18
Venting	4.34 (1.82)	3.17(0.99)	3.72(1.40)	3.33(1.21)	P=0.167 U= 383 z=-1.38
Religion	2.84 (1.17)	2.63 (1.59)	3.03 (1.69)	2.27(0.69)	P=0.673 U=508 z= 0.422
Humour	3.75 (1.80)	4.20(2.30)	3.75(1.80)	3.83(2.32)	P=0.528 U=524 z= 0.63
Acceptance	6.34 (1.33)	5.93 (1.51)	6.22(1.54)	5.67(1.86)	P=0.870 U= 491 z= 0.163
Positive reframing	3.84 (1.69)	4.30 (1.99)	3.97(1.49)	3.33(1.52)	P=0.097 U=597 z= 1.66
Planning	5.00 (1.92)	4.50 (1.87)	4.75(1.93)	3.83(1.60)	P=0.598 U= 517 z= 0.53
Active coping	5.28 (1.80)	5.10 (1.54)	5.34(1.88)	4.40(1.75)	P=0.320 U= 549 z= 0.99

Appendix 27a. Correlations. Combined group

Baseline factors correlation for total sample (combined groups C and M)

Correlations	PSS_10	STAI	RR_MSQ	RP_MSQ	EF_MSQ	A_HADS	D_HADS	TOT_HADS	Self_distraction	Active_coping	Denial	Subst_use	Emotional_support	Instrumental_support	Behavioral_disengagement	Venting	Positive_reframing	Planning	Humour	Acceptance	Religion	Self_blame	ASC	PGIC	HIT6_DIFF	HIT6_PRE	HIT6_post	HIT6_% Diff	Mean_Stress	Mean_diet	Mean_sleep	Mean_meds	BMI
PSS_10	1																																
STAI	.538**	1																															
RR_MSQ	-.487**	-.449**	1																														
RP_MSQ	-.351**	-.432**	.856**	1																													
EF_MSQ	-.442**	-.453**	.781**	.815**	1																												
A_HADS	.673**	.355**	-.437**	-.306**	-.419**	1																											
D_HADS	-0.082	0.087	-0.243**	-.384**	-.253**	0.014	1																										
TOT_HADS	.508**	.340**	-.495**	-.465**	-.486**	.831**	.568**	1																									
Self_distraction	0.173**	0.208**	-0.081	0.011	-0.116**	0.146**	-0.028	0.104**	1																								
Active_coping	-0.126**	-0.147**	0.093**	0.230**	0.234**	-0.012	-0.103**	-0.067**	.410**	1																							
Denial	.429**	.262**	-.260**	-0.111**	-0.196**	.501**	-0.120**	.345**	.287**	0.087**	1																						
Subst_use	.295**	0.198**	-0.228**	-0.153**	-.283**	.264**	-0.030**	0.201**	0.093**	-0.186**	.338**	1																					
Emotion_support	0.14**	-0.037**	-0.197**	-0.156**	-0.232**	0.097**	0.110**	0.141**	0.030**	0.134**	0.202**	.314**	1																				
Instrumental_support	0.130**	-0.028**	-0.194**	-0.115**	-0.063**	0.052**	-0.113**	-0.020**	0.069**	.364**	0.181**	0.115**	.485**	1																			
Behavioral_disengagement	.504**	.341**	-.358**	-.304**	-.506**	.521**	0.010**	.434**	0.026**	-.318**	.259**	.395**	-0.014**	-0.224**	1																		
Venting	.327**	0.180**	-0.243**	-0.121**	-0.248**	.319**	0.029**	.279**	0.095**	.265**	0.182**	0.223**	.395**	.387**	.375**	1																	
Positive_reframing	-0.213**	-0.213**	0.159**	0.220**	.263**	-0.098**	-.256**	-0.223**	.323**	.499**	0.080**	-0.111**	0.210**	.475**	-.351**	0.084**	1																
Planning	-0.106**	-0.121**	-0.021**	0.038**	-0.005**	0.067**	-0.022**	0.043**	.356**	.673**	0.237**	0.038**	.384**	.438**	-0.212**	.293**	.565**	1															
Humour	-0.037**	0.011**	0.031**	0.012**	-0.061**	-0.005**	-0.116**	-0.069**	.385**	0.107**	0.196**	0.209**	-0.067**	0.142**	0.088**	0.109**	.371**	.281**	1														
Acceptance	-0.193**	-0.149**	-0.066**	-0.052**	-0.074**	-0.125**	0.160**	-0.014**	0.235**	0.181**	-0.008**	0.046**	0.195**	0.180**	-0.036**	0.131**	0.072**	0.159**	0.215**	1													
Religion	.271**	0.064**	-.340**	-0.215**	-0.146**	0.188**	-0.169**	0.060**	0.176**	0.222**	.266**	0.084**	0.096**	.675**	-0.003**	0.213**	.356**	.346**	0.177**	0.036**	1												
Self_blame	.583**	.281**	-.438**	-.326**	-.478**	.499**	-0.065**	.374**	.257**	0.040**	.391**	.292**	.282**	.273**	.326**	.465**	-0.029**	0.225**	0.061**	-0.053**	.381**	1											
ASC	.320**	.289**	-.444**	-.474**	-.411**	0.217**	0.157**	.266**	.273**	0.166**	0.194**	0.023**	0.165**	0.165**	0.101**	.255**	0.146**	.288**	0.188**	0.084**	0.238**	.460**	1									
PGIC	0.074**	.259**	-0.129**	-0.084**	-0.167**	0.051**	0.132**	0.115**	0.236**	0.173**	0.216**	0.137**	.282**	.283**	0.063**	.305**	0.016**	.361**	-0.007**	-0.036**	.261**	.287**	.258**	1								
HIT6_DIFF	-0.105**	-0.107**	0.045**	0.026**	0.104**	-0.001**	-0.067**	-0.038**	-0.120**	-0.122**	0.051**	-.279**	-0.126**	-0.122**	-0.038**	-0.167**	0.105**	-0.008**	0.062**	-0.028**	-0.074**	-0.046**	0.044**	-.484**	1							
HIT6_PRE	.453**	.410**	-.838**	-.764**	-.782**	.384**	.335**	.502**	0.172**	-0.071**	.296**	.323**	0.223**	0.202**	.319**	.324**	-0.217**	0.101**	0.020**	0.114**	.343**	.446**	.392**	.317**	-.318**	1						
HIT6_post	.352**	.309**	-.761**	-.705**	-.663**	.363**	.267**	.448**	0.074**	-0.158**	.318**	0.100**	0.118**	0.101**	.274**	0.183**	-0.128**	0.090**	0.065**	0.088**	.269**	.388**	.404**	-0.059**	.440**	.711**	1					
HIT6_PerCDiff	-0.109**	-0.116**	0.058**	0.054**	0.124**	0.022**	-0.072**	-0.022**	-0.129**	-0.114**	0.059**	-.257**	-0.109**	-0.115**	-0.027**	-0.163**	0.114**	0.016**	0.076**	-0.025**	-0.084**	-0.068**	0.006**	-.482**	.993**	-.329**	.425**	1				
Mean_Stress	0.201**	-0.157**	-0.076**	-0.046**	-0.107**	0.232**	-0.056**	0.160**	0.136**	0.101**	-0.066**	.293**	0.167**	-0.004**	0.179**	0.025**	-0.066**	0.050**	-0.041**	-0.006**	0.038**	0.118**	-0.079**	-0.001**	-0.236**	0.105**	-0.076**	-0.220**	1			
Mean_diet	0.196**	-0.159**	-0.074**	-0.042**	-0.105**	0.229**	-0.056**	0.157**	0.136**	0.100**	-0.069**	.293**	0.166**	-0.006**	0.177**	0.024**	-0.067**	0.049**	-0.042**	-0.004**	0.036**	0.116**	-0.082**	-0.002**	-0.236**	0.102**	-0.078**	-0.221**	1.000**	1		
Mean_sleep	0.197**	-0.158**	-0.073**	-0.042**	-0.104**	0.229**	-0.058**	0.156**	0.136**	0.101**	-0.069**	.292**	0.166**	-0.006**	0.176**	0.024**	-0.067**	0.049**	-0.042**	-0.005**	0.037**	0.115**	-0.082**	-0.001**	-0.237**	0.102**	-0.079**	-0.221**	1.000**	1.000**	1	
Mean_meds	0.201**	-0.155**	-0.080**	-0.049**	-0.110**	0.232**	-0.053**	0.162**	0.135**	0.098**	-0.066**	.295**	0.168**	-0.005**	0.178**	0.022**	-0.069**	0.047**	-0.041**	-0.002**	0.036**	0.117**	-0.077**	-0.003**	-0.237**	0.106**	-0.075**	-0.221**	1.000**	1.000**	1.000**	1
BMI	0.137**	0.054**	-0.060**	-0.191**	-0.075**	0.235**	0.051**	0.221**	0.054**	0.029**	0.069**	-0.051**	-0.070**	0.137**	0.121**	0.202**	-0.157**	-0.112**	0.176**	0.042**	0.014**	0.083**	0.166**	0.128**	-0.118**	0.018**	-0.071**	-0.134**	-0.107**	-0.109**	-0.109**	-0.108**	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix 27b. Correlations. Group M

Baseline factors correlation for group M

Pearson Correlation Group M	PSS_10	STAI	RR_MSQ	RP_MSQ	EF_MSQ	A_HADS	D_HADS	TOT_HADS	Self distraction	Active coping	Denial	Substance use	Emotional support	instrumental support	Behavioral disengagement	Venting	Positive reframing	Planning	Humour	Acceptance	Religion	Self Blame	ASC	PGIC	HIT6 DIFF	HIT6 PRE	HIT6 Post	HIT6 %Diff	Mean Stress	Mean Diet	Mean Sleep
PSS_10	1																														
STAI	.563**	1																													
RR_MSQ	-.561**	-.400*	1																												
RP_MSQ	-0.294	-.417*	.693**	1																											
EF_MSQ	-.426*	-.514**	.679**	.824**	1																										
A_HADS	.736**	.448*	-.554**	-0.317	-.430*	1																									
D_HADS	-0.216	-0.073	-0.028	-.411*	-0.033	-0.155	1																								
TOT_HADS	.564**	.375*	-.529**	-.517**	-.416*	.843**	.402*	1																							
Self_distraction	0.112	-0.060	0.047	0.138	0.024	0.081	-0.287	-0.081	1																						
Active_coping	-0.109	-0.201	0.084	0.204	0.188	0.151	-0.104	0.083	.420*	1																					
Denial	.389*	0.218	-0.188	0.147	-0.047	.482**	-.621**	0.109	.411*	0.162	1																				
Subst_use	0.099	0.002	-0.149	-0.066	-0.224	0.230	-0.148	0.132	0.030	-0.213	0.338	1																			
emotion_support	0.055	-0.121	-0.106	0.000	-0.104	0.044	-0.007	0.036	0.196	0.205	0.153	0.322	1																		
instrumental support	0.091	0.028	-0.267	-0.029	-0.012	0.123	0.060	0.146	0.299	.449**	0.310	0.128	.621**	1																	
Behavioral disengagement	.536**	0.255	-.478**	-0.346	-.585**	.605**	-0.220	.441*	-0.044	-0.186	0.241	.370*	-0.102	-0.286	1																
Venting	0.273	0.139	-0.161	0.068	-0.080	.402*	-0.167	0.281	0.122	.392*	0.240	0.259	.417*	0.323	.358*	1															
Positive reframing	-0.142	-0.162	0.316	.436*	.351*	-0.019	-0.242	-0.149	.547**	.461**	0.235	-0.087	.386*	.428*	-0.328	0.207	1														
Planning	-0.218	-0.099	0.178	0.140	0.071	0.042	0.027	0.054	.477**	.691**	0.240	0.045	.460**	.583**	-0.228	.387*	.628**	1													
Humour	-0.138	-0.011	0.230	0.202	0.067	-0.143	-0.329	-0.312	0.346	0.062	0.244	0.324	0.189	0.030	-0.029	0.145	.445*	0.272	1												
Acceptance	-0.229	-0.307	-0.198	-0.125	-0.122	-0.228	0.079	-0.168	0.307	0.200	0.031	-0.021	0.311	0.202	-0.057	0.096	0.039	0.202	0.077	1											
Religion	0.246	0.044	-.448*	-0.118	-0.090	0.301	-0.071	0.240	0.279	.421*	.376*	-0.033	0.247	.687**	-0.016	0.193	0.282	.490**	-0.081	0.118	1										
Self_blame	.472**	0.268	-0.276	-0.147	-.364*	.525**	-0.334	0.305	0.310	0.137	.428*	0.292	.365*	0.280	0.337	.442*	0.116	0.239	-0.085	-0.146	0.225	1									
ASC	0.047	0.203	-0.044	-0.238	-0.238	0.056	0.054	0.081	0.338	0.160	-0.005	-0.215	0.072	-0.058	0.129	0.166	0.286	0.215	0.260	0.123	-0.073	0.070	1								
PGIC	-0.260	-0.065	0.305	0.217	0.127	-0.054	0.131	0.021	0.167	0.272	0.107	0.077	.363*	.469**	-.384*	0.103	0.296	.488**	0.051	0.100	0.145	0.010	0.080	1							
HIT6_DIFF	0.053	0.153	-0.092	-0.079	-0.011	-0.107	-0.177	-0.195	-0.122	-0.286	0.103	-0.171	-0.212	-0.252	0.140	-0.052	-0.225	-0.276	-0.061	-0.067	-0.150	0.017	0.137	-.558**	1						
HIT6_PRE	.446*	.363*	-.692**	-.618**	-.589**	.480**	0.136	.519**	0.109	0.062	0.213	0.227	0.145	.356*	0.222	0.220	-0.183	0.150	-0.068	0.234	.495**	0.327	-0.027	0.019	-0.263	1					
HIT6_post	.405*	.421*	-.636**	-.565**	-.484**	0.298	-0.038	0.255	-0.014	-0.189	0.258	0.040	-0.061	0.076	0.297	0.134	-0.337	-0.110	-0.106	0.133	0.274	0.279	0.094	-.453**	.627**	.587**	1				
HIT6_PerCDiff	0.062	0.161	-0.117	-0.093	-0.023	-0.089	-0.177	-0.179	-0.126	-0.291	0.115	-0.147	-0.210	-0.244	0.158	-0.034	-0.226	-0.276	-0.049	-0.049	-0.134	0.018	0.128	-.572**	.997**	-0.230	.652**	1			
Mean_Stress	0.290	-0.087	-0.345	-0.305	-0.305	.443*	0.084	.457**	0.132	0.078	0.001	.458**	0.199	0.136	0.314	0.109	-0.063	0.001	0.060	0.018	0.209	0.162	-0.105	-0.112	-0.153	0.336	0.143	-0.127	1		
Mean_diet	0.286	-0.091	-0.343	-0.302	-0.303	.441*	0.085	.455**	0.130	0.077	-0.001	.459**	0.201	0.135	0.314	0.109	-0.064	0.000	0.060	0.019	0.208	0.160	-0.107	-0.112	-0.153	0.334	0.141	-0.127	1.000**	1	
Mean_sleep	0.287	-0.090	-0.343	-0.302	-0.303	.441*	0.083	.454**	0.131	0.078	-0.001	.458**	0.200	0.136	0.313	0.109	-0.062	0.000	0.061	0.018	0.209	0.160	-0.106	-0.111	-0.154	0.334	0.140	-0.127	1.000**	1.000**	1
Mean_meds	0.289	-0.087	-0.347	-0.306	-0.305	.442*	0.087	.458**	0.131	0.076	-0.004	.456**	0.197	0.133	0.315	0.106	-0.065	-0.006	0.061	0.021	0.204	0.159	-0.104	-0.115	-0.154	0.333	0.140	-0.127	1.000**	1.000**	1.000
BMI	0.095	-0.119	0.008	-0.053	0.037	0.162	0.053	0.179	0.087	0.253	0.101	0.024	-0.038	-0.041	0.072	0.109	-0.163	0.007	0.138	0.076	-0.167	-0.089	0.081	0.115	-0.231	-0.023	-0.213	-0.242	0.062	0.061	0.061

Appendix 27c. Correlations. Group C

Baseline factors correlation for group C

Pearson Correlation Group C	PSS_10	STAI	RR_MSQ	RP_MSQ	EF_MSQ	A_HADS	D_HADS	TOT_HADS	Self distraction	Active coping	Denial	Substance use	Emotional support	instrumental support	Behavioral disengagement	Venting	Positive reframing	Planning	Humour	Acceptance	Religion	Self Blame	ASC	PGIC	HIT6_DIFF	HIT6 PRE	HIT6 Post	HIT6 % Diff	Mean Stress	Mean Diet	Mean Sleep	Mean Meds
STAI	.512**	1																														
RR_MSQ	-.445*	-.424*	1																													
RP_MSQ	-.403*	-.415*	.928**	1																												
EF_MSQ	-.456*	-0.343	.817**	.808**	1																											
A_HADS	.597**	0.293	-.393*	-0.321	-.449*	1																										
D_HADS	0.010	0.119	-0.318	-0.343	-0.343	0.185	1																									
TOT_HADS	.446*	0.282	-.466*	-.427*	-.521**	.840**	.689**	1																								
Self_distraction	0.226	.401*	-0.131	-0.044	-0.184	0.217	0.151	0.243	1																							
Active_coping	-0.166	-0.138	0.138	0.289	0.331	-0.235	-0.132	-0.247	.401*	1																						
Denial	.473**	0.286	-0.306	-0.286	-0.303	.527**	0.324	.568**	0.153	-0.020	1																					
Subst_use	.571**	.390*	-0.288	-0.218	-0.332	0.317	0.059	0.267	0.151	-0.162	0.329	1																				
Emotional support	0.231	-0.080	-0.218	-0.257	-0.293	0.181	0.168	0.227	-0.216	0.001	0.246	0.272	1																			
Instrumental support	0.158	-0.132	-0.124	-0.155	-0.065	-0.026	-0.304	-0.187	-0.158	0.260	0.033	0.084	0.307	1																		
Behavioral disengagement	.435*	0.347	-0.207	-0.249	-.393*	.440*	0.170	.418*	0.060	-.595**	0.263	.415*	-0.008	-0.223	1																	
Venting	.426*	0.001	-0.240	-0.273	-0.353	0.254	0.141	0.265	-0.031	-0.011	0.028	0.086	0.205	.549**	0.218	1																
Positive reframing	-0.271	-0.206	0.027	0.070	0.168	-0.179	-0.236	-0.262	0.169	.577**	-0.046	-0.120	0.089	.550**	-0.354	0.062	1															
Planning	0.000	-0.232	-0.112	0.005	-0.006	0.098	-0.122	0.005	0.222	.653*	0.218	0.000	0.244	0.275	-0.297	0.047	.562*	1														
Humour	0.082	0.084	-0.119	-0.118	-0.191	0.121	0.070	0.128	.443*	0.170	0.177	0.128	-0.295	0.254	0.286	0.229	0.304	0.329	1													
Acceptance	-0.196	-0.110	0.069	0.026	0.018	-0.022	0.180	0.083	0.154	0.152	-0.069	0.097	0.008	0.140	-0.101	0.077	0.134	0.086	0.353	1												
Religion	0.296	0.044	-0.273	-0.252	-0.156	0.099	-0.268	-0.076	0.094	0.044	0.212	0.189	-0.076	.671**	-0.032	0.261	.430*	0.227	0.352	-0.039	1											
Self_blame	.704**	0.220	-.510**	-.416*	-.523**	.494**	0.087	.412*	0.187	-0.089	0.341	0.274	0.124	0.244	0.251	.491**	-0.108	0.173	0.212	-0.027	.485**	1										
ASC	.580**	0.331	-.655**	-.596**	-.506**	.372*	0.206	.389*	0.214	0.170	0.360	0.249	0.241	0.330	0.036	.408*	0.070	0.341	0.161	0.036	.419*	.747**	1									
PGIC	.446*	0.343	-0.248	-0.180	-0.185	0.239	-0.110	0.115	0.297	0.019	.362*	0.147	-0.067	0.055	.370*	0.134	-0.093	0.173	0.102	-.464*	.411*	.496**	.458*	1								
HIT6_DIFF	-0.250	-0.181	-0.004	0.008	0.047	0.139	0.192	0.209	-0.061	0.140	0.061	-.404*	0.176	0.083	-0.080	-0.014	.367*	.439*	0.107	0.125	0.036	0.024	0.031	-0.067	1							
HIT6_PRE	.478**	0.342	-.896**	-.839**	-.864**	.375*	.389*	.491**	0.177	-0.237	0.355	.413*	0.201	0.068	0.316	0.294	-0.190	-0.005	0.137	-0.035	0.255	.479**	.620**	0.280	-0.205	1						
HIT6_post	0.305	0.217	-.846**	-.786**	-.787**	.434*	.477**	.584**	0.131	-0.141	.370*	0.155	0.292	0.112	0.251	0.269	0.033	0.250	0.191	0.039	0.261	.465**	.602**	0.225	.387*	.823**	1					
HIT6_PerCDiff	-0.255	-0.194	0.039	0.070	0.096	0.158	0.159	0.205	-0.079	0.142	0.067	-.370*	0.191	0.072	-0.064	-0.047	0.356	.452*	0.118	0.104	-0.004	-0.026	-0.035	-0.082	.988**	-0.250	0.338	1				
Mean_Stress	0.049	-0.309	0.182	0.193	0.116	-0.064	-0.253	-0.186	0.129	0.125	-0.173	0.019	0.079	-0.193	-0.086	-0.286	-0.051	0.092	-0.127	-0.060	-0.134	0.039	-0.073	0.017	-0.321	-0.135	-0.314	-0.308	1			
Mean_diet	0.044	-0.311	0.186	0.198	0.119	-0.068	-0.254	-0.190	0.130	0.125	-0.178	0.017	0.075	-0.196	-0.089	-0.288	-0.051	0.090	-0.128	-0.057	-0.137	0.036	-0.077	0.013	-0.323	-0.138	-0.318	-0.310	1.000**	1		
Mean_sleep	0.044	-0.310	0.187	0.199	0.121	-0.069	-0.255	-0.192	0.129	0.126	-0.179	0.016	0.074	-0.196	-0.090	-0.289	-0.052	0.089	-0.130	-0.059	-0.137	0.035	-0.078	0.015	-0.323	-0.140	-0.319	-0.310	1.000**	1.000**	1	
Mean_meds	0.053	-0.306	0.177	0.188	0.110	-0.062	-0.251	-0.184	0.127	0.121	-0.167	0.027	0.086	-0.192	-0.089	-0.290	-0.054	0.093	-0.127	-0.055	-0.134	0.040	-0.069	0.012	-0.323	-0.129	-0.309	-0.310	1.000**	1.000**	1.000**	
BMI	0.189	0.202	-0.111	-0.280	-0.162	0.309	0.058	0.260	0.033	-0.195	0.045	-0.129	-0.102	0.289	0.203	.464**	-0.159	-0.214	0.199	0.022	0.133	0.230	0.227	0.250	-0.043	0.057	0.029	-0.073	-0.287	-0.289	-0.288	-0.29

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Appendix 28. Fear-avoidance model