



Middlesex University

*in collaboration with
Northern College of Acupuncture*

**Effects of Shiatsu on the Health-Related Quality of Life of a
Person with Secondary Progressive Multiple Sclerosis:
a Mixed Methods N-of-1 Trial within a
Whole Systems Research Case Study**

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MSc Advanced Oriental Medicine

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Abstract

Background: MS is a chronic neurological disorder with high prevalence in Finland. Most people with MS will develop Secondary Progressive MS (SPMS) over the years. People with MS report lower than the average Health-Related Quality of Life (HRQoL) and use CAM for their symptoms. Interventions of personalised nature like shiatsu have an insufficient evidence base. The n-of-1 trial is a promising study design for personalised interventions in chronic conditions yet it has not been used a lot in CAM research.

Aims and Objectives: The aim was to investigate if shiatsu affects the HRQoL of a person with SPMS. Objectives were to design and implement a mixed methods n-of-1 trial within a whole systems research case study and to reflect on the implementation and the appropriateness of the design.

Methodology: Six-periods counterbalanced mixed methods n-of-1 trial within a whole systems research case study was used. The short version of the MSQLI, data collected from the semi-structured interview and case notes were used to assess the effect of the treatment. Structured personal reflection was included. The collected data analysed quantitatively and qualitatively and synthesised as a descriptive case study.

Findings: The study was able to document improvements in spasticity, bowel function, sleep and relaxation, fatigue and pain. No adverse events occurred. Preliminary estimations of the onset and wash-out of shiatsu effects were inferred. Advantages and drawbacks of the design are discussed to improve future applicability.

Conclusion: Shiatsu was able to improve some domains of the HRQoL of a person with SPMS. It was a safe treatment with no adverse events. Mixed methods n-of-1 trial within a whole systems research case study was an appropriate design for the study.

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List of Abbreviations (Alphabetical Order)

Complementary and Alternative Medicine (CAM)

Evidence Based Medicine (EBM)

Health-Related Quality of Life (HRQoL)

Health Status Questionnaire (SF-36)

Minimal Clinically Important Difference (MCID)

Multiple Sclerosis (MS)

Multiple Sclerosis Quality of Life Inventory (MSQLI)

Oriental Medicine (OM)

Participant Information Sheet (PIS)

Patient-Reported Outcome Measures (PROM)

Persons with MS (PwMS)

Quality of Life (QoL)

Randomised Controlled Trial (RCT)

Relapsing Remitting Multiple Sclerosis (RRMS)

Schedule for the Evaluation of Individual QoL (SEIQoL)

Secondary Progressive Multiple Sclerosis (SPMS)

Traditional Chinese Medicine (TCM)

Whole Systems Research (WSR)

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Chapter 1: Introduction

1.1. Background

1.1.1. Multiple Sclerosis

Multiple Sclerosis (MS) is a complex, chronic, inflammatory neurological disorder that affects patients physically, psychologically and socially (Hunter, 2016). It is estimated to affect about 2.3 million people worldwide (Browne et al., 2014). The average sex ratio prevalence in Europe is about two women to one man (Kingwell et al., 2013), with an increasing incidence rate in some areas (Trojano et al., 2012). There is a significant association between latitude and prevalence in Europe (Simpson et al., 2011), putting Finland in the high-risk region. In Finland, the prevalence varies between 5.1 and 11.6 new diagnoses per 100.000 people per year in different areas of the country (Sumelahti et al., 2003). In addition, it had been found that during the last three decades in the high-risk north-western areas of the country, the incidence of MS is increasing as well as the rate in young women of the area (Sumelahti et al., 2014; Krokki et al., 2011).

Most Persons with MS (PwMS) are initially diagnosed with the Relapsing Remitting Multiple Sclerosis (RRMS). After an average period of 20 years, the majority develop Secondary Progressive Multiple Sclerosis (SPMS) (Koch et al., 2010). SPMS is characterised by irreversible disease progression (Lublin et al., 2014). Its underlying pathology is not much understood, making the available pharmaceutical treatments for RRMS ineffective for the SPMS patients (Ciotti and Cross, 2018).

A combination of genetic, environmental and lifestyle factors interact and have a causal role in MS (Olsson, Barcellos and Alfredsson, 2017). Recent advancements

in the disease-modifying treatments have helped with controlling the progress of the disease (Vargas and Tyor, 2017), leading the concept of NEDA (No Evidence of Disease Activity) to become the primary treatment target for MS (Lu et al., 2018; Giovannoni et al., 2018).

A comprehensive management programme is recommended, centred on the PwMS to minimise the impact of the disease and maximise the Quality of Life (QoL) (Thompson et al., 2018). A significant part of such programs nowadays is offered in specialised rehabilitation or neurologic centres across Europe (Rasova et al., 2016). Only a small part of the physiotherapeutic interventions offered in Northern Europe are of Oriental Medicine (OM) origin (Martinková et al., 2018). Besides that, PwMS very often use various Complementary and Alternative Medicine (CAM) systems (Gotta, Mayer and Huebner, 2018; Esmonde and Long, 2008), not only to help themselves with symptom management but as part of a keen interest in wellness (Motl et al., 2018; Dunn, Bhargava and Kalb, 2015). The situation is similar also in the Nordic countries in spite of the well-established public health-care system (Salamonsen, 2016). A recent survey on the usage of CAM by people with MS in the Nordic countries found out that at least one in two patients had used CAM during the last year (Skovgaard et al., 2012).

1.1.2. Quality of Life

QoL is a concept with roots in the 1946 definition of health by the World Health Organisation (WHO) (Katz, 1987), stating that “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (International Health Conference, 2002). There have been many attempts

to be defined but there is no definitional consensus (Post, 2014). Yet, its multidimensional character is generally accepted (Bernham, 1999).

PwMS report experiencing a lower level of Health-Related Quality of Life (HRQoL) compared to the general population or other chronic disease populations (McCabe and McKern, 2002; Hermann et al., 1996; Rudick, 1992). HRQoL in MS correlates with the function of the nervous system, mental and social complications (Benito-León et al., 2003), fatigue, pain, sleep disturbances, emotional issues, physical disability and disease progression (Beiske et al., 2007) as well as present comorbidities (Berrigan et al., 2016).

The measurement of QoL by standardised Patient Reported Outcome Measures (PROM) is common practice, yet it is questionable whether such measures can represent the QoL of individual patients (Carr and Higginson, 2001). Especially regarding the assessment of QoL of PwMS of the more advanced SPMS, it has been suggested that semi-structured interviews might be a more appropriate approach (Giovannetti et al., 2016).

1.1.3. Shiatsu

Shiatsu is considered CAM in the European context (EFCAM, 2018). It is a form of East Asian bodywork, which similar to other modalities of the OM whole system of healthcare (Ritenbaugh et al., 2003) is historically derived from the traditional Chinese medicine (Beresford-Cooke, 2011a; Cheung, 2011). It has taken on unique characteristics while developing by integrating the culture and contemporary realities of 20th century Japan (Park et al., 2012). In Japanese, shiatsu translates to “finger pressure” and it has been defined by the Japanese Ministry of Welfare as:

Shiatsu technique refers to the use of fingers and the palm of one's hands to apply pressure to particular sections on the surface of the body for the purpose of correcting the imbalances of the body, and for maintaining and promoting health. It is also a method contributing to the healing of specific illnesses.

(Ikenaga, 2018)

In many European countries, it is significantly different to the way it is taught and practised in Japan (Adams, 2002). European practitioners use various approaches in their treatment (Robinson, Lorenc and Liao, 2011; Long, 2007b) but they share at least the following characteristics with the Japanese style: a) diagnosis and therapy are combined, b) the body is the only tool used, no mechanical devices, c) treat the whole body (Namikoshi, 2013 p.22).

Due to the lack of an evidence-base about shiatsu, for research purposes acupressure has been considered in the past a form of shiatsu (Robinson, Lorenc and Liao, 2011) and shiatsu has been confused for acupressure (Mehta et al., 2017), but their differences are significant (Cabo et al., 2018). A similar confusion exists in relation to massage (Annussek, 2015). In a recent paper, the author of the present study argued that acupressure and massage are modalities that cannot be inclusive of the basic shiatsu styles, while the shared characteristics of various shiatsu styles are not necessary characteristics of massage or acupressure (Tsiormpatzis, 2019).

For our study we accept a recent definition of shiatsu that does not justify misconception regarding its relevance to acupressure or massage, reading as:

Shiatsu is a manual therapy applied by leaning forward in a relaxed manner with the weight of one's body to an optimum point, and the correct use of fingers, palms, etc., in order to apply sustained, stationary pressure on different parts of the body for the purpose of correcting the imbalances of the body, and for

maintaining and promoting health. It is a holistic therapy that aims to treat most of the body in each session.

(Cabo et al., 2018, p.8)

As applied in many European countries, the receiver lies fully clothed on a futon, and the practitioner applies pressure to the body using fingers, palms, elbows, knees etc., while other techniques such as stretches, joint mobilisations as well as much gentler touch could be included. A typical session lasts about an hour, and the practitioner might also suggest exercise or dietary and lifestyle changes (Pirie, Fox and Mathers, 2012). The mechanisms of its action are not yet scientifically accessible, yet there has been some evidence for its effects in various health conditions (Robinson, Lorenc and Liao, 2011). Furthermore, the Shiatsu Therapy Research Lab in Japan has presented some studies showing physiological effects of shiatsu in humans. Those include effects on the cardiovascular system, blood pressure, peripheral circulation, muscle pliability, spinal mobility and muscle stiffness, electrogastrogram results, skin temperature, autonomic nervous system, pelvic angle, pupil diameter and pulse rate (Japan Shiatsu College, 2013).

Shiatsu is a personalised treatment, approaching the receiver as an organic whole with interconnected physical, emotional and psychosocial aspects (Long, 2009). As a whole system of healthcare, following a Whole System Research approach with mixed methods and single-subject design could be considered an appropriate methodology for its investigation (Verhoef et al., 2005).

While some (six) possible adverse event reports for shiatsu have been identified by reviews (Posadzki and Ernst, 2013; Ernst, 2003; Grant, 2003), those were of low quality, not always describing shiatsu, occasionally related to inappropriately excessive pressure and not necessarily supporting causality. One of the

conclusions of the biggest shiatsu study ever conducted, which included 948 participants in three European countries (Long, 2007a), is that Shiatsu, when performed by qualified practitioners, is a safe therapy with no lasting adverse effects (Long, Esmonde and Connolly, 2009).

1.1.4. Single Subject Research Designs

Individual case reports are an essential educational tool, often used by practitioners of CAM to show the benefits of their employed methods, (Witt & Linde, 2011, p.162). Yet their scientific value is considered to be at the base of an evidence hierarchy which pinnacles in meta-analyses (Schencking et al., 2016). In contrast, single-subject research designs, while retaining the individualised nature of the case reports, are experimental and relevant both for research and evidence-based practice (Byiers, Reichle and Symons, 2012).

Single-subject research designs are carefully designed studies where the sole unit of observation is an individual patient who acts as his/her own control (Lillie et al., 2011). They are undertaken using a protocol involving multiple measurements of the desired outcome across time (Porcino, 2016). They are used in medical and rehabilitation research (Germain et al., 2019; Koseki et al., 2019) and they are methodologically well established in those fields (Haegele and Hodge, 2015). While not yet well integrated in CAM research, they have the potential to contribute to the evaluation of CAM (Teut and Linde, 2013). They are considered a feasible research approach for the practitioners and a useful tool both for clinical research and for pilot studies while developing bigger and more expensive trials (Johnston and Mills, 2004).

N-of-1 trials belong to the family of single-subject research designs, and this methodology has been proposed as very appropriate for trials in the contemporary era of personalised medicine (Schork, 2015). They are considered ideal to evaluate the effectiveness of a treatment of chronic conditions, offering a rigour similar to Randomised Controlled Trial (RCT) (Vohra, 2016). Considered as a variation of the classical RCT design, they are an approach compatible with CAM whole systems evaluation (Verhoef et al., 2005). Re-analysing in single-subject level the data from previous group crossover RCT, Shadish, Rindskopf and Boyajian (2016) concluded that under conditions that need to be investigated further, their results could accurately approximate the results of an RCT.

1.2. Rationale

Interventions of personalised nature like shiatsu might be possible to contribute in the improvement of the QoL for patients with complex diseases such as SPMS. To the researcher's knowledge, shiatsu have an insufficient evidence base for its possible effects in HRQoL of persons with SPMS, while no studies have been conducted in the field of CAM bodywork using a mixed methods n-of-1 design under a whole system research approach. N-of-1 trials strengths could contribute in developing the evidence for shiatsu in SPMS.

1.3. Aims and Objectives

The aim is to investigate if shiatsu affects the HRQoL of a person with SPMS.

It is hoped that, besides the expected improvement of the condition of the patient-participant, the results of the study will help in designing a series of similar studies. Those, when aggregated, will help to understand better how shiatsu could

contribute to the rehabilitation of PwMS and help in integrating its practice in MS rehabilitation schemes aimed to improve the HRQoL of PwMS.

The objectives are to:

- design and implement a mixed methods n-of-1 trial within a whole systems research case study, using as sources of data the patient intake notes, a HRQoL PROM, a semi-structure interview and the case-records.
- reflect on the implementation and the appropriateness of the design.

1.4. **Research Question**

Does shiatsu affects HRQoL of a person with SPMS?

1.5. **Hypothesis**

Research Hypothesis: Shiatsu treatments have a significant effect on the HRQoL of a person with SPMS.

Alternative (null) Hypothesis: Shiatsu treatments have no significant effect on the HRQoL of a person with SPMS.

Chapter 2: Literature Review

The following chapter will present a review of the literature aimed to provide a background against which the study is being conducted. The first section is constituted by two connected narrative overviews and will attempt to provide a background for the justification of methodological decisions in the light of wider contextual and theoretical underpinnings. In those overviews, aspects of methodological issues in CAM research will be presented and the position of n-of-1 methodologies will be discussed. To do that, a dialectical approach will be followed, presenting the narratives in a way that highlight internal contradictions of the issues that are developing to the scope of the study. A narrative overview summarising the recent literature on MS and HRQoL will follow. Finally, two literature reviews will attempt to identify the evidence for shiatsu in MS and for shiatsu in HRQoL, appraising its relevance to clinical practice.

2.1. Aspects of the Problem of Methodology in CAM

Research: A Narrative Overview

Since the emergence of the modern Evidence Based Medicine (EBM) in the early 1990s (Sur and Dahm, 2011; Claridge and Fabian, 2005), health care has been extensively transformed in a way that the need for scientific research is a fundamental requirement of medicine (Kamath and Guyatt, 2016). EBM came to take the place of what could be called “expert based medicine” (Smith and Rennie, 2014). The transfer from the one paradigm to the other was not easy and resisted by the medical profession (Grahame-Smith, 1995). EBM today faces many challenges, and it has been claimed that it needs to develop a lot further to bypass

them (Djulgovic and Guyatt, 2017; van der Marck, Melis and Rikkert, 2017; Ioannidis, 2016; Gupta, Wander and Gupta, 2016; Sheridan and Julian, 2016; Brush and Halperin, 2016; Greenhalgh et al., 2014). In this debate, it has even been suggested that the evidence based movement is an example of microfascism that scholars should deconstruct (Holmes et al., 2006). However, it is clear that EBM is here to stay (Sheridan, 2016).

CAM practitioners and researchers get engaged with delay in the EBM debate (Wilson and Mills, 2002). Multiple issues surround the adoption of EBM research methods by CAM (Veziari, Leach and Kumar, 2017; Walker et al., 2014; Coulter et al., 2014). CAM modalities are of a complex nature, usually involving a combination of multiple traditional or novel interventions. The focus of EBM on the “gold standard” RCTs (especially the placebo-controlled ones), a research method designed to answer questions about the efficacy and safety of pharmaceuticals (Bothwell et al., 2016), can cause problems in clinical medical fields (Jones and Podolsky, 2015) including CAM research (Vickers, 1996).

It has been suggested that to fit into these RCT designs, CAM practice has been simplified in standardised treatments, and therefore alienated from their whole system nature (Fønnebø et al., 2007; Carter, 2003), reaching very limited and sometimes not clinically relevant outcomes (Jonas, 2001). The reductionist nature of RCTs (Beresford, 2010) is difficult to fit with complex interventions (Walach et al., 2006). However, early in the debate, scholars were suggesting the appropriateness of RCTs for CAM evaluation (Walker and Anderson, 1999; Vickers et al., 1997). To remedy the problems, pragmatic trials (Ford et al., 2016) have been debated as being a possible solution (MacPherson, 2004) or “propaganda tools” (Ernst and Canter, 2005). More recently, Archer and Forshaw (2015)

discussing an example of successfully applying RCT methodology to evaluate the effect of yoga in gynaecological cancer, suggested that the application of modified RCT designs might be more appropriate for CAM, including the partially-randomised preference trial proposed by Brewin and Bradley (1989). A key consideration here is that the preference for methodologies applied in standardised group populations contradicts the real-life application of most of CAM treatments which is strongly personalised (Fulder, 1998). Thus methods that could accommodate personalised treatment strategies are needed, to make research in CAM more relevant (Khorsan and Crawford, 2014; Caspi and Bell, 2004). Andrade and Portella (2018) in their integrative review of research methods in CAM mention possible methodological alternatives feasible for CAM research including Whole System Research, mixed methods, n-of-1 and single-subject research designs. In addition, they call for more attention to the research skills literacy in CAM schools, an issue discussed and researched early on by Mills et al. (2002b; a)

2.2. The Position of N-of-1 Trials: A Narrative

Overview

The n-of-1 trial is a research design with a long history. Its roots go back to experimental trials of therapy documented during the 17th century (Mirza et al., 2017). The first modern application of this experimental methodology was reported in 1953 (Glasziou, 2011; Hogben and Sim, 1953). While such a methodology was frequently applied in psychology studies (Guyatt and Jaeschke, 1990), it remained unnoticed by the medical community until its reappearance in 1986 (Guyatt, 1986). Since then, these trials have developed further. Research centres for medical n-of-1 trials had been established around the world (Kravitz et al., 2008). There are

even pharmaceutical organisations offering ready n-of-1 drug kits that simplify the process of such trials in pharmaceutical interventions (Yee, 2016). Unfortunately, besides their relevance and development, their potential has remained mostly unfulfilled (Guyatt, 2016; Kravitz et al., 2009).

In the era of EBM and under conditions, n-of-1 trials had been considered of the highest strength evidence for treatment decisions, sometimes even higher than systematic reviews, meta-analysis and RCTs (Guyatt et al., 2000). They claim this position in part due to their promise to assist in therapeutic precision (Kravitz et al., 2008). This quality could satisfy the contemporary needs of personalised medicine (Schork, 2015) and patient-centred medicine, patient-oriented research (Sacristán, 2013). In contrary, recent discussions in the area of big genomic data put in question their possible contribution (Ioannidis and Khoury, 2018). Even so, n-of-1 trials can contribute to implementing the concept of a learning healthcare system (Sacristán and Dilla, 2018) by effectively integrating clinical research and medical care (Sacristán, 2015). Methodologically, to further advance their potential in individual care, a mixed methods approach to n-of-1 clinical interventions has been proposed (van Ness, Murphy and Ali, 2017).

The appropriateness of n-of-1 trials as a methodology for CAM research has been proposed. They consider an individual patient as the sole unit of observation (Lillie et al., 2011) and are suggested for “individually tailored therapies” (Institute of Medicine, 2001: p.16). Thus, it is a design that seems to be appropriate for trials of whole systems of healthcare such as most of CAM, where the treatment is personalised (Verhoef et al., 2005). It has also been proposed that since both n-of-1 trials and the basic principles of Traditional Chinese Medicine (TCM) both focus on individualised treatment and choice of relevant outcome measures, “the

central concept of n-of-1 trials is consistent with the essence of TCM” (Li et al., 2013, p.193). Moreover, n-of-1 trials are of value for CAM “through bridging the gap between research and clinical practice, allowing for an individualised approach, and incorporating patient values” (Johnston and Mills, 2004, p.981). Johnston and Mills (2004) highlight also the possibility to use the n-of-1 methodology in CAM practice for diagnostic purposes or to identify individual responders when the evidence is not conclusive. Similarly, they suggest that n-of-1 trials can help clarify the optimal dose of a CAM intervention and “to investigate the true placebo effect” (Johnston and Mills, 2004, p.982).

The debate for the appropriateness of this innovative design in CAM evaluation has highlighted obstacles too. Ernst (1998) suggest that while n-of-1 trials have advantages for CAM research, they should ideally be used for interventions that have tested efficacy, to decide if the treatment is helpful for the specific patient. As a significant constraint, he considered the oversensitivity of CAM to carry-over effects. Hart and Sutton (2003) inspired by a trial reported by Coxeter et al. (2003) indicate the “switch on and off” problem, i.e. the need of the treatment to have a relatively short-term action and rapid onset-removal of the effect. They argue that this demand is in contrast to most CAM where the effects might be slow. Additionally, they consider the lifestyle changes included in many CAM modalities which are not easy to switch on and off. Discussing their trial, Coxeter et al. (2003) also highlight the carryover issue. They describe that the length of the treatment was determined based on stakeholder opinion due to lack of previous half-life and onset of effect evidence.

A recent systematic review identified that n-of-1 clinical trials had mostly assessed pharmaceutical interventions (87%) (Li et al., 2016). This stratification poses

challenges in the usage of the design in non-pharmaceutical CAM interventions, including the issue of carry-over effect and washout period, the possible healing effect of the intervention, as well randomisation and blinding (Guyatt et al., 1988). Those challenges are familiar to other clinical areas too. In the field of the behavioural sciences, from where the single-subject experimental design originated (Tate and Perdices, 2015), workarounds had been developed decades ago (Tate et al., 2016; Barlow and Hersen, 1992; Kazdin, 1982). In oncology, n-of-1 trials are modified in ways that make them more exploratory design (Collette and Tombal, 2015). Methods developed in those areas of inquiry might be appropriate for usage in CAM trials too.

The issue of the carry-over effects is discussed in the single-subject design literature (Senn, 2002, pp. 10-14). Carry-over effects could potentially distort the results of the periods following the initial treatment (Mills et al., 2009), a problem usually solved in pharmacological studies by including a wash-out period (D'Angelo, Potvin and Turgeon, 2001). In addition, statistical tests had been proposed to check for pharmacological carry-over effects (Senn, 2002, pp. 310-322), even if it had been argued that there is no benefit by using them (Senn, 2002, pp. 295-309; Senn, 1988). For non-pharmacological treatments, where the concepts of pharmacokinetics and pharmacodynamics are not applicable, the solution of including wash-out periods is not feasible (Chen et al., 2014). Hills & Armitage (1979) suggest that carry-over effects are difficult to detect and the results difficult to interpret unless the researcher is confident about their amplitude due to previous knowledge. A way to address possible lack of previous knowledge could be to use ideas proposed in different contexts. In the study of pharmacodynamics "Physiological Effect Models" are applied when the effect of a

drug in the organism is unknown quantitatively, using the physiological results of its effect instead to measure its effect (Holford and Sheiner, 1981). Cleophas (1990) suggests that “looking at the data” could be a valuable way to address the issue, as long as this is supported by rich description and transparent, open availability of the data for each period. Armitage (1991) suggests that using the baseline data from the period before the treatment could partially remedy the situation. Jackson, MacPherson and Hahn (2006) adopted a similar approach in a series of six n-of-1 trials on acupuncture for tinnitus. Yet, by adopting a single AB design, they could not avoid the limitation that it is not possible to suggest reproducibility of the effect (Teut and Linde, 2013).

2.3. Multiple Sclerosis and Quality of Life: A Narrative

Overview

HRQoL is a concept with many dimensions, covering physical, mental, emotional and social functioning (Kes et al., 2013). The symptoms that the PwMS experience in their daily life has a detrimental effect on their HRQoL (Crayton, Heyman and Rossman, 2004; Benito-León et al., 2003). Such symptoms include – but are not limited to – fatigue and walking activity levels (Vister et al., 2017), balancing issues, pain and spasticity, bladder and bowel dysfunction, sexual dysfunction, vision and hearing problems, swallowing and breathing difficulties, cognitive impairment (Zwibel and Smrtka, 2011; Crayton and Rossman, 2006) and depression (Ziemssen, 2009). Also it has been suggested that the temperament of each PwMS might play a more critical role in their HRQoL compared to current disability status, immunomodulatory treatments, and affective co-morbidities (Friedrich et al., 2018). Also, relationship issues and family dynamics (Lysandropoulos and Havrdova,

2015), as well as the diminished working ability with the accompanying economic burden and growing isolation, contribute their part to lowering the level of QoL (Zwibel and Smrtka, 2011).

HRQoL might be considered as the more relevant care outcome for PwMS (Lysandropoulos and Havrdova, 2015). There is conflicting evidence for the effect that the dominant MS treatment approach using Disease Modifying Treatments usually have on the HRQoL for PwMS (Jongen, 2017; Grossman et al., 2010). Considering major treatment gaps for MS, Zwibel & Smrtka (2011) recognise that improvement of HRQoL is an unmet need for many patients. A multidisciplinary approach combining medical treatment with rehabilitation (di Fabio et al., 1997) including cognitive (Wilski and Tasiemski, 2016; Sumowski and Leavitt, 2013) and psychological support (Thomas et al., 2006) following individualised, patient-centred principles (Vore et al., 2011) could be an efficient approach in enhancing the QoL of PwMS.

HRQoL is by definition assessed using Patient-Reported Outcome Measures (PROM) (Mitchell et al., 2005). Those instruments can be divided in general or disease-oriented (Miller and Allen, 2010) and they can include both objective factors (such as the clinical picture, the social status, social and living conditions, number and intensity of social contacts) and subjective factors (such as perception of symptoms, fitness and self-image, satisfaction from work, economic situation, family life, social life, received support) (Bandari et al., 2010). The main limitations of the currently available PROM for the evaluation of HRQoL in MS are their insensitivity to change and their partiality (Lysandropoulos and Havrdova, 2015). The website of the US National Multiple Sclerosis Society (n.d.-a) suggests three instruments to measure HRQoL in PwMS: Health Status Questionnaire (SF-36)

(Stewart, Hays and Ware, 1988), Multiple Sclerosis Quality of Life-54 (MSQOL-54) (Vickrey et al., 1995) and Multiple Sclerosis Quality of Life Inventory (MSQLI) that includes SF-36 too (Fischer et al., 1999). Beside those standardised PROM, Giovannetti et al. (2016) focussed on people severely affected by MS suggest a different approach, the Schedule for the Evaluation of Individual QoL (SEIQoL) interview. Comparing SEIQoL with standard PROM Giovannetti et al. (2016) found a negligible correlation between them. Their study suggested that the HRQoL of severely affected by MS people could be more appropriately appraised using semi-structured interviews since their flexibility allow the persons themselves to identify what is essential for them. Also, this personalised approach enhances patients self-awareness and support a shared decision-making approach (Oliver et al., 2016).

2.4. Shiatsu and Multiple Sclerosis

A search in PubMed was completed 10/04/2019, to identify studies related to shiatsu for MS. The search query was applied using the terms “shiatsu”, and “multiple sclerosis” in all fields and Boolean searches were used in the following manner:

[(shiatsu) AND multiple sclerosis]

without limitation of publication date, type of study or language.

The query returned two studies (Bastani, Sobhani and Emamzadeh Ghasemi, 2015; Branas et al., 2000) and their full texts were accessed.

The study by Branas et al. (2000) was a rapid and systematic review of the treatment of fatigue in MS. The review mentions the existence of anecdotal reports

about alternative therapies without any reference to shiatsu while it finally includes only two pharmaceutical interventions in the full systematic review. It was thus excluded as not relevant to shiatsu.

The article by Bastani et al. (2015) presents a two-arm RCT of 100 women with MS applying for two weeks and twice daily 18 minutes of self-acupressure in three specific acupoints or self-touch without pressure at the same points, considered as placebo. The study was about acupressure and not relevant to shiatsu practice, as it has been explained earlier in the description of shiatsu (§1.1.3). It was thus excluded as not relevant to shiatsu.

Trying to understand why such results appeared, it was discovered that the confusion between shiatsu and acupressure is structurally build-in to the indexing system of PubMed with the term “shiatsu” translated automatically to ["acupressure"[MeSH Terms] OR "acupressure" OR "shiatsu"].

In addition, the same day the same terms were used, with the necessary modification of the strategy according to each database needs, in AMED - The Allied and Complementary Medicine Database, Alt HealthWatch, WebOfScience, CiNii, ScienceDirect. The queries returned three articles, two from AMED and one from ScienceDirect, and their full text were accessed.

The articles from AMED were both from the Shiatsu Society News and their full text were accessed. Both was opinion essays based on clinical experience without providing further evidence for their claims. Booker (1998) presents a TCM overview of MS and its relevance to shiatsu. He suggests focusing on the Kidneys, Bladder, Spleen and Liver channels, and Stomach and Large Intestine channels if there is

motor impairment of the limbs. He believes that shiatsu practitioners can play a role in prolonging remission and helping PwMS to achieve a better QoL. The article is a relevant overview for the clinicians who wish to get some initial clinical ideas for shiatsu styles based in TCM aetiological background. Rycroft (2009) describe his approach of working the San Jiao channel when treating PwMS. His long term strategy is to improve mobility and slow down the progress, giving great importance in the empowerment of the PwMS. He suggests that an intense series of treatments can lead to a self-sustaining programme where further treatments are needed only occasional occasionally. This is an observation with which the author of the present study agrees, based to his clinical experience.

The paper from ScienceDirect was an abstract from the CAMSTRAND Conference by Esmonde, van Wersch and Harland (2014). It briefly describes the protocol and preliminary results of a qualitative study on the therapist effect in shiatsu treatment of PwMS. The preliminary results show the importance of the therapeutic interaction and of an understanding relation between the PwMS and the shiatsu practitioner. Those preliminary results tend to agree with the clinical experience of the author.

None of the three articles identified are of a type that could permit a critical appraisal of their quality.

The search strategy for all queries can be found in table 1.

Table 1: Search Strategy

Date	Search Terms	Database Searched	Field Searched	Papers Found	Papers Selected
10-04-19	[shiatsu AND multiple sclerosis]	Pubmed	All	2	0
10-04-19	[shiatsu AND multiple sclerosis]	AMED	All	2	2
10-04-19	[shiatsu AND multiple sclerosis]	Alt Healthwatch	All	0	0
10-04-19	[shiatsu multiple sclerosis]	CiNii	Freeword	0	0
10-04-19	[shiatsu AND multiple sclerosis]	ScienceDirect	Title, Abstract, Author-specified keywords	1	1

Because of the insufficient peer-reviewed evidence available through the databases, a hand-search in the personal library of the author identified the following sources of not peer-reviewed literature, included here to set an idea of the context of the practical work of shiatsu in MS (Aveyard, 2007, pp.34-5). All of those resources, share the characteristic of the studies identified in AMED. Either from textbooks, conference proceedings or other sources, they are opinion pieces based on clinical experience without providing further evidence for their claims. All are relevant to clinical practice, even if with the author has different opinion on some aspects commented below.

Taylor (2007), presenting at the European Shiatsu Congress, considers shiatsu as offering positive symptom management and the emotional, physical and spiritual support of PwMS. After presenting a general framework for understanding the MS symptomatology from the Five Phases perspective, he reports some OM related diagnostic conclusions, as well as some tips from his clinical experience. Five phases theory in OM is a system of correspondences that is used to classify body systems and to interpret physiology and pathology in the human body. It can also guide treatment and prognosis (Lozano, 2014).

In the same Congress, Blarer (2007) presented the importance of strengthening the Lungs, a dimension that is not often addressed when dealing with MS. After referring to various factors related to the emotional QoL of PwMS, he presented a comprehensive view of TCM approaches in the condition and a brief case study.

Jarmey in his book, suggests that shiatsu can help to “reduce stress and boost the immune system, thus potentially reducing the risk or severity of symptoms recurring” (Jarmey, 1996, pp.137-8) in PwMS. He also proposes the usage of Sotai exercises to strengthen the muscles while he considers as important meridians those of the Spleen in the inside of the leg and the Pericardium in middle and inside of the arm. In addition, he suggests that the Bladder meridian in the back and legs can be helpful for a short-term increase of the vitality and mobility of the person. He concludes that due to the unpredictable nature of the disease, nothing is guaranteed.

Kawada & Karcher are of the opinion that “Shiatsu cannot cure this disorder, but it can slow the process of deterioration and provide psychological help to the patient” (Kawada and Karcher, 2002, pp.175-6). Their approach is based on the extraordinary vessels, suggesting that the practitioner should work on the Du Mai and Yang Qiao Mai to promote and increase the yang circulation. They suggest not to treat someone tired or shaking and to keep the length of the session under 30 minutes, principles that the author of the present study found clinically not justifiable. On the contrary, his clinical practice had highlighted that the shiatsu session should be modified according to the specific needs of the specific patient at the specific moment. Both short and long sessions (even as long as two hours) could be well received and useful, while shiatsu can also be used as first-aid

treatment with extremely tired or even fatigued patients as well as in severe cramping or shaking events.

Kennedy (2014, pp.159-61) describes a case study of a PwMS suffering from pain. The first significant shift in client's situation occurred after working the San Jiao meridian from the head down the neck and along the outside of the arm. In the future sessions, the main focus was in the Tai Yin channels (deficient Lungs channels in hands combined with excess Spleen channels in legs) as well as the deficient Large Intestine channels of the hands.

In his diploma thesis, Rycroft (2005) presents some case studies of his work with shiatsu for nerve damage. He includes a case, diagnosed as primary progressive MS, which included six shiatsu sessions and clinical reflection. One of the sessions was offered in a treatment table. The practitioner gave a lot importance to the Zen shiatsu diagnosis and the outcome of the treatments was mostly relevant to body awareness and lifestyle changes.

Cameron (n.d.) reports a case study of a PwMS with damaged Achilles tendon, treated with eight shiatsu treatments. The case is presented in the context of Zen shiatsu. The damaged Achilles tendon almost healed, and the associated oedema was resolved, while the PwMS reported further benefit from shiatsu, including being more relaxed especially with his family.

Finally, the author of the present study explores the relevance of the extraordinary Fu and vessels to MS as part of his post-graduate shiatsu diploma (Tsiormpatzis, 2014). The presentation includes a summary of a case study of a woman with SPMS treated with shiatsu twice weekly for three months, showing improvement in Lower Urinary Tract Symptoms and self-reported QoL.

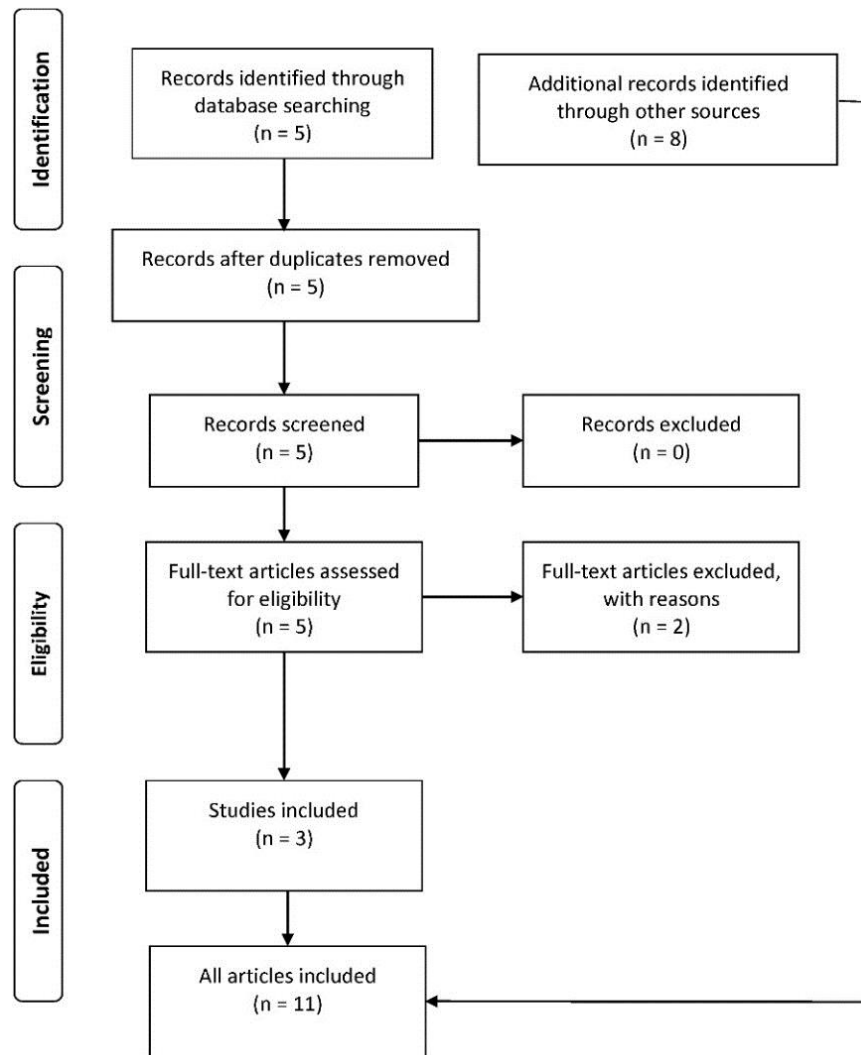


Figure 1: PRISMA flow diagram for Shiatsu and MS

Overall, the literature for effects of shiatsu in MS is very limited, not of experimental nature and does not permit a critical appraisal of its quality. Yet it can be said that based to anecdotal sources shiatsu is used with PwMS and practitioners use various approaches according to their background.

2.5. Shiatsu and Health-Related Quality of Life

A search in PubMed was completed 11/04/2019, to identify studies related to shiatsu and QoL. The terms used were “quality”, “life” and “shiatsu”. The search query was applied in all fields and using Boolean searches in the following manner:

[(shiatsu) AND quality) AND life]

without limitations in language, publication date or type of study. Due to the observation made in the previous search regarding the term “shiatsu” (§2.3), the automatically translation of the search to:

(("acupressure"[MeSH Terms] OR "acupressure"[All Fields] OR "shiatsu"[All Fields]) AND quality[All Fields]) AND ("life"[MeSH Terms] OR "life"[All Fields])

was modified to:

(("shiatsu"[All Fields]) AND quality[All Fields]) AND ("life"[MeSH Terms] OR "life"[All Fields])

The query returned eight studies, and their abstracts were screened for relevance. One study (Craske et al., 2009) was about QiGong without any reference to shiatsu and thus was excluded as not relevant to shiatsu. The rest of the studies abstract was relevant to shiatsu and their full text was searched.

One article (Argash and Caspi, 2008) had only the abstract in English with the full report in Hebrew and unable to reached. According to the abstract, the purpose of the article was to describe what is known about the usage of shiatsu in support of cancer care. Based to the experience in the integrative medicine unit of the Davidoff Comprehensive Cancer Centre in 2006, it is suggested that shiatsu can help with symptoms such as fatigue, muscular pain and body image dissatisfaction, improving QoL throughout the course of illness.

The comment by Lanza et al. (2019) is related to a single-blind randomized controlled pilot study of them (Lanza et al., 2018) examining shiatsu as an adjuvant therapy for depression in people with dementia. In their comment, they reply to

possible criticism and misconceptions regarding their original study. They position their study in its pilot context with its limitations such as a very small sample size, limited number of tests used, and absence of a follow-up period. They also comment the common (and logical) to similar studies lack of double blinding as well as the possible placebo effect. Yet they insist to their conclusions that shiatsu may play a role in promoting psychological well-being in people with dementia, since the combination of once-weekly shiatsu together with physical activity for 10 months improved depression in Alzheimer's disease patients compared to physical activity alone.

The review and meta-analysis about the effectiveness of different styles of massage in fibromyalgia by Yuan, Matsutani and Marques (2015) considers shiatsu as massage and includes a controlled pilot study by Yuan, Berssaneti and Marques (2013). The study, which compares shiatsu with educational guidance, is considered with a high risk of bias. Pain, pressure pain threshold, fatigue, sleep and HRQoL were statistically significant improved for the shiatsu group.

Burke (2014) present a longitudinal case study of Zen shiatsu, measuring stress reduction in a child with autism spectrum disorder. In the study, a seven-year-old boy was given 20-min Zen shiatsu weekly for six weeks. The changes were measured with a special stress scale designed for children with autism by the boy before and after each treatment, while a relevant HRQoL questionnaire was completed by the parents before the initiation and at the end of the six-week period. All examined domains of HRQoL found to improve after the six-week period as well as the stress levels decrease after each treatment. The paper presents a detailed description of the treatment approach and it worth to notice that the treatments were given in a treatment table. In lack of a better option. the quality of the study

appraised with the help of the CASP Cohort Study Checklist (Critical Appraisal Skills Programme, 2018) and found to be good with only the follow-up considered not adequate, even if in the discussion it is suggested a longer assessment period.

The report for the biggest ever cross-European prospective pragmatic observational study on shiatsu which included 948 participants (Long, 2008), even if does not address specifically measurement of QoL, shows some relevant effects.

The participants reported improvements in symptom severity (such as stress, skeletomuscular problems, fatigue and emotional issues), changes in overall perception of health condition and in their lifestyle, that they attributed to shiatsu.

The quality of the study appraised with the help of the CASP Cohort Study Checklist (Critical Appraisal Skills Programme, 2018) and found to be good even if issues with recruitment and measuring of effect exists and are discussed in the article.

The paper by Soffer et al. (2001) presents a survey with the characteristics of the patients visiting the Complementary Medicine Clinic in Clalit Health Services Clinic in Israel during the first two years of its operation. One of the reasons for visiting the clinic is related to hope of improvement in aspects of QoL and shiatsu together with acupuncture were the most commonly used modalities. Yet the study does not offer any useful clinical details regarding shiatsu.

Finally, the article by Stevensen (1996) describes the complementary cancer therapy programme offered at the Royal London Homoeopathic Hospital NHS Trust. In that it is noted that the complementary therapies used aim to enhance the QoL. One of the offered therapies is shiatsu, yet there are no useful clinical details regarding shiatsu.

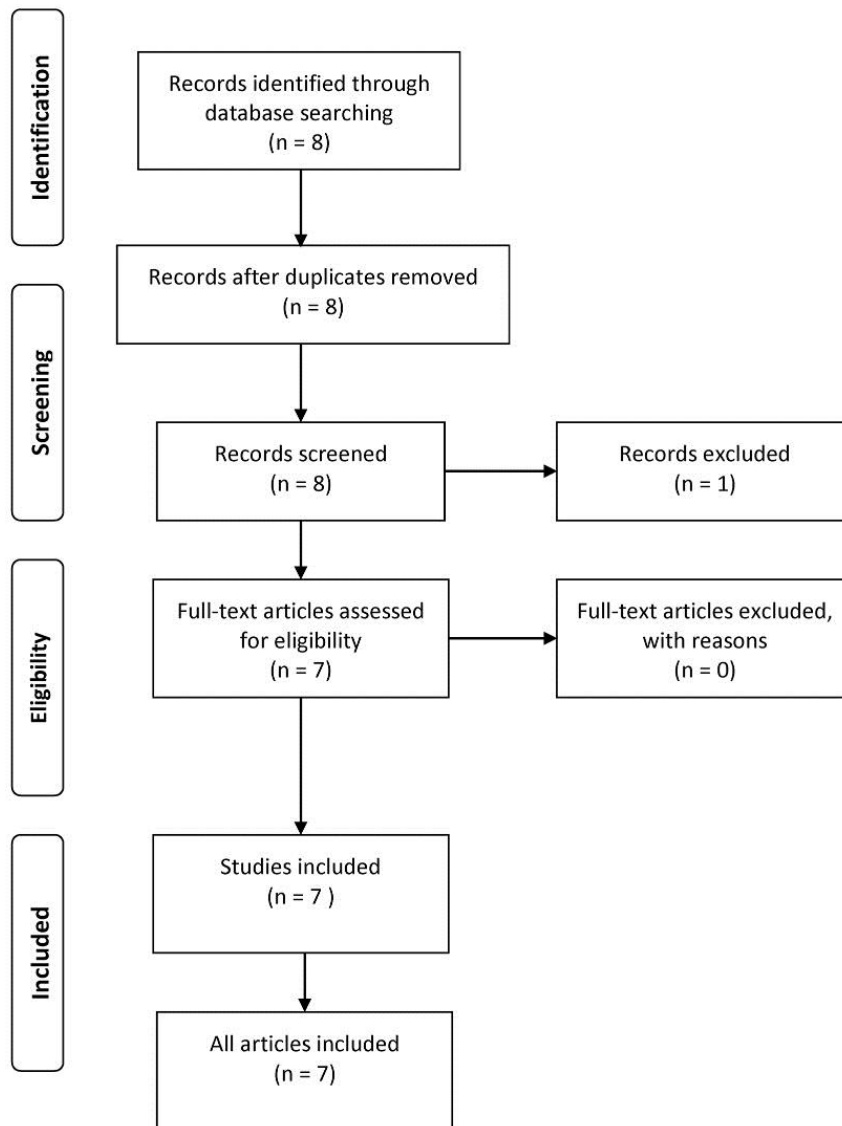


Figure 2: PRISMA flow diagram for Shiatsu and HRQoL

Overall, the literature for effects of shiatsu in HRQoL is very limited. The existing clinical evidence is of good quality even if not without problems. Only one study examines a big population while other two are small pilot studies and one a case study with one participant. The limited evidence suggests that shiatsu has the potential to contribute in improvement of HRQoL, yet more research is necessary to confirm it. It should be noted that the relevance of measuring QoL to the clinical practice was until recently a debated issue between clinicians (Higginson and Carr, 2001; Fitzpatrick et al., 1992). Thus, it is expected that QoL will be under-

investigated in the field of shiatsu where it seems that the very limited evidence base has been created partly by clinicians. A more detailed review of all available studies on shiatsu might reveal more evidence related to its effects in HRQoL when that was not a specific outcome of the studies.

2.6. Summary

The aim of the study is to investigate if shiatsu affects the HRQoL of a person with SPMS. The literature review indicates that the evidence for effects of shiatsu in MS is very limited and of very low quality, mostly anecdotal reports of cases by practitioners. In those reports it can be seen that shiatsu practitioners use various approaches for the treatment of PwMS without reaching a clinical consensus for styles or techniques. Considering the effect of shiatsu in QoL, the evidence is similarly limited yet it can be suggested that shiatsu has the potential to contribute in HRQoL improvements. The importance of the HRQoL for PwMS position it as a very highly relevant care outcome and its improvement is an unmet need for many patients. To meet that need, a multidisciplinary approach following individualised, patient-centred principles is considered appropriate. Those characteristics are usually guiding shiatsu as applied in the clinical setting thus worth to explore further its relevance to HRQoL. To proceed with such an investigation, it is important to consider the methodological approaches that will provide both high quality evidence and respect the individualised nature of each PwMS situation and shiatsu practice. N-of-1 trial designs are well suited for individualised modalities and can provide high quality evidence, yet there are issues that limits their applicability in non-pharmacological CAM research, with the issue of carry-over effects being of significant importance. Carry-over effects are difficult to detect and the results

difficult to interpret unless there is confidence about their amplitude due to previous knowledge. Due to the lack of previous knowledge about the effect of shiatsu in MS and HRQoL, mixed methods (including besides the quantitative data from PROM qualitative sources of data such as semi-structure interviews and clinical notes) that could provide rich description of the effects and other possibly contributing factors might provide a solution to the problem of carry-over. Thus, a mixed methods approach of n-of-1 designs might be an appropriate methodological approach to investigate the effect of shiatsu in the HRQoL of PwMS.

Chapter 3: Methodology

The following chapter will open with a brief discussion of the philosophical underpinnings of the research approach. It will then present the rationale of choosing the methodology, critiquing both quantitative and qualitative approaches that could be taken to answer the research question. It then outlines why the mixed methods, case study and n-of-1 trial design is appropriate to the research question. After those preliminary elements, the study design will be presented in detail as well as the data analysis plan. The chapter will close with a brief outline of ethical issues and study limitations.

3.1. Philosophical Underpinnings

OM, including shiatsu, is an example of whole systems of healthcare. It uses individualised, non-reductionist approaches to diagnosis and treatment, “in order to maximize the patients’ capacity to achieve mental and physical balance and restore their own health” (Ritenbaugh et al., 2003, p.32). The concept of holism (Freeman, 2005) is a cornerstone of its underlying principles (Hao, Jiang and Gu, 2017; Tai, 2012). It considers the individual patient’s characteristics as significant factors that interact according to natural laws (Unschuld, 2016) with external influences (environmental as well as social) during the process of the formation of illnesses (Boyanton, 2016). Its conceptual structure, based on the dialectical concept of constant change, sees health as a dynamic interaction between the inner environment and the exterior world (Kaptchuk, 1987).

Whole Systems Research (WSR) is an innovative research design recently developed for the study of whole systems of healthcare which had been used in

OM studies (Pritzker and Hui, 2012). WSR is relevant to complex interventions and calls for consideration of the “model validity” (Jonas, Lewith and Walach, 2002) as a central feature of all CAM studies (Ritenbaugh et al., 2003). In that approach, the philosophical assumptions underlying the examined whole system should drive the entire research process (Verhoef, Vanderheyden and Fonnebo, 2006).

Following a WSR approach, the above-referred characteristics of OM call for a dialectical understanding of reality by the researcher. The investigation should consider the individual case as an organic whole, constituted by organically linked components (the context, the processes, the intervention, the outcomes, the experiences (Paterson et al., 2009)). These components only exist through their relationship with the others, and are in constant change and development. Changes in the case occur due to the internal interactions of those organically linked components. By understanding the causes of those changes, it becomes possible to highlight trends and directions of their future development (Pavlidis, 2010).

3.2. The Rationale for Choosing Methodology – Research Design

3.2.1. Quantitative and Qualitative Approaches in Clinical Health Research

The quantitative approach of inquiry (collecting, analysing and displaying data in numerical format (Donmoyer, 2008, p.713)) has dominated clinical health research for decades (Britten, 2005). The most commonly encounter experimental design is the RCT which is considered the gold standard of medical knowledge (Bothwell et

al., 2016; Jones and Podolsky, 2015), being at the top of the EBM hierarchy of evidence (Sackett et al., 1996). RCTs are studies that can control efficiently confounding variables isolating the effect of the tested treatment, achieving high levels of internal validity and implying causality. Unfortunately, this is often at the cost of the external and model validity of the study (Khorsan and Crawford, 2014), making this approach not favourable for assessing the efficacy of CAM (Verhoef, Casebeer and Hilsden, 2002) or patients with multiple comorbidities (Fortin, 2006).

Qualitative research methods aim to seek answers by asking non-quantifiable questions related to the examined objects or processes. Thus they are more appropriate approaches for “what”, “how”, “why” types of questions (Green & Thorogood, 2004, p.5). Their relevance to EBM lies in their ability to examine questions that are not easily answerable by the quantitative approach (Green and Britten, 1998; Pope and Mays, 1995). Due to their orientation towards a naturalistic inquiry (i.e. the investigation of phenomena within and in relation to their naturally occurring context (Owen, 2008, pp.547-50; Schwandt, 2007, pp.206-7), they can be considered to a very great degree trustworthy. Trustworthiness is a concept that applies to qualitative research in a way analogous to the concepts of validity and reliability of the quantitative approach (Guba, 1981).

3.2.2. The Mixed Methods Synthesis

Advocates of the quantitative and qualitative approaches have for years stated that they are incompatible (Johnson and Onwuegbuzie, 2004; Howe, 1988). A third approach had also appeared and is developing, namely the mixed methods research approach (Johnson, Onwuegbuzie and Turner, 2007). There are many

definitions of mixed methods research available. In the first issue of the Journal of Mixed Methods Research, it is defined as:

[...] research in which the investigator collects and analyzes data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or a program of inquiry. A key concept in this definition is integration [...]

Tashakkori & Creswell (2007, p.4)

More recently, during 2011, the NIH's Office of Behavioural and Social Sciences Research released a "best practices" guide for mixed methods research in the health sciences where mixed method research is defined as:

[...] a research approach or methodology:

- focusing on research questions that call for real-life contextual understandings, multi-level perspectives, and cultural influences;
- employing rigorous quantitative research assessing magnitude and frequency of constructs and rigorous qualitative research exploring the meaning and understanding of constructs;
- utilizing multiple methods (e.g., intervention trials and in-depth interviews);
- intentionally integrating or combining these methods to draw on the strengths of each; and
- framing the investigation within philosophical and theoretical positions.

(Creswell et al., 2011, p.4)

Mixed methods are suggested as an optimal approach to WSR investigations (Verhoef et al., 2005). They fit well with the Evidence House idea of Jonas (2001), being able to generate evidence containing both statistically causal inferences and more complex, non-reductive qualitative explanations. The mixed methods

approach is also able to accommodate well the dialectical methodology of researching an organic whole since it enables the usage of the appropriate analytical or synthetic processes to examine different phases of its historical development, especially when used in a program of scientific inquiry (Patelis, 2011).

3.2.3. Case Study

The rationale presented for the use of mixed methods research also applies well in the case study method as one direction of inquiry to be followed. Case study method is needed when complex phenomena are to be understood (“how” and “why” questions), with the demand of an extensive, in-depth description of a “case”, retaining a holistic and real-world, naturalistic perspective (Yin, 2014, p.4). Some scholars have defined the case study method as not being “a methodological choice but a choice of what is to be studied” (Stake, 2005, p.443). The more methodological-focused way that Yin (2014, p.16) and Gillham (2000, p.1) have defined the case study method, seems preferable when we have to deal with the dialectical understanding of an organic whole. Their definitions indicate that this case study method would be preferred when the boundaries between phenomenon and context of the case may not be directly evident (Yin, 2014, pp.214-5), and when the investigated case can be understood only in context (Gillham, 2000, p.1).

In addition, a case study is a method which is not limited in the quantitative or qualitative approach but uses various types of data (Gillham, 2000, p.2), thus it is compatible with mixed methods research (Yin, 2014, p.65). Considering its relevance to EBM, case studies can complement quantitative experimental designs, like RCTs. Moreover, the case study method is a good approach in

performing pilot studies, to form a working hypothesis and better focus new research (Yin, 2014, p.40).

3.2.4. N-of-1 or Single-Subject Clinical Trial

According to a recent definition:

N-of-1 trials are multiple crossover trials in single individuals. They are ideal to evaluate treatment effectiveness in chronic conditions. N-of-1 trials offer the rigor of randomized controlled trials (RCTs), while allowing opportunities for treatment and its evaluation to be tailored to individual patients.

Vohra (2016, p.1)

N-of-1 clinical trials have been conducted concerning more than 50 health conditions for a variety of interventions (Punja et al., 2016a). Since they consider an individual patient as the sole unit of observation (Lillie et al., 2011), it is a design that seems to be appropriate for trials of whole systems of healthcare such as OM and shiatsu, where the treatment is personalised (Verhoef et al., 2005).

While their reporting quality varies and can improve (Li et al., 2016; Tate et al., 2016; Vohra et al., 2015; Shamseer et al., 2015), it has been found that, under certain conditions, the results of a single subject trial accurately approximates the results of an RCT (Shadish, Rindskopf and Boyajian, 2016). Furthermore, it is possible to get embedded in bigger RCTs (Avins, Bent and Neuhaus, 2005) or even to combine results of n-of-1 trials with RCTs for meta-analysis purposes (Punja et al., 2016b).

3.3. Study Design

The study was a six periods single-subject crossover experiment (n-of-1 clinical trial), using a minimally optimal (Carriere et al., 2015, pp.74-5) counterbalanced design, alternating paired two-week blocks of standard care (A) or intervention plus standard care (B) (AB BA AB) (Figure 3).

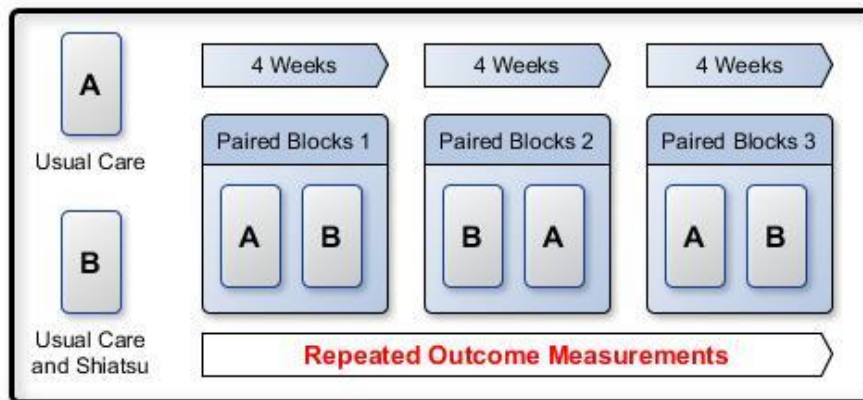


Figure 3: N-of-1 Trial Design Model

3.3.1. Study Personnel

The practitioner-researcher was a shiatsu and OM practitioner with seven years of clinical practice, of which the last five focused on PwMS. In addition, he was MSc candidate in Advanced Oriental Medicine.

The researcher's group of the study consists of:

Anders Romberg, PT, PhD (Principal Investigator)

Stergios Tsiormpatzis, MSc Candidate (Researcher and Practitioner)

Karen Charlesworth, Msc, MBAcC (College Research Director)

Dr Kathryn Murphy, MBChB, BSc (Hons) DFFP, DRCOG, MRCP, PGDip Acu
(College Medical MSc Supervisor)

Trina Ward, PhD, MPhil, BSc (Hons) (College MSc Supervisor)

Lisa Esmonde, PhD Candidate, BSc (College MSc Supervisor)

3.3.2. Participants and Eligibility Criteria

The patient was an elective volunteer participant who satisfied the eligibility criteria.

Eligibility criteria include:

- ✓ SPMS patient
- ✓ Between 35 and 65 years old
- ✓ Living in the central Uusimaa area
- ✓ Speaking good English language
- ✓ Agrees to the study protocol

Exclusion criteria include:

- ✗ Suffering from chronic or excessive fatigue
- ✗ Receiving shiatsu, acupuncture or another form of OM during the last six months
- ✗ Inability to complete short questionnaires without assistance

3.3.3. Data Collection and Instruments

3.3.3.1. Patient Intake Notes

Details required to form a natural history of the disease for the patient and to provide a clinically useful initial picture were collected. Also, enquiries were made

into the patient's expectations from the trial, and the initial MSQLI (described below) was completed.

3.3.3.2. Health-Related Quality of Life

The short version of the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Fischer et al., 1999) was the HRQoL instrument. It was chosen due to its coverage of multiple domains in a way that could be completed in a reasonable amount of time. The instrument was modified to be completed every two weeks, at the initial baseline and the end of each of the six periods.

3.3.3.3. Experience and Adverse Events

A semi-structured interview with the patient was made at the end of the trial to explore the experience of the treatment, the influence of the trial in the life of the patient and to discuss possible adverse events.

3.3.3.4. Case Records

The case records as usually kept by the practitioner which include reporting of adverse events as inquired into the patient after each session are part of the evidence.

3.3.4. Ethical Approval

Ethical approvals for the trial were given by The Northern College of Acupuncture Research Ethics Committee (REC) (11/09/2017) and by the Helsinki and Uusimaa Hospital District Coordinating Ethics Committee (HUS/648/2017, 8/8/2017).

3.3.5. The Timeframe of the Study

The timeframe of the study shows in table 2 and the Gantt Chart in figure 4.

Table 2: Timeline of the study

START DATE	END DATE	DESCRIPTION	DURATION (days)
12 September 2017	20 September 2017	Recruitment	9
20 September 2017	20 September 2017	Informed Consent	1
20 September 2017	20 September 2017	Intake Notes	1
22 October 2017	22 October 2017	Initial MSQLI	1
06 November 2017	15 January 2018	Clinical Part	70
15 January 2018	15 January 2018	Semi-Structured Interview	1
30 January 2018	30 January 2018	Transcript Accepted	1

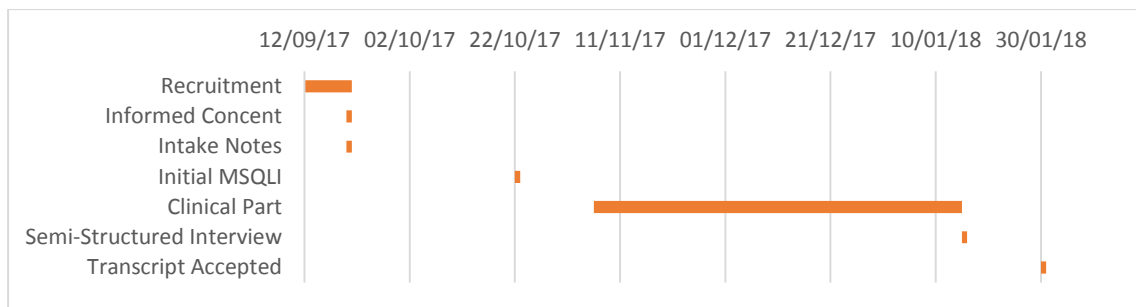


Figure 4: Gantt Chart of the study

3.4. Detailed Description

Following the ethical approval, a “Letter of Invitation” was shared to former patients of the practitioner and used to inform possible participants from the PwMS that belonged to their social circles. The first person who responded positively was screened and satisfied the eligibility criteria. The Participant Information Sheet (PIS) and the consent form were provided in electronic format, while a face-to-face meeting arranged between the patient and the researcher-practitioner. During this initial meeting, the PIS and concerns of the participant were discussed and the consent form signed. In addition, intake notes were taken, and the initial-baseline

MSQLI was administered. The scheduling of the trial was agreed at that meeting to be renewed weekly.

The trial took place in six periods of paired two-week blocks of standard care (A) followed by intervention plus standard care (B) (AB BA AB). The standard care period (A) includes whatever care the patient normally receives only. The intervention plus standard care period (B) includes whatever care the patient normally receives and two weekly shiatsu sessions. It was made clear that the patient may withdraw from the trial in any phase, without giving any explanation.

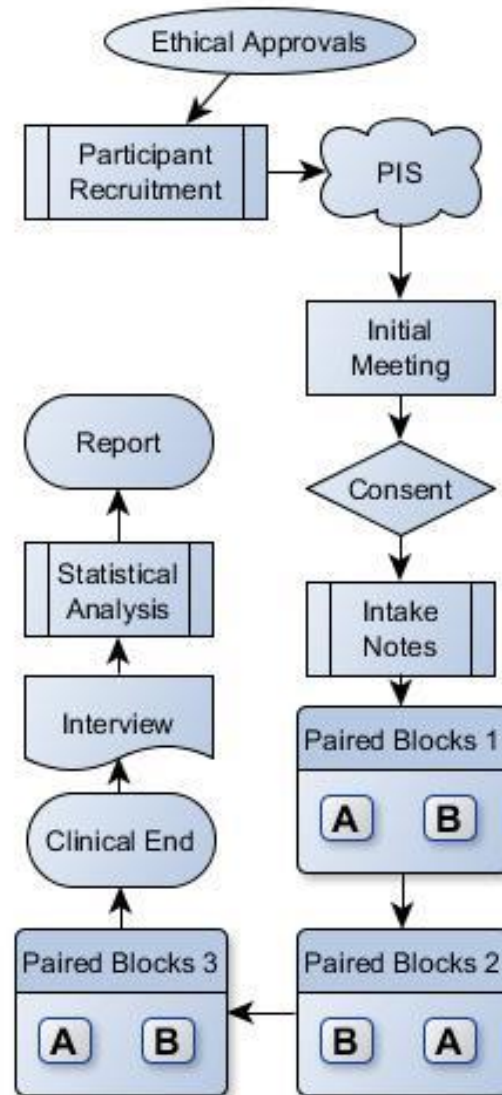


Figure 5: Clinical Trial Flow-Chart

Besides the initial baseline, the MSQLI was completed at the end of each two-week period, seven times in total.

At the end of the trial, a semi-structured interview took place as described earlier. The interview was digitally recorded after obtaining patient consent, with verbatim transcription and thematic analysis to follow. The transcript was checked for accuracy by the participant.

A statistical analysis of the trial and a descriptive case study analysis follow at the end of the trial. With all the analysis completed, the synthesis began, resulting in the dissertation report and a poster (see Figure 5).

3.5. Case Study Analysis

A descriptive case study analytic strategy (Tobin, 2009) was used, to outline the case. This begun with a familiarisation phase covering all types of collected data, then the clinical case was described, followed by a statistical analysis of the questionnaires and thematic analysis of the interview. The thematic analysis follows flexibly the six-step Braun and Clarke (2006) approach. Due to the single, short interview included in the thematic analysis, after the 1st (familiarisation with the data) and 2nd (generation of initial codes) steps, the 3rd (search for themes) and 4th (review themes) steps were compacted in one, followed by the 5th step (definition of themes), while the 6th step (writing up) is completed in the synthesis of the findings that follows (§ 4.5). Those results together with the reflection of the researcher contribute to the discussion for the articulation of a descriptive theory.

3.6. Statistical Analysis

Due to the limited data collection points of just one participant where the samples are not independent within subjects, the assumptions of the commonly used statistical tests were not satisfied (Chen and Chen, 2014; Mengersen, McGree and Schmid, 2015; Schmid, Duan and The DEcIDE Methods Center N-of-1 Guidance Panel, 2014). Thus, the statistical analysis as described in the Detailed Research Proposal (Tsiormpatzis, 2017), following both a Changing Criterion and a Pre-Post logic, was not feasible. The Wilcoxon signed-rank test was used as the theoretically appropriate to statistically analyse the paired data and get an answer to the

hypothesis of the study. Yet, as explained in the Appendix 2, it was later realised that it cannot answer the hypothesis. In addition, a visual presentation of the score results was presented and a table where the baseline scores were compared to the scores at the end of the trial (end of the 6th block). All calculations were made using the LibreOffice 6.0.2. The description of the actual process of analysis can be found in Appendix 2.

3.7. Reflection

A structured reflection on the role of the practitioner-researcher in the process of implementation of the study is included in the report of the results, following the Gibbs' reflective cycle (Gibbs, 1988 cited in Finlay, 2008, p.8). It is hoped that this will improve the self-awareness of the researcher and improve the quality of his future investigations.

3.8. Ethical Issues

3.8.1. Practitioner Qualification and Insurance

The practitioner, who is also the researcher, is fully qualified to carry out the shiatsu treatment, having completed three years of shiatsu and OM training, one-year postgraduate shiatsu diploma and nursing education for MS care. He has five years of experience as a care-partner for PwMS. His practice (including research activities) is insured via "if..." insurance company, a member of the Finnish Patient Insurance Centre, according to the Finnish Patient Injuries Act (585/1986).

3.8.2. Informed Consent and Confidentiality

The patient in the study signed a consent form, having read a fully detailed PIS. The patient was made aware that they can complain about any aspect of the

treatment or the study, either directly to the researcher or by contacting the Principal Investigator.

All the data collected were held confidentially, according to the Finnish Personal Data Act (523/1999), the UK Data Protection Act (1998) and the EU General Data Protection Regulation (GDPR). The identity of the patient remained anonymous throughout the study and afterwards. The practitioner did not reveal any identifiable clinical data since there was not any case of medical emergency or legal demands.

3.8.3. Audio Recording and Data Storage

The interview was digitally recorded after obtaining patient consent. All other data were initially collected in paper format and transferred in electronic format weekly. After the electronic transfer, the audio recorder was irreversibly erased while the paper data were irreversibly destroyed using a paper shredder and burning the shredded pieces in a wood stove. All electronic data are kept until the end of the study in an encrypted and password-protected folder of a private NAS station (Synology) in the office of the researcher and then irreversibly deleted using the appropriate software. The NAS station uses a RAID disk structure to ensure the safety of the data by automatic, synchronous backup in three different hard disks. Besides the built-in safety of the Linux-based NAS architecture, Synology's anti-virus software is also active. The NAS station is not connected to external networks (e.g. internet) and does not have options for wireless connectivity. It is stored in the private office of the researcher where he had exclusive access. EU General Data Protection Regulation (GDPR) Data Processing Diary for this study can be found in Appendix 1.

3.8.4. Research and Clinical Care of a Vulnerable Patient

Due to the patient-centred nature of the intervention, the study kept a good balance between the research aims and the clinical care of a vulnerable patient, providing new knowledge which could benefit PwMS.

3.9. Limitations of the Study

3.9.1. Randomisation and Blinding

The bodywork nature of the proposed intervention does not allow the application of randomisation and blinding (Mehling, DiBlasi and Hecht, 2005). Yet, the n-of-1 trial crossover design bypasses the concerns of selection bias that the lack of randomisation cause, since the same person is at the same time the control of the trial.

3.9.2. Maturation and Regression

While maturation of the case is unavoidable due to the progressive nature of the disease, it was not expected to appear regression, for the same reason (Donnellan and Shanley, 2007). Thus there was no danger of regression to the mean.

3.9.3. Credibility

Since the practitioner of the study is also the researcher, the following processes were followed to help establish the credibility of the study:

- Synthesis of data collected from various sources
- Supervision and peer debriefing
- Interview transcript checking by the patient

Also, the issue is present in the reflection of the researcher.

Chapter 4: Findings

4.1. Description of the Clinical Case

The participant was a 57 years old woman with SPMS. Her first symptoms appeared when she was 20, but she remained undiagnosed until age 32. Six years after diagnosis she had reached a stage where she could walk alone for a kilometre (EDSS {3.5-4}) while four years later, at 42, she was already in the SPMS stage. One year later she had to use a wheelchair for most of her movements, and at age 47 she was essentially restricted to a wheelchair (EDSS 7.5). At that time her perimenopause began and continued for about four years. At age 49 the MS related medication (B-Interferon) was interrupted, and a year later she had surgery based on the Chronic Cerebrospinal Venous Insufficiency (CCSVI) approach, which helps with fatigue but not with other symptoms.

At the time of her recruitment in the trial, she was mainly restricted to a wheelchair, and she retains many self-care functions with effective use of arms and needs help to move from bed to the wheelchair (EDSS 8). Following the OM-based staging approach proposed by Blackwell and Macpherson (2000), she was at the last, fourth stage where deficiency dominates with tiredness, urinary issues and considerably stiff and spastic muscles. Due to the restriction to a wheelchair, she does not move a lot, and she experiences back and buttocks pain, stiffness and spasticity in her legs and her right hand. However, there is no nerve pain, and she does not need painkillers. She has to use daily medication for spasticity (Baclofen & Spasmolin). Neurogenic bladder symptoms with chronic repeated inflammation were also under control with continued daily use of antibiotic medication (Nitrofur-C). She suffers from chronic constipation and sleep problems; frequently waking

at night. In the early morning she wakes up with a sense that everything feels bad without knowing why. She has a balance problem, heat makes her worse, and often she finds it difficult to express herself in words. Being in receipt of a pension due to disability since age 46, today she feels her retirement is a gift. In her diet, she avoids meat products.

After the interruption of the MS medication, she had appointments with a neurologist every three years and 95 physiotherapy sessions per year, of which 25 are in a pool and the other 70 by visiting the physiotherapist in the health care centre. She enjoys most the visits to the pool, and she feels satisfied with the amount of care that she receives.

On inquiring about her expectations from the trial, she expresses her disbelief in any possible benefit from shiatsu. In addition, when questioned about which one symptom she would like to be primarily addressed she chooses spasticity.

4.1.1. Shiatsu Treatments

The treatments were given in the house of the participant according to a schedule agreed weekly. Due to her difficulties to change from wheelchair to the futon in the floor, she suggested having the sessions in a hard bed without springs. The bed was at the right height for her to move from and to the wheelchair with the help of the practitioner. Members of her family were present in the same big, open room but not focused on the treatments. All twelve (12) treatments included in the plan of the trial were completed successfully, with sessions varying between 60 and 90 minutes, according to the judgment of the practitioner. In the beginning of each treatment after the first and at the final interview, the participant was asked for her feelings after the previous treatment as well as for possible adverse events or

effects from it. A therapeutic relationship was established without strong rapport. The communication remained mostly focused on health, partly due to language limitations. The aim of the treatment was focused on the main complaint as expressed by the participant in the first meeting (spasticity) and modified according to the issues raised before each session. The principles of treatment were informed by a general OM-based understanding of the condition of the participant. The method of treatment was specified by incorporating palpation of the body during each session. A detailed description of the treatments as described in the case notes can be found in Appendix 3.

4.2. Questionnaire Results and Statistical Tests

The raw data of the completed MSQLI are available in the Data Repository (Tsiormpatzis, 2018). The scores of all the MSQLI domains are presented in tables 3 and 4, showing that the initial period established a stable baseline of two weeks, while the Social Functioning Scale (SF), Role-Emotional Scale (RE) and the Impact of Visual Impairment Scale (IVIS) remained stable during the whole duration of the trial.

Table 3: Health Status Questionnaire SF-36 scores

	Initial	A	B	B	A	A	B
		1st Block	2nd Block	3rd Block	4th Block	5th Block	6th Block
Health Transition Item (1-5)	3	3	3	2	3	3	3
Physical Functioning Scale (PF)	5	5	5	10	5	5	5
Role-Physical Scale (RP)	0	0	0	50	50	50	75
Bodily Pain Scale (BP)	84	84	72	74	84	84	84
General Health Scale (GH)	35	35	25	25	30	30	35
Vitality Scale (VT)	30	30	30	30	30	20	30
Social Functioning Scale (SF)	50	50	50	50	50	50	50
Role-Emotional Scale (RE)	100	100	100	100	100	100	100
Mental Health Scale (MH)	84	84	88	92	92	96	92
Physical Components Summary Scale (PCS)	20.852	20.852	17.508	23.409	24.449	23.821	27.665
Mental Component Summary Scale (MCS)	58.280	58.280	59.933	58.603	58.653	58.604	57.702

Table 4: Rest of MSQLI scores

	Range (better-worst)	Initial	A	B	B	A	A	B
			1st Block	2nd Block	3rd Block	4th Block	5th Block	6th Block
Modified Fatigue Impact Scale - 5 Item Version (MFIS-5)	0-20	14	14	5	3	5	7	4
MOS Pain Effects Scale (PES)	6-30	8	8	8	7	9	7	7
Sexual Satisfaction Scale (SSS)	4-24	12	12	13	14	13	13	12
Bladder Control Scale (BLCS)	0-22	1	1	0	0	1	0	1
Bowel Control Scale (BWCS)	0-26	9	9	3	0	2	4	2
Impact of Visual Impairment Scale (IVIS)	0-15	0	0	0	0	0	0	0
Perceived Deficits Questionnaire - 5 Item Version (PDQ-5)	0-20	6	6	5	3	1	1	1
Mental Health Inventory - 5 Item Version (MHI-5)	100-0	84	84	88	92	92	96	92
MOS Modified Social Support Survey - 5 Item Version (MSSS-5)	100-0	80	80	70	70	70	75	70

Table 5 shows the rest of the MSQLI scores transformed in 0-100 scale with 0 indicating the worst and 100 the best possible score:

Table 5: Rest of MSQLI scores in 0-100 scale

	%	A	B	B	A	A	B
	Initial	1st Block	2nd Block	3rd Block	4th Block	5th Block	6th Block
Modified Fatigue Impact Scale - 5 Item Version (MFIS-5)	30.00	30.00	75.00	85.00	75.00	65.00	80.00
MOS Pain Effects Scale (PES)	91.67	91.67	91.67	95.83	87.50	95.83	95.83
Sexual Satisfaction Scale (SSS)	60.00	60.00	55.00	50.00	55.00	55.00	60.00
Bladder Control Scale (BLCS)	95.45	95.45	100	100	95.45	100	95.45
Bowel Control Scale (BWCS)	65.38	65.38	88.46	100	92.31	84.62	92.31
Impact of Visual Impairment Scale (IVIS)	100	100	100	100	100	100	100
Perceived Deficits Questionnaire - 5 Item Version (PDQ-5)	70.00	70.00	75.00	85.00	95.00	95.00	95.00
Mental Health Inventory - 5 Item Version (MHI-5)	84.00	84.00	88.00	92.00	92.00	96.00	92.00
MOS Modified Social Support Survey - 5 Item Version (MSSS-5)	80.00	80.00	70.00	70.00	70.00	75.00	70.00

The results of the statistical tests are presented in the tables 6 and 7.

Table 6: Health Status Questionnaire SF-36 results

	W-	W+	W
Health Transition Item (1-5)	0	1	0
Physical Functioning Scale (PF)	1	0	0
Role-Physical Scale (RP)	1	0	0
Bodily Pain Scale (BP)	0	3	0
General Health Scale (GH)	1.5	4.5	1.5
Vitality Scale (VT)	1	0	0
Social Functioning Scale (SF)	STABLE		
Role-Emotional Scale (RE)	STABLE		
Mental Health Scale (MH)	1.5	1.5	1.5
Physical Components Summary Scale (PCS)	3	3	3
Mental Component Summary Scale (MCS)	2	1	1

Table 7: Rest of MSQLI results

	W-	W+	W
MFIS-5	6	0	0
PES	1	0	0
SSS	2	4	2
BLCS	4	5	4
BWCS	6	0	0
IVIS	STABLE		
PDQ-5	1	2	1
MHI-5*	1.5	1.5	1.5
MSSS-5	0	3	0

The interpretation of the ranked results from the statistical tests alone is not straightforward and can't answer our hypothesis, since the statistical tests are not powered enough to permit rejection of the null hypothesis, as explained in appendix 2. To make better sense of the scores they are also visually presented, as commonly happens in reports of n-of-1 trials (Gabler et al., 2011).

Figures 6 and 7 visually present the changing scores of the SF-36 domain and the rest of the MSQLI domains during time.

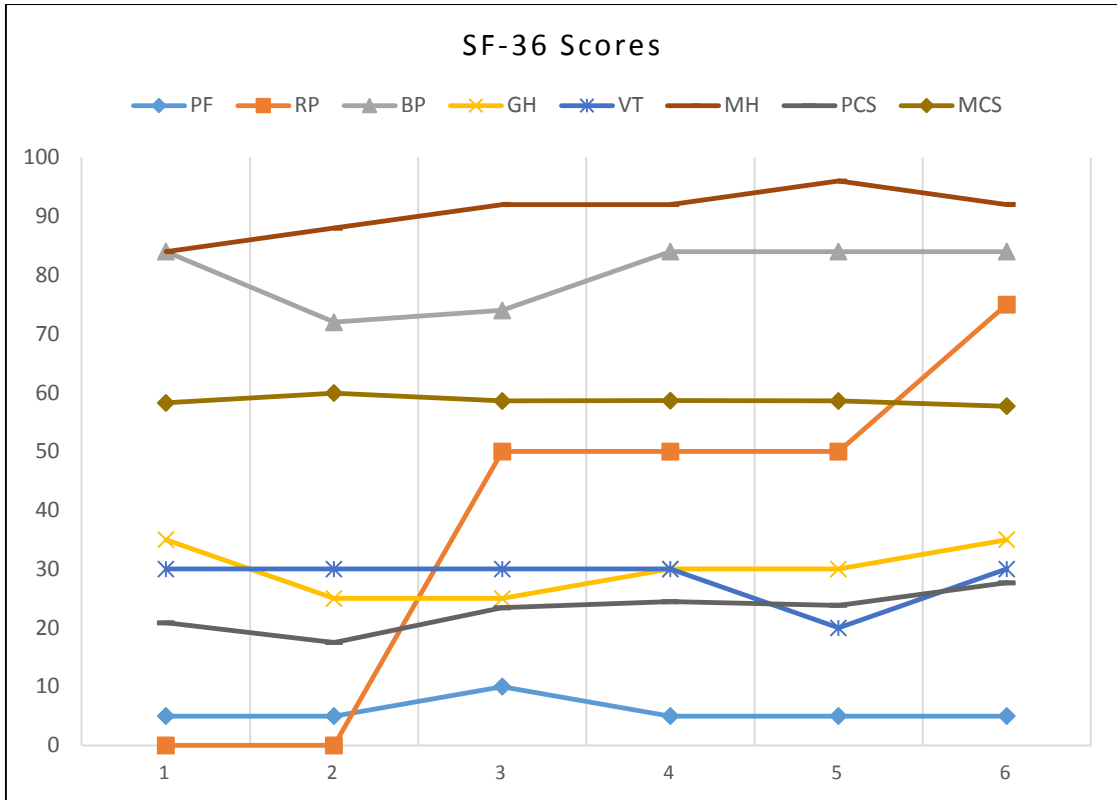


Figure 6: SF-36 Scores

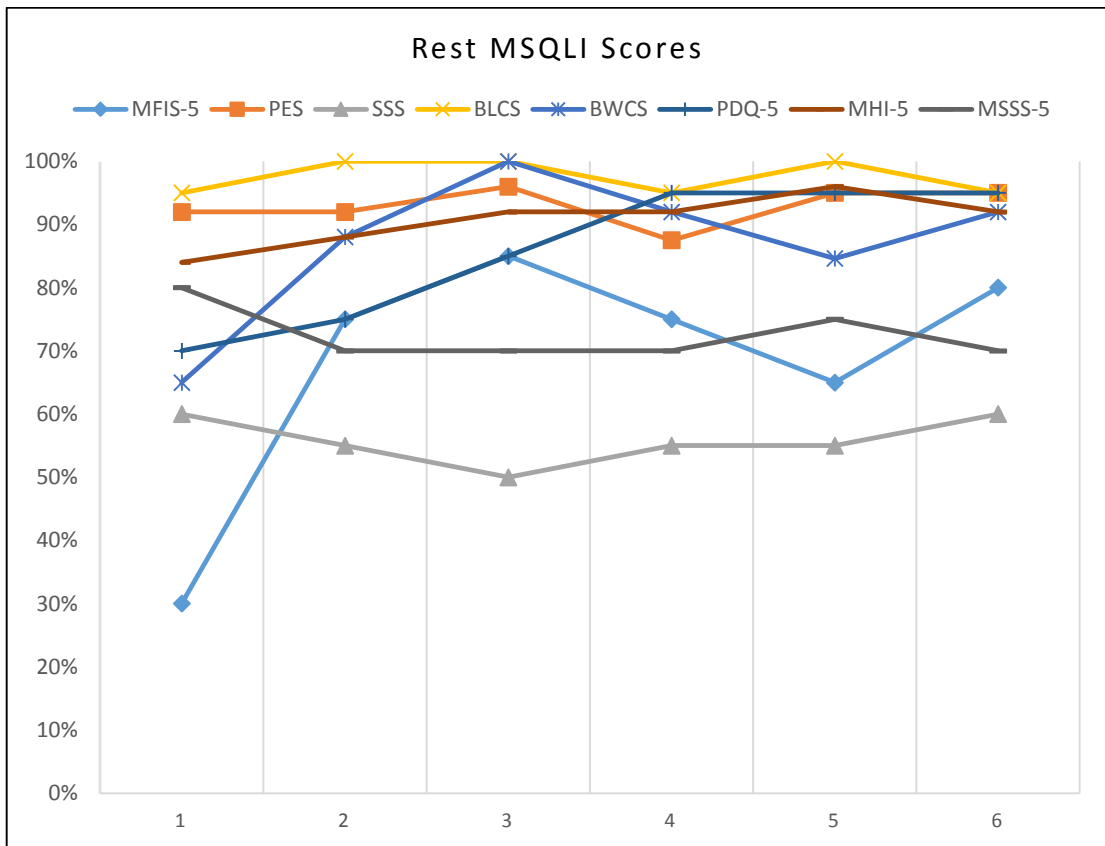


Figure 7: Rest of MSQI Scores

Table 8 summarises the pre-post score comparison for all the domains between the baseline and the end of the trial after the sixth block:

Table 8: Pre-Post Comparison of all domains

	Worst	Stable	Better
SF-36	Mental Components Summary Scale (MCS)	Health Transition Item	Role-physical Scale (RP)
		Physical Functioning Scale (PF)	Mental Health Scale (MH)
		Bodily Pain Index (BP)	Physical Components Summary Scale (PCS)
		General Health Scale (GH)	
		Vitality Scale (VT)	
		Social Functioning Scale (SF)	
		Role-Emotional Scale (RE)	
Rest	MOS Modified Social Support Survey - 5 Item Version (MSSS-5)	Sexual Satisfaction Scale (SSS)	Modified Fatigue Impact Scale - 5 Item Version (MFIS-5)
		Bladder Control Scale (BLCS)	MOS Pain Effects Scale (PES)
		Impact of Visual Impairment Scale (IVIS)	Bowel Control Scale (BWCS)
			Perceived Deficits Questionnaire - 5 Item Version (PDQ-5)
			Mental Health Inventory - 5 Item Version (MHI-5)

4.3. Thematic Analysis of the Interview

The verbatim transcript of the interview can be found in Appendix 4. The text of the interview was thematically analysed following flexibly the six-step framework proposed by Braun and Clarke (2006). Since the aim of the semi-structured interview as explained earlier (§ 3.3.3.3) was to explore the experience of the treatment, the influence of the trial in the life of the patient and to discuss possible adverse events, a theoretical approach was taken, coding relevant data (Maguire,

M., & Delahunt, 2017). Due to the single, short interview included in the thematic analysis, the 3rd (search for themes) and 4th (review themes) steps were compacted in one, while the 6th (writing up) step is completed in the synthesis of the findings that follows (§ 4.5). In table 8 the themes that occurred are presented together with the corresponding codes and their frequency of occurrence.

Table 9: Themes and Codes

THEMES				
Effects of the treatment	Practical aspects of trial	Comparison with usual care	Adverse events	Expectations
CODES				
Spasticity (8)	Regularity (3)	Usual care (6)	Spasticity (8)	Temporality (2)
Constipation (5)	Following trial (2)	Physical treatment (2)	Adverse event (2)	Expectations (2)
Sleep (5)	Treatment breaks (2)	Muscular work (2)	More carefully (1)	Recommendation (1)
Relaxing (4)	Cloths (1)	More carefully (1)		
Pains (3)	Home-visit (1)			
Lower-back (2)				
Right-hand (1)				
Legs (1)				

The definitions of the themes that occurred (5th step) are as follows:

- **On the effects of the treatment**

The participant focuses a lot and continuously return to the effect that the treatment as such had in her life. Those include:

Relief from spasticity (“I was actually quite astonished that it releases my spasticity so well”).

Relief from constipation (“the other good thing that was also that my stomach was very... working very well when I got this shiatsu... constipation was released”).

Relief from local pains (“local things like local pain in my lower back”).

Improvement in the function of her right hand (“especially my right hand has been better after shiatsu, much better”).

The relaxing nature of the treatment (“it has been very relaxing in general... was so relaxing and pleasant”).

Improvement in sleep (“let’s say the sleeping, I have slept better because my legs have been not so spastic... they have been more relaxed during the nights... that’s quite big thing because I always sleep so badly, so little things make the difference”).

- **On practical aspects of the trial**

The participant considered the trial easy to follow. One of the aspects that make it so was the lack of need to remove her clothes: “that was very nice because it’s so exhausting to take off your clothes and put them back again and such things”. Similarly, the fact that the practitioner visited her at her home: “it was great that you were coming to my house”. This was so despite the length and intensity of the trial since as she said she “have time”. On the contrary, she expresses her dislike for the periods without shiatsu (“I didn’t like the breaks”) and her preference to had shiatsu continuously (“I would like to have treatment also all the time”).

- **Comparison with usual care**

The participant thinks that shiatsu complements her usual care nicely by taking care of aspects not addressed during this care. She is satisfied with the amount of the usual care she receives (“I have quite a lot of that usual care, I have 95 times a year so there is much possibilities, much time to do different things”). Moreover, she believes that the fact that her usual care is focused on muscle strengthening is something that she needs (“I need muscles in my legs so that I can stand up”). Inquired about the possibility of covering more aspects in her usual care she responded that this is possible and sometimes she receives massage “but I usually have to ask”.

- **On adverse events**

Inquired about adverse events she reported none, and she continued by mentioning positive effects. While speaking about the spasticity on her legs, she thinks that sometimes it was relieved too much, causing difficulties in standing up and “changing from chair to bed or toilet seat”, “but otherwise... it has been very nice feeling when they are not so spastic”.

- **On expectations**

Confirming her claim at the initial meeting, the participant said that she “didn’t expect anything, actually. I didn’t know about shiatsu anything. I haven’t read about it anything. So, I didn’t actually know what to expect”. She feels “quite astonished” by some effects. She considers that “it helps in some extent, mostly temporally, for the spasticity and also for the constipation and it releases your pain areas”, thus “I would recommend it” as a complement to the usual care that those with MS receive.

4.4. Personal Reflection on the role of the practitioner-researcher

Description – What Happened?

While being the researcher who conceives, plans and implements the study, I was also the practitioner who offer the treatments to the participant.

Feelings – What I was thinking and feeling?

As a therapist, I felt restricted in what I was allowed to do. I was working with an idea of “pure” shiatsu therapy, unconsciously trying to help me as a researcher to get a specific effect as much as possible. Thus I was avoiding speaking too much about peripheral aspects (e.g. nutrition) and proposing the usage of other OM modalities (e.g. cupping, guasha) that I might have used in my regular practice.

As a researcher, even if besides the intensive mode of treatment the development of rapport between the participant and me was limited, I was thinking that this dual role does not let the participant speak freely during the interview, adding a potential bias in it.

Evaluation – What was good and bad about the experience?

A potentially good influence of this experience might be that the participant considers me “professional” in my work. Also, being a volunteer practitioner in my own study removes any concerns regarding the cost of the treatment both for the participant and myself.

The experience made me aware that as a practitioner researcher my relationship with the patient was necessarily different to that between myself solely as practitioner.

Analysis – Can I make a sense of the situation?

Being a researcher-practitioner was a bias factor that was anticipated from the beginning. The fact that this research project was part of an MSc which had no funding another practitioner could not be employed. Yet, the implementation of the research project had highlighted bias factors I had not previously thought of.

Conclusion – What else I could do?

If the aspects highlighted above had become conscious earlier, it might be possible to work for their partial resolution. Further familiarisation with relevant literature might offer clues on a way out of the situation.

Action Plan – What I would do in a similar situation?

I would avoid getting into a similar situation, in which I am the single practitioner and the researcher. That is not easy to avoid since there are not many funding possibilities for this area of investigation. In case of occurrence of a similar situation, the new areas of possible bias should be considered from the planning stage. Perhaps planning from the beginning the investigation for OM as a whole system of healthcare instead of shiatsu as a single modality could liberate me as a practitioner and do better justice to OM and shiatsu as well as to the participant.

4.5. Synthesis of Clinical Results

The clinical results of the study are to be considered based on triangulation of all types of the collected data. As described in the methodology section (§ 3.6), due to the limited data collection points of the specific single-subject design, the statistical test used was the Wilcoxon signed-rank test. Yet, as detailed in appendix 2, the test has no power to reject the null hypothesis. Thus, the raw scores in conjunction with the visual presentation of the scores and the comparison of the baseline to the end scores are used. The quantitative results are here just one indication of the effects, together with what was documented in the case notes by the practitioner and described by the participant in her interview.

Spasticity

The primary symptom that the patient wanted to address at the beginning of the trial was spasticity. This was even if she uses daily medication for it. Spasticity was also the major complain during the first three sessions (period B1) and the three sessions after the four weeks without shiatsu (period B3). Unfortunately, the MSQLI does not include a domain for spasticity. The issue of the missing domain was identified and commented on by the participant twice during the period B2 after spasticity ceased to be the primary complaint and the first MSQLI for a period with shiatsu treatment was completed. Besides, relief from spasticity was one of the effects of the treatment that the patient mentions as very positive during the interview. She considers it as one of the temporary benefits that a PwMS could have from shiatsu and attributes to this relief the improvement in sleep she experienced. However, the relief of the spasticity is also considered to cause

difficulties in changing from one place to another, since she had been used to have very spastic legs that could statically support her weight.

Bowel Function and Bladder Control

Relief from constipation was the second important aspect that the participant mentioned in her interview regarding the effects of the treatment and a reason to recommend shiatsu in PwMS. Similarly, the case records indicate that during the 3rd session of the B1 period that after the 2nd session the participant reported that her chronic constipation gets relieved. This fact was confirmed again by her comments during the 4th and 8th sessions. Besides, the Bowel Control Scale indicates improvement during the shiatsu periods. Looking at the scores over time we see that during the B1 period there was an improvement of more than 23% which continued improving during the B2 period to reach the best possible score. During the A2 and A3 periods, there was a decline with a rhythm of about 8% for each of the periods. The improvement recovers about 8% during the last B3 period.

The scores for the Bladder Control Scale suggests slight improvement during the first two shiatsu periods, yet it should be noted that those were always inside the best 5% of the possible scores. In addition, the patient was on long-term daily medication for bladder issues that seems to work effectively. Thus, the chances for real effect of shiatsu in her case could be considered safely negligible.

Sleep and Relaxation

During the interview at the end of the trial, the participant inquired about essential domains for her life that were addressed by the trial. Improvement of sleep was a major one, attributed by her mostly to the improvement of her spasticity as well as improvements of pain in her lower back. Also, the case notes of the practitioner

indicate that during the treatments the participant falls asleep at least four times. This is connected by the participant with the relaxation she experiences from shiatsu, something different from her usual care that is focused on muscular work.

Fatigue

The issue of fatigue had not been mentioned to the practitioner during the treatment periods or in the interview of the participant. Yet two of the scales of the MSQLI are relevant to fatigue and shows improvement. The Modified Fatigue Impact Scale – 5 Item Version assess the effects of fatigue on physical, cognitive and psychosocial functioning (The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, 1997, pp.3-4). By looking at the scores during time, we see a sharp improvement during the B1 period that continue rising during the B2 period to move from 30% to 85%. During the usual care periods A2 and A3 there is some worsening that stops at 65% at the end of the break, to recover again at 80% at the end of the last B3 period. While the SF-36 subdomain Vitality Scale that intends to measure energy levels and fatigue (Ware et al., 1993, p.3:8), suggest a mostly stable situation. Only during the A3 period there was a slight worsening that recovers in the previous value during the last B3 period.

Pain

The issue of pain was not indicated as a major one by the participant during the intake and no pain medication was used. By looking at the case records of the practitioner, we can see that in the first session some pain in the sacrum was a major complaint together with spasticity. During the three first treatments of the B1 period, some pains occurred during the treatment, on the legs and in the neck area. During the fourth session (last of the B1 period) those pains had already stopped

appearing. Some pain in specific points was indicated again during the seventh and eighth sessions of the B2 period. Yet, the pain was not mentioned in any of the post-treatment inquiries for adverse effects.

The Bodily Pain Scale subdomain of the SF-36 shows an interesting paradox. From the scores of each period and their visual presentation, we see that the periods with shiatsu did worst. This is due to a decrease in the score during the B1 and B2 periods of shiatsu which return to the original levels afterwards and remains until the end of the trial. On the contrary, the participant in her interview indicates that the treatment offer relief from local pains and this is one of the aspects that she would say to a PwMS to recommend shiatsu. The MOS Pain Effects Scale assess the degree to which pains affect mood, ambulation, sleep, work, recreation and enjoyment (The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, 1997, p.4). The scores from the beginning are very close to the best possible score. There is a slight improvement during the B2 period followed by worsening and improvement during the A2 and A3 period, to remain in the improved level during the last B3 period. It worth to mention that the Bodily Pain Scale follows a different time-trend, implying the idea that the pain caught in it does not correlate with effects assessed by the MOS Pain Effects Scale.

Mental and Cognitive Issues

During the intake the participant mention waking up with unexplained bad feeling as well as that she finds it difficult to express herself with words. In MSQLI, the Role Emotional Scale of the SF-36 which is mostly relevant to psychiatric conditions (Ware et al., 1993, p.3:7) gets the highest possible score during the whole study period. The Mental Components Summary Scale, offering a standardised

distribution-based interpretations gained from US population with mean set to 50 and standard deviation 10 (Jenkinson, 1998; The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, 1997, pp.22-23) where scores above 50 indicate better health than the mean of the general population and below 50 indicate worst health (Jenkinson, 1998), seems to have remained almost stable during the whole period of the trial (57.7-59.9). While the Mental Health Scale (as well as the Mental Health Inventory – 5 Item Version which is derived from it) which covers four mental health dimensions (anxiety, depression, loss of control and psychological well-being) (Ware et al., 1993, p.3:9) suggest complex interactions. During the B1 and B2 periods, there is a slight improvement that remains stable for the A2 period and increases slightly during the A3 period to return to the level of B2 at the last B3 period. Comparing the before and after trial scores, there is a slight improvement. In the Perceived Deficits Questionnaire which covers cognitive aspects such as attention, retrospective and prospective memory, planning and organisation (The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, 1997, pp.5-6), we see that during the B1 and B2 periods with shiatsu, there is an improvement that continues during the A2 period and remains stable till the end of the trial. Besides, in the interview an overall enthusiasm for the treatments was expressed, while at the last 12th session worries regarding the end of the trial were expressed. Finally, the Sexual Satisfaction Scale which addresses the degree of satisfaction with aspects of sexual life, both for the patient and her partner (The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, 1997, pp.4-5) suggests stability, with no other indications for this domain in any of the other data sources.

Functioning and Roles

During the intake the participant said that she feels her retirement is a gift. The Social Functioning Scale which indicates whether the social activities of the patients have been affected by their health problems (Ware et al., 1993, p.3:9) remained unaffected during the whole trial period. On the contrary, the Role-Physical Scale that refers to role limitations (problems with daily activities) due to physical health (Ware et al., 1993, p.3:7) shows sharp improvement during the 3rd block. From the worst possible score during the baseline and the first period of shiatsu, it rises to the middle of the scale after the second period of shiatsu and remains stable for the four weeks without treatment to rise again in the three-quarters of the scale after the new introduction of shiatsu during the 6th block.

The Physical Functioning Scale assesses the levels and kinds of physical limitations (like lifting and carrying groceries, climbing stairs, bending, kneeling and walking moderate distances as well as self-care activities). Considering most physical limitations as chronic, it estimates the severity of each limitation without considering its duration (Ware et al., 1993, p.3:4-6). The score remained at a very low level. A minimal fluctuation occurs during the 3rd block of the trial, that subsides to the original level in the 4th block and does not recover.

Social Support

In the intake the participant expressed her satisfaction with the amount of care she regularly receives, even if in the interview she indicates that with shiatsu areas not usually addressed in her usual care were covered. The MOS Modified Social Support Survey – 5 Item Version which is relevant to emotional, informational, tangible and affectional support as well as with positive social interaction (The

Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, 1997, pp.6-7) suggests some worsening during the B1 period that tends to remain until the end of the trial.

General Health and Expectations

During the intake the general health situation of the participant was described as very compromised, while she expressed her disbelief that the treatments could help her. The interview after the end of the trial indicates that her expectations were changed and she could expect to get temporary improvements by shiatsu and she believed that shiatsu complements her usual care nicely by addressing otherwise ignored aspects. The areas discussed above shows that indeed there were improvements in some domains of her quality of life. From the rest of the MSQLI domains we can see that the Health Transition Item that aims to get information regarding changes in health status during the year before the administration of the SF-36 (Ware et al., 1993, p.3:10) remained mostly stable. The General Health Scale which evaluates with self-perceived questions the current health situation, resistance to illness and health outlook (Ware et al., 1993, p.3:8), shows a slight worsening during the B1 and B2 periods, which take a positive direction during the A2 and A3 periods, to recover to its original score after the B3 period, at the end of the trial. The Physical Components Summary Scale (which is similar to the Mental one described earlier) shows a slight worsening during the B1 period to get slightly better during the B2 period. Then remained almost stable for the two break periods (A2-A3) and slightly improve during the last B3 period. Finally, the Impact of Visual Impairment Scale which is related to difficulties with simple visual recognition tasks that cannot be corrected by visual aids (The Consortium of Multiple Sclerosis

Centers Health Services Research Subcommittee, 1997, p.5) remained stable during the duration of the trial, getting the best possible score.

Adverse Events

The participant was asked about possible adverse events in every session. No adverse events were reported. In the interview she indicates that shiatsu treatment was more careful in addressing some of her issues (local pains). Speaking of her main issue (spasticity) she indicates the problem that occurred by improving it (difficulty in standing up from chair to bed or toilet). When asked in the interview if she identified this as an adverse event she showed some confusion and declared no further adverse events.

Summary of Clinical Results

Jaeschke, Singer and Guyatt (1989) define Minimal Clinically Important Difference (MCID) as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management”. Summarising the previously synthesised clinical findings of the trial, it can be suggested that the specific PwMS may have experience MCID in some domains of her QoL and symptomatology. Those are:

- 1) Spasticity
- 2) Bowel function
- 3) Sleep and Relaxation
- 4) Fatigue
- 5) Pain.

No clear adverse events occurred.

Chapter 5: Discussion

5.1. Spasticity, Quality of Life and Ambulation

Spasticity is a prevalent symptom that PwMS need to manage (Gelber and Jozefczyk, 1999). It has a negative influence on their QoL (Zwibel, 2009) and daily activities (Bethoux and Marrie, 2016). It can have an impact in many areas, including fatigue, depression, anxiety, pain, bladder function (Milinis, Tennant and Young, 2016), bowel function and sleep (Pozzilli, 2014). It is recognised that spasticity in MS cause substantial costs both regarding HRQoL and economically (Stevenson et al., 2015; Svensson, Borg and Nilsson, 2014). Even so, spasticity is generally undertreated, since its pharmacological management is not so efficient (Berger, 2013). There are also non-pharmacological options for the management of spasticity in MS, with acupuncture and other CAM playing a possibly positive role, besides the lack of adequate evidence (Hughes and Howard, 2013).

In the case of the participant, spasticity could be considered undertreated, despite the use of pharmacological agents and physical therapy. The improvement of spasticity as reported by the participant, occurred after three shiatsu treatments during two weeks, got worse after about four weeks without shiatsu and improved again after three more shiatsu treatments during the two-week period at the end of the trial. In addition, the issues of fatigue, sleep problems, bowel function and possible mental issues that the literature suggests to be impacted by spasticity, were influenced by the treatment. The participant herself attribute the sleep improvement in the relief from leg spasticity.

Yet a small paradox accompanied the improvement. Even if spasticity was the primary symptom that the participant wanted to address, the observed improvement seems to cause ambulation-related difficulties too. The participant had been used to have very spastic legs that could statically support her weight during movement from the wheelchair to the toilet seat or the bed. The improvement of the muscles of her legs seems to be addressed with priority during her usual physical therapy, so that she has the possibility to stand-up. Leg spasticity is associated with impaired ambulation (Balantrapu et al., 2014) and the participant is essentially restricted to a wheelchair. Thus possible future treatment for her spasticity should consider in a comprehensive way the sustainability of her basic ambulation.

5.2. Sleeping

The participant during her interview commented on the improvement of her sleep, attributing it mostly in the improvement of the spasticity and her lower back pain. Sleep disturbances in MS remains mostly undiagnosed (Brass, Li and Auerbach, 2014) even if they affect approximately 60% of the PwMS (Sakkas et al., 2019) and can live their marks in the routine MS neuroimaging (Foschi et al., 2019). Problems with sleep had been associated with fatigue in PwMS (Veauthier and Paul, 2014; Kaminska et al., 2011; Stanton, Barnes and Silber, 2006) and in general population (Stanton, Barnes and Silber, 2006), while diagnosed sleep disorder may be associated with poor HRQoL in PwMS (White, Sullivan and Drerup, 2019). The results of the treatment on sleep supports previous evidence of a possible effect of shiatsu in sleep disturbances by improving sleep quality (Qin

et al., 2019; Yuan, Berssaneti and Marques, 2013) or reduced time to fall asleep and longer sleep time (Brown et al., 2014).

5.3. Was Pain an Adverse Event?

Even if pain was not a major complain for the participant and she considered shiatsu offering relief from local pains so that she would recommend it to PwMS, the scores of the questionnaires and the case notes shows a complex picture. In the Bodily Pain Scale the scores shows a slight worsening during shiatsu periods. The case notes indicate that some temporary pains occurred during the treatment, but those were not mentioned in the post-treatment inquires for adverse effects. Also, the MOS Pain Effects Scale suggests that the pain captured from the Bodily Pain Scale did not lead to effects in the domains it assesses. Considering all the sources of data, it is suggested that the temporary pain occurrences during treatment as well as the temporary worsening in the Bodily Pain Scale was a form of theory and experientially consistent “transitional effect” (type-3), according to the typology of negative responses for shiatsu developed by Long, Esmonde and Connolly (2009).

5.4. Perceptions

After the beginning of the shiatsu treatments the perception of the participant regarding her health and social support begin to show signs of worsening. That is documented with slight worsening in the scores of the General Health Scale and the MOS Modified Social Support Survey – 5 Item Version. Perceptions of health status and HRQoL of PwMS have been found to differ significantly between the PwMS themselves and those of their neurologists (Ysrraelit et al., 2018; Kremenutzky and Walt, 2013). Physical activity correlate with a better health

status perception (Stuifbergen, 1997) while levels of social support, which includes any the supportive input received from the social environment and can include almost any type of social interaction (Helgeson, 2003), are positively associated with perceived health status in PwMS (Krokavcova et al., 2008). Considering the interview with the participant, where she commented that shiatsu complements her usual care nicely by addressing usually ignored aspects, it is possible to speculate that the worsening documented in the relevant scales is related to realisations occurred due to the effects of shiatsu. This finding could be attributed to the comparison with the usual care together with the expressed worries about not being able to continue the treatment after the end of the trial. Those are elements that might have downgraded her perception about her general health condition as well as her perception of the support she usually receives.

5.5. Statistical Analysis?

The first methodological issue that occurred during the trial was the difficulty with statistical testing. Due to ethical concerns related to the possible burden to a patient that is considered vulnerable, the minimum points of data collection were included in the study plan. This limits the possible approaches that statistical analysis could take, in the form of rank testing with zero power to reject the null hypothesis. Thus the statistical testing was used only for educational purposes while the raw scores were another factor to be triangulated with the data from the semi-structured interview and the case records.

The issue of the appropriate statistical analysis of single-subject trials is not new. Most of the published reports of n-of-1 trials use only visual comparisons, and of those reporting statistical analysis most use simple statistical tests such as t-test

(Gabler et al., 2011). When the minimum required (three per period) data points are collected (Sunderland, 1990), visual inspection of data for changes of level (the average performance of a period), trend (direction of change during a period), and variability (scale of change during a period) is straightforward for substantial and fast changes. As Byiers, Reichle and Symons (2012) argue, in the clinic, the practitioners are interested in large effects, something that visual inspections alone can provide. Unfortunately, in the present study, there were not enough points of data collection to allow a useful visual analysis.

In addition to the visual presentation, a statistical analysis, as advocated by the authors of the Design and Implementation of N-of-1 Trials: A User's Guide (Kravitz et al., 2014; Schmid, Duan and The DEClIDE Methods Center N-of-1 Guidance Panel, 2014) was attempted. The proposed in the Detailed Research Proposal (Tsiormpatzis, 2017) statistical analysis follows Chen and Chen (2014) suggestion for the simpler possible paired t-test or equivalent as most appropriate for n-of-1 trials. Yet, the limited points of data collection did not provide enough data to permit such tests. Experimenting with an easy way to provide a basic statistical interpretation by using the Wilcoxon signed-rank test was not of much help either, even if the statistics were possible to calculate. The test with so few data points has zero power to reject the null hypothesis. While contextually, as Van Ness, Murphy and Ali (2017) note, the clinical meaning of a rank test is debatable.

This ineffective statistical experience suggests that the opinion of Ernst (1998) who claims that complex statistical approaches are required, is more realistic. He also suggests that 20 or more treatment periods might be necessary to minimise type I and II errors. Practical reasons make this demand extremely difficult to apply in the context of shiatsu studies. Usage of daily diaries might help with this difficulty.

Moreover, Sunderland (1990) had proposed that more than ten points of data collection per period are required for statistical analysis with time-series analysis as the most appropriate way. The experience of this trial supports the general idea that the more observations, the better.

Above all, it should not be ignored that any statistical inferences of this study could refer only to what occurred during the specific trial with the specific PwMS. It is not possible to gain any valid inferences for other persons and situations. This is the limit even when the most appropriate statistical analysis for single-subject trials is used. The purpose of applied research should be to discover inferences with clinical meaning, not just statistical significance (Byiers, Reichle and Symons, 2012). Generalisation could come only in a clinical context, relying on the common scientific rationale that “similar” outcomes should occur in “similar” situations in the future (Edgington, 1996).

5.6. How Much is Enough? The “Half-Life” of Shiatsu

The second issue has to do with the quantity, frequency and length of the study. In this trial, a minimal approach was taken with six biweekly periods of twelve treatments in total. While some change in the HRQoL was documented, the potential of the methodology to clarify the “half-life” or “wash-out” period of shiatsu could be further exploited in a more protracted trial.

Only some of the PROM-assessed domains provides interesting clues towards this aim. The results of the Role-Physical scale suggest that two consecutive treatment periods (four weeks) were necessary to document improvement that persists for two control periods (four weeks) and continue improving during the last treatment period (two weeks). Similar trends show the results of the Bowel Control Scale and

the Modified Fatigue Impact Scale – 5 Item version, with improvement occurring after a treatment period (two weeks) to maximise after the second consecutive treatment period (four weeks). Then a partial reversal of the improvement occurs during the following two control periods (four weeks) to improve again after the re-introduction of the last treatment period (two weeks).

Also, the improvement in spasticity as documented outside PROM, suggests that one period of treatment (two weeks) was enough to bring some improvement that subsides during the two control periods (four weeks) and improve again after a treatment period (two weeks).

Summarising those preliminary results, it can be suggested that four weeks of shiatsu treatment (eight treatments) are enough to provide evidence of effect in some domains. However, four weeks of wash-out period are not enough to show a full reversal of the effect. In addition, when the partial reversal occurs, the re-occurrence of improvement demands shorter treatment periods. Unfortunately, the weak statistical analysis does not permit more specific suggestions for the “half-life” of shiatsu.

It should also be noted that in this study, for logistical reasons, there was no follow-up period. Informal contact of the author with the participant four months after the conclusion of the trial reveals that the effect had already reversed during that time. The suggestion someone could get from this is in agreement with existing guidelines on the field of Chinese and integrative medicine regarding the usefulness of sufficient follow-up time (Liu, Chen and The Guideline Development Team, 2015).

Shiatsu in Europe is usually offered in weekly sessions, either for short periods of a few treatments or as a long-term treatment that can continue for months or years. Yet, similar to concerns expressed about physical therapy (Riddoch and Lennon, 1994), it is not known what type of treatment and for how long it should be offered to optimise the results. To the knowledge of the practitioner, the amount of physical therapy offered to PwMS in Finland depends on the disability level and the needs of each patient. This can vary during the years and according to the results, with weekly or biweekly physical therapy sessions available. In a recent RCT pilot study by Lanza et al. (2018) for shiatsu as adjuvant therapy for depression in patients with Alzheimer's disease, shiatsu was offered once per week for ten consecutive months. Also, in the Chinese context, modalities similar to shiatsu such as tuina, are often offered daily, similarly to acupuncture (Ilic et al., 2012; Ming and Xiaoyan, 2008). While such treatment schedules might seem strange in Europe, the author of the study has positive clinical experience in offering daily shiatsu treatment for periods of two months with PwMS. Such an intensive mode of treatment, even for shorter period, have been used earlier in the research context of acupuncture n-of-1 trials (Jackson, MacPherson and Hahn, 2006). In regard to shiatsu and considering the chronic nature of MS, an intensive and long-term treatment perspective seems more appropriate.

In addition, even if the specific participant is considered a vulnerable patient, she travels twice weekly to receive physiotherapy. She expresses no difficulties in following a schedule of two concurrent shiatsu treatments per week, which she found very relaxing and pleasant. In her case, thoughts for a more intensive treatment schedule could be feasible. It worth noting that there is conflicting

evidence regarding the preferences of patients for longer or shorter length of n-of-1 trials (Moise et al., 2018; Kravitz et al., 2009).

5.7. What and How to Measure

Another methodological issue is related to the measuring of the effect of the treatment. As indicated already earlier, the chosen PROM even if widely used in HRQoL research for PwMS have some weaknesses. It requires further longitudinal testing to determine sensitivity to detect change in MS patients since it is not tested for change over time. Also, in the SF36 domain, the summary scores are standardised for the US population. Moreover, while it covers a broad spectrum of HRQoL areas it does not cover essential domains for the specific patient.

Those issues could be considered integral parts of the concept of outcome and QoL measures as used in individualised trials of complex treatments since the underpinnings of outcomes are usually population-based and appropriate for pharmaceutical trials but not so for complex interventions (Paterson et al., 2009; Carr and Higginson, 2001). This pilot strongly supports the need for richer methods to measure the effect of the treatment. Without various data sources, the interpretations of the PROM would be challenging and important aspects could be lost. The mixing of data such as the case records and the interview with the scores of the PROM was able to provide some conclusions, yet it is not known how better those could be if the design were able to accommodate powerful statistical analysis and more relevant PROM. More qualitative and patient-specific measures could be used to offer more relevant and potentially more robust conclusions. Such could be the earlier discussed (O'Boyle, 1994) SEIQoL or the MYMOP (Paterson, 1996).

5.8. Shared Decision Making

A way to deal with the massive demand for long-term data that occurred from the discussion of this study could be to include a shared decision making (Barry and Edgman-Levitan, 2012) aspect in the design of the trial. The involvement of patients in the making of the clinical decisions is central to patient-centred clinical care even if the healthcare professionals struggle to implement such a framework in practice (Meneer et al., 2018; Topp et al., 2018). Besides its clinical relevance, the shared decision making concept could also be applied in a research setting (Poureslami et al., 2018).

Shared decision making could take different forms to satisfy the needs that occur from this study. Adaptive design has been proposed as a way around some of these issues (Mirza et al., 2017; Duan, Kravitz and Schmid, 2013; Byiers, Reichle and Symons, 2012; Sunderland, 1990). In an adaptive design, the protocol of the trial includes flexibility so that aspects of the trial will be defined after the recruitment of the participant and with their active involvement. Thus, considering this study, it could be possible to define a way to better monitor the issue of spasticity that was the chief complaint of the participant. Similarly, it could be possible after a detailed baseline period to define together with the participant in a more useful way the meaning of the variations that might occur in different domains. In addition, instead of fixed treatment periods, it could be agreed that the length of each period could be modified following the observed variation and trend of the scores or just by the preference of the participant. The same could apply to the number of treatments per period and the repetitions, thus the total length of the trial. Those ideas have been already applied in a pragmatic context of n-of-1 trials under the name of Single Patient Open Trials (Mirza et al., 2017; Smith, Yelland and Del Mar, 2015).

5.9. The Practitioner as a Researcher

Issues related to the role of the practitioner as researcher revealed during the structured reflection. The bias introduced by the role of the researcher during the interview is a topic that has been discussed earlier in the literature. As Broom (2005) mentions while discussing the use of qualitative interviews in CAM research, the position of the researcher is unavoidably influencing the research from its conception. In addition, as Pirie (2003) recognises in her PhD thesis on delivering shiatsu in general practice, the effect of this dual role in the honesty of the participant responses was a concern. She believes that including external interviewer would not remedy the situation since the participant would know that she (the practitioner-researcher) will analyse the data thus favourable feedback would be more expected. However, since the aim of her study was not to evaluate the effectiveness of shiatsu, she considers the issue addressable by acknowledging and reflecting on it. Moreover, she notices the fact that a researcher is also the practitioner inevitably means that the researcher has a positive attitude for the tested modality, shiatsu. Yet Lewith (2004) had argued that this applies to all kind of health practitioners and is not necessarily something negative since this “belief system” of health professions are in fact integral to the clinical practice. Even more, Wardle (2016) suggests that engaging practitioners in CAM research is essential to improve the validity and ensure that the therapies are evaluated as they are used in practice. To that aim, Andrade and Portella (2018) encourage the inclusion of EBM and critical research reading courses in the curriculum of CAM schools, so that practitioners are better prepared to participate in research projects.

Besides, this study highlights a possible drawback of that approach. Due to this dual role, the practitioner was self-restricted to the applied methods during the clinical treatment. This was beside the fact that the approved study protocol poses no restrictions for the practice and he could include any appropriate aspect of shiatsu. Yet, even if the literature indicates that lifestyle consultation and nutritional advice could be parts of shiatsu practice (Pirie, Fox and Mathers, 2012; Long and Connolly, 2008) the practitioner-researcher still sought to avoid them during the trial. Instead, he altered his real-life clinical practice and remained close to the more technical definitions of shiatsu provided in the introduction (§1.1.2.). He similarly avoids usage of other OM modalities like cupping, even if they are often integrated into a shiatsu session (Chirali, 2014). Even if this issue is considered as “unconscious”, it might be explainable by his engagement with the designing of the trial, that made him more aware of possible issues. In more concrete terms, since lifestyle changes are not easy to “switch off”, treatments that include lifestyle changes are ruled out from candidates of n-of-1 trials evaluation (Hart and Sutton, 2003). Moreover, due to his contact with the shiatsu practitioners’ community in Finland, the practitioner knew that other OM modalities are rarely part of the shiatsu offered in the country.

5.10. Shiatsu in the Specific Context

In the context of the trial, the treatment offered was very close to the real-life practice of the specific practitioner, besides the issues highlighted in the reflection of the practitioner and the previous part of the discussion. Yet this does not mean that the shiatsu practised by the specific practitioner is representative of shiatsu in general (Beresford-Cooke, 2011b).

A general feature of the shiatsu offered in the trial that deviates from the norm in Europe is the fact that it was offered in a bed. While originally shiatsu was offered on a futon on the floor, modern Japanese practitioners found more comfortable and safe for the practitioner to work in a massage table or bed (Adams, 2002). This way of work has also been introduced in the US (Dubitsky, 1997) but it has not flourished in Europe. For this study to work on a bed was proposed by the participant due to her difficulties with movement. This is a promising way to work for patients with disabilities, restricted to bed or wheelchair. Moreover, working at a table, bed or chair could make shiatsu more easily to offer in a hospital or healthcare-centre setting, as a recent service evaluation of a UK cancer centre where shiatsu as well a range of CAM were available shows (Browne, Bush and Cabo, 2018). Even if many practitioners might not have training and experience of working on a table, it should be their responsibility to adjust their practice in a way possible to accommodate the needs of the receiver. Shiatsu schools from their side should offer training to promote safe and effective ways to adjust a shiatsu session for table, bed or chair.

Shiatsu in Finland is not developed professionally (Tsiormpatzis, 2019; Shiatsu Finland ry, 2016). There are no training standards established in the country, and there are practitioners with as little as one hundred hours of total training. Thus, shiatsu is neither recognised as part of healthcare or health profession nor covered by health insurance or patient insurance. This situation is challenging both from practice and research perspective. For this study, the researcher-practitioner had been trained in Greece and UK in a level that allows him to have patient insured practice. While even if shiatsu is not recognised as part of healthcare and health profession, the regional ethics committee considers this project as medical

research. Thus, several challenges for shiatsu should be addressed before further research in the country could be considered.

Moreover, the described situation of shiatsu in the country raises possible ethical concerns too. Even if the study shows MCID, as shiatsu seems to help the specific patient, currently there is no way it could be integrated into her care and management plan. No social structure could support her in receiving shiatsu and there were no practitioners that the researcher could suggest to her. It should be considered that all costs of the trial were covered out-of-pocket by the practitioner-researcher who volunteered the shiatsu treatments and the considerable transport costs related to the treatments and the necessities of the study.

This is very concerning since the participant herself expresses her dislike of the periods that she did not receive shiatsu and she was concerned about how she could continue after the end of the trial. In contrast with the current status in the country, she considers that shiatsu could complement her usual care nicely. It can be noted that the yearly cost of severe MS in Finland reaches 110.000 euros per PwMS, a cost that is “essentially due to the high requirement of professional services and informal care in the advanced disease stage” (Ruutiainen et al., 2016). Moreover, most patients would welcome a personalised trial if it can limit their out-of-pocket costs (Moise et al., 2018).

5.11. Implications for Practice, Training and Policy

The results of this study are not generalisable but refer to the specific participant in the specific setting. Yet some indicative implications exist both for practice, training and policy. For shiatsu in practice, it can be suggested that a denser treatment schedule, compared to the commonly used once-weekly treatment,

might be more effective in chronic and severe conditions. The practitioners should be ready to adjust their treatment in various settings and work in bed, table or chair. Shiatsu schools should prepare the future practitioners for work as healthcare providers in various setting and assist current practitioners to this adjustment. Also, EBM and research skills courses should be included in their curriculums. Professional shiatsu associations should ensure that it is possible for patients to reach professionally competent practitioners. The policy-makers should consider how shiatsu as a method that is not currently considered healthcare could be integrated into the healthcare and management plan of severely diseased chronic patients when found of being of help.

5.12. Limitations of the study

The discussion above had highlighted some of the limitations of this study. The study includes very few data collection points, making any statistical analysis difficult and of limited use. The length of the periods was not long enough to permit a full appreciation of the speed of effect and wash-out of shiatsu. No follow-up evaluation was included. The included instrument was not personalised enough and missed important, for this specific participant, domains, such as spasticity and sleep. The dual researcher-practitioner role unexpectedly downgraded the WSR approach and inserted potential bias in the interview. The interview and the clinical interaction between the participant and the practitioner-researcher were not optimal since they communicated mostly in English, which is a second language for both of them.

Chapter 6: Conclusion

To the knowledge of the author, this is the first study to investigate if shiatsu affects the HRQoL of a person with SPMS, by implementing a mixed methods n-of-1 trial within a whole systems research case study.

Besides its drawbacks, the study succeeds to show that in the specific setting with the specific severely diseased patient who already receives physical therapy according to her needs, shiatsu was able to improve the HRQoL of a person with SPMS influencing spasticity, bowel function, sleep and relaxation, fatigue and pain. Shiatsu was a safe treatment, and no adverse events occurred.

In addition, to the knowledge of the author, this is the first study that attempted and partially succeed to exploit the advantages of the employed design in order to systematically determine the speed of shiatsu's effect onset and wash-out. it's the conclusions from this study with one participant could be considered as a base for future investigations that will exploit this potential of similar n-of-1 designs to determine in a robust way frames for those parameters. Thus, four weeks of biweekly shiatsu treatment could be considered a minimum "dose" to provide evidence of effect in some domains of HRQoL While four weeks of wash-out period can show partial reversal but are not enough to show a full reversal of the effect.

Methodologically, the study shows that n-of-1 trials that combine multiple sources of data in a mixed method approach could be used in order to investigate the effects of bodywork in the context of CAM interventions for chronically diseased patients, even if this is not without impediments. It is suggested that an improved version of such a design that will consider the findings of this study could be

promising as part of a research program to investigate CAM bodywork systems of care (such as shiatsu) of chronic conditions (such as progressive MS).

6.1. Suggestions for Future Studies

A research program consisting primarily of multiple studies following the fundamental design principles of this study is suggested to evaluate the effect of shiatsu as a personalised treatment for PwMS. More flexible and rich design is needed, with an adaptive and shared decision-making approach. The minimum length of the periods should be four weeks with two treatments offered weekly, with at least the minimally optimal counterbalanced design of six periods or randomised design. The minimum amount of data collection points per period should permit a useful visual and robust statistical analysis. Follow-up evaluations are recommended. Personalised instruments and diaries are preferable, and a qualitative interview in the beginning is warranted to ensure relevance of the monitored domains. Ideally, more practitioners specialised in this population should be included, after receiving relevant basic research skills training. The design, analysis and reporting of the trials, as well as the interviews at the end of the trial, should be made and analysed by researchers who ideally are not members of the practitioner's team yet being practitioners themselves. The same research program could aim concurrently to determine the onset and wash-out of shiatsu effect. A cost-effectiveness aspect would be useful to be included in such a research program.

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Appendix 1. GDRP Data Processing Diary

1. Date	2. Data being processed	3. Data source	4. Processing activity	5. Sharing	6. Storage, anonymization and back-up
12/09/2017 to 20/09/2017	1. Email addresses 2. Health data concerning eligibility status	Potential participants	1. Screening for inclusion according to eligibility criteria 2. Sending PIS and Consent Form to eligible participants	Not shared	All data collected was anonymised and securely stored and backed up to private NAS as described in DRP.
20/09/2017	Informed Consent	Participant	Signed consent form received as paper copy	Not shared	Signed form scanned and securely stored and backed up to private NAS as described in DRP. Paper copy stored in a locked closet at the private office of the researcher where he has exclusive access.
20/09/2017	Detailed health history	Participant and Researcher	Keeping intake notes during initial meeting	Not shared	Intake notes was anonymised, scanned and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics Application.
22/10/2017	MSQLI	Participant	Completed MSQLI received as paper copy	Not shared	Completed and anonymised MSQLI digitised and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics Application.
06/11/2017	MSQLI	Participant	Completed MSQLI received as paper copy	Not shared	Completed and anonymised MSQLI digitised and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics Application.

1. Date	2. Data being processed	3. Data source	4. Processing activity	5. Sharing	6. Storage, anonymization and back-up
06/11/2017 to 12/11/2017	Case records	Participant and Researcher	Keeping case notes after each treatment session	Not shared	Case notes was anonymised, scanned and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
13/11/2017 to 19/11/2017	Case records	Participant and Researcher	Keeping case notes after each treatment session	Not shared	Case notes was anonymised, scanned and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
20/11/2017	MSQLI	Participant	Completed MSQLI received as paper copy	Not shared	Completed and anonymised MSQLI digitised and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
20/11/2017 to 26/11/2017	Case records	Participant and Researcher	Keeping case notes after each treatment session	Not shared	Case notes was anonymised, scanned and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
27/11/2017 to 03/12/2017	Case records	Participant and Researcher	Keeping case notes after each treatment session	Not shared	Case notes was anonymised, scanned and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
03/12/2017	MSQLI	Participant	Completed MSQLI received as paper copy	Not shared	Completed and anonymised MSQLI digitised and securely stored and backed up to private NAS as described in DRP. Paper copy was destroyed as per DRP and NCA's Ethics.

1. Date	2. Data being processed	3. Data source	4. Processing activity	5. Sharing	6. Storage, anonymization and back-up
17/12/2017	MSQLI	Participant	Completed MSQLI received as paper copy	Not shared	Completed and anonymised MSQLI digitised and securely stored and backed up to private NAS as per DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
02/01/2018	MSQLI	Participant	Completed MSQLI received as paper copy	Not shared	Completed and anonymised MSQLI digitised and securely stored and backed up to private NAS as per DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
02/01/2018 to 07/01/2018	Case records	Participant and Researcher	Keeping case notes after each treatment session	Not shared	Case notes was anonymised, scanned and securely stored and backed up to private NAS as per DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
08/01/2018 to 14/01/2018	Case records	Participant and Researcher	Keeping case notes after each treatment session	Not shared	Case notes was anonymised, scanned and securely stored and backed up to private NAS as per DRP. Paper copy was destroyed as per DRP and NCA's Ethics.
15/01/2018	MSQLI	Participant	Completed MSQLI received as paper copy	Not shared	Completed and anonymised MSQLI digitised and securely stored and backed up to private NAS as per DRP. Paper copy was destroyed as per DRP and NCA's Ethics.

1. Date	2. Data being processed	3. Data source	4. Processing activity	5. Sharing	6. Storage, anonymization and back-up
15/01/2018	Interview recording consent	Participant	Signed consent form received as paper copy	Not shared	Signed form scanned and securely stored and backed up to private NAS as per DRP. Paper copy stored in a locked closet at the private office of the researcher where he has exclusive access.
15/01/2018	Semi-structured interview	Participant and Researcher	Digital audio recording of semi-structured interview as per DRP	Not shared	The recorded files were transferred and securely stored and backed up to private NAS as described in DRP. The digital recorder was irreversibly erased as per DRP.
15/01/2018 to 30/01/2018	Semi-structured interview recording	Researcher	Verbatim transcript of the recorded interview	Not shared	The verbatim transcript was securely stored and backed up to private NAS as per DRP.
30/01/2018	Verbatim transcript of the recorded interview	Researcher	Accuracy check by the participant	Not shared	The verbatim transcript was securely stored and backed up to private NAS as per DRP.
01/02/2018 to 02/06/2018	Detailed Health History, Case Records, MSQI, Interview Transcript	Researcher	Analysis and synthesis of the data - Writing of Dissertation	Not shared	Multiple versions of the dissertation were securely stored and backed up to private NAS as per DRP.
24/05/2018	MSQI	Researcher	Upload to Data Repository	Not shared	Data Repository of NCA
02/06/2018	Case records and interview transcript	Researcher	Inclusion in the dissertation as appendixes	Not shared	Dissertation with appendixes were securely stored and backed up to private NAS as per DRP.
02/06/2018	Dissertation Full Draft	Researcher	Submission for feedback	With the study personnel	Dissertation full draft was securely stored and backed up to private NAS as per DRP.

Appendix 2. Description of Statistical Analysis

1) Transform data scale.

For easier processing and interpretation, the data values were transformed in a directional scale 0-100 using the Percent of Maximum Possible (POMP) formula (Moeller, 2015; Cohen et al., 1999):

$$f(z) = 100 \times \frac{z - \min}{\max - \min}$$

where z the original score value, $f(z)$ the transformed value, \min and \max the original minimum and maximum score values in the instrument. Thus all scores are transformed in a [0,100] scale with zero indicating the worst possible score and 100 the best possible.

2) State the Null and Research Hypotheses.

The Null hypothesis of the study was that the periods including shiatsu treatment (block B) had no significant effect on the outcome variables (HRQoL of a person with SPMS).

The Research hypothesis of the study as planned was that the periods including shiatsu treatment (block B) had a significant positive effect on the outcome variables (HRQoL of a person with SPMS). Thus the test should be one-sided. Yet, during a preliminary analysis this directionality was not always present. Thus, the Research Hypothesis had to be modified as: “the periods including shiatsu treatment (block B) had a significant effect on the outcome variables (HRQoL of a person with SPMS).” and the test should be two-sided.

3) Calculation of the Wilcoxon Signed-rank test (Wilcoxon, 1945, 1950)

- a) Find the difference between each pair of scores.
- b) Rank the differences, ignoring any “0-differences” and ignoring the sign of the difference. N is the number of differences, excluding the “0-differences”. Give the lowest rank to the smallest difference, ignoring whether it is a positive or negative difference. In case of tied scores, get the average rank.
- c) Add together the ranks belonging to scores with a positive sign ($W+$).
- d) Add together the ranks belonging to scores with a negative sign ($W-$).
- e) The W statistic is the smallest between $W+$ and $W-$

4) Interpretation of the W statistic

Usually tables of critical values are used for the number of differences (N). In that cases, the W statistic is significant if it is less than or equal to the critical value. There are no tables of critical values for the Wilcoxon signed rank test with N smaller than 5 since with such small samples there are no possible values of W that would be significant (McCornack, 1965; Sen and Krishnaiah, 1984).

With such small N as in our data ($N \leq 3$) by simple enumerations we can calculate exact frequencies of the sum of the positive ranks and the sum of the negative ranks for $N \leq 3$, that provide us with a picture of the exact distribution of the Wilcoxon signed-rank statistic for such small samples (Bellera, Julien and Hanley, 2010). Thus for $N=3$ (when no “0-differences” are present) the possible combinations are $2^3=8$, for $N=2$ (when one “0-difference” is present) the possible combinations are $2^2=4$ and for $N=1$ (when two “0-differences” are present) there are only $2^1=2$ combinations. The probabilities under the null hypothesis to get any of the combinations for $N=1$ are $P=1/2=0,5$. The probabilities under the null hypothesis to

get any of the combinations for $N=2$ are $P=1/4=0,25$. The probabilities under the null hypothesis to get any of the combinations for $N=3$ are $P=1/8=0,125$ except for the most “extreme” cases of $W+=3$ or $W-=3$ (1+2 or 3) where the probabilities are $P=2/8=1/4=0,25$. Considering all the above, we can see that for $N\leq 3$ there is no W value that for the Wilcoxon signed-rank test could give a P value (calculated probability, defined as “the probability of finding the observed, or more extreme, results when the null hypothesis H_0 of a study question is true” (Buchan, 2000)) $P\leq 0,125$. Thus we can conclude that with the given data the Wilcoxon signed-rank test is not possible to answer our hypothesis, yet the calculation of the W statistic is provided here for educational purposes.

Appendix 3. Description of Treatments – Case Records

Period B1

1st session (6/11/17)

Complains: Spasticity, pain in the sacrum

Main Treatment: In the prone position (inquired): Leg Tai Yang Bladder, HuaTuoJiaJi points, Du Mai, sacrum, scapulas, stretching, mobilisations, palming, three fingers, thumb pressure.

In the supine position (turned with practitioners help): neck, head, legs mobilisation, GB20 static pressure.

Feeling / Comments: Some pain in the legs, pain in the head/neck.

Inquired Adverse Effects: None, everything fine

Practitioner Observations: Noisy room. Very stiff muscles, extremely spastic legs especially in the back side under the knees, legs under the knees cold, hands under the elbow cold (always), right side more restricted, legs move better towards the centre. Legs felt “melting” during treatment. Stiff neck muscles with restricted mobility.

2nd session (9/11/17)

Complains: Spasticity

Main Treatment: In the supine position: Liver Jitsu, Stomach Kyo. Mobilisations, stretching, palming, 3 fingers, thumbs, Leg Jue Yin Liver, Leg Tai Yin Spleen, Leg Shao Yang Gall Bladder, Leg Yang Ming Stomach, Leg Shao Yin Kidney, ST36, Kid6-BL62, Kid3-BL60, SP4-GB41

In chair: hands, shoulders, neck

Feeling / Comments: Really good generally, some pain, pain in GB20

Inquired Adverse Effects: None, everything fine

Practitioner Observations: Room much quieter. Leg spasticity “melt” during the treatment. While working the Leg Yang Ming Stomach, she fell asleep.

3rd session (16/11/17)

Complains: Spasticity

Main Treatment: In the supine position: right Arm Tai Yin Lung very Jitsu, mobilisations, stretching. Mobilisations, stretching, palming, 3 fingers, thumbs, Leg Jue Yin Liver, Leg Shao Yang Gall Bladder, Leg Yang Ming Stomach, Leg Shao Yin Kidney. Upper back release with palms. Neck, head.

Feeling / Comments: Very good. Only slight pain in the area of C7. After previous treatment, the digestive system works much better than very long time with constipation relieved.

Inquired Adverse Effects: None, everything fine

Practitioner Observations: Quiet room. Able to deeply connect with points in Leg Yang Ming Stomach, during which she fell asleep.

4th session (19/11/17)

Complains: Stiff back

Main Treatment: In the prone position: Deep work in Leg Tai Yang Bladder in the back and legs, Du Mai, sacral, neck, head.

Feeling / Comments: Very good. No pain. Stools still normal! Mention removal of gallbladder years ago.

Inquired Adverse Effects: None, everything fine

Practitioner Observations: Quiet room. Slow, deep work, she fell asleep.

Period B2

5th session (20/11/17)

Complains: None

Main Treatment: In the supine position: Jitsu Liver, mobilisations, stretching, palming, 3 fingers, thumbs, Leg Jue Yin Liver, Leg Tai Yin Spleen, Leg Yang Ming Stomach, Leg Shao Yin Kidney, ST36, Kid6, SP4, SP6.

In the chair: Arm Yang Ming Large Intestine, shoulders, neck

Feeling / Comments: Very good. Yesterday's treatment release back problem. No pain. The MSQLI does not cover the spasticity issue that is for her the most important.

Inquired Adverse Effects: None.

Practitioner Observations: The body is much more responsive compared to other times.

6th session (23/11/17)

Complains: Legs

Main Treatment: In the prone position: Leg Tai Yang Bladder, Leg Shao Yin Kidney, Leg Shao Yang Gall Bladder, stretching, mobilisations, palming, three fingers, thumb pressure. Sotai exercises.

Feeling / Comments: Very relaxing. A reminder that the MSQLI does not cover the spasticity issue that is for her the most important.

Inquired Adverse Effects: None.

Practitioner Observations: None

7th session (28/11/17)

Complains: Urination difficulties

Main Treatment: In the prone position (inquired): Leg Tai Yang Bladder, sacrum, buttocks, stretching, mobilisations, palming, thumb pressure. Sp6. Feet bottom.

In the chair: Arm Yang Ming Large Intestine, neck.

Feeling / Comments: Relaxing session. Some pain points. The right hand works much better after last treatment.

Inquired Adverse Effects: None.

Practitioner Observations: The areas around KID2 in both feet were tender, an area that corresponds to the bladder organ in reflexology.

8th session (01/12/17)

Complains: None

Main Treatment: In the supine position: mobilisations, stretching, palming, 3 fingers, thumbs, Leg Yang Ming Stomach, Arm Yang Ming Large Intestine, Leg Shao Yang Gall Bladder, neck, head. ST36, GB 34, Kid6-BL62, Kid3-BL60, SP4-GB41, LI7-11

Feeling / Comments: Relaxing session. Pain in some hand points. The leg works a lot better after last treatment. Stools are still normal.

Inquired Adverse Effects: None.

Practitioner Observations: None

BREAK

Period B3

9th session (02/01/18)

Complains: Spasticity

Main Treatment: In the prone position: Leg Tai Yang Bladder, Leg Shao Yin Kidney, Leg Shao Yang Gall Bladder, stretching, mobilisations, palming, three fingers, thumb pressure.

In the supine position: Leg Yang Ming Stomach, Leg Jue Yin Liver, Leg Tai Yin Spleen, stretching, mobilisations, palming, three fingers, thumb pressure.

Feeling / Comments: Nice session. Legs and hand spasticity get worse during the break (A period).

Inquired Adverse Effects: None.

Practitioner Observations: General body stiffness worst than before the break.

10th session (04/01/18)

Complains: Spasticity

Main Treatment: In the prone position: Leg Tai Yang Bladder, Leg Shao Yin Kidney, stretching, mobilisations, palming, three fingers, thumb pressure.

In the supine position: Leg Yang Ming Stomach, Leg Jue Yin Liver, Leg Tai Yin Spleen, Leg Shao Yang Gall Bladder, stretching, mobilisations, palming, three

fingers, thumb pressure. Neck, shoulders, head, Arm Yang Ming Large Intestine points.

Feeling / Comments: Relaxing. Legs spasticity and the right hand difficulties remain.

Inquired Adverse Effects: None.

Practitioner Observations: She fell asleep in the supine position, the body more responsive compared to the previous session.

11th session (08/01/18)

Complains: Leg spasticity

Main Treatment: In the supine position: Leg Yang Ming Stomach, Arm Yang Ming Large Intestine, Arm Tai Yin Lung, stretching, mobilisations, palming, three fingers, thumb pressure. Neck, shoulders, scapula, head.

Feeling / Comments: After last treatment spasticity improved and the hand somehow better but still not totally ok.

Inquired Adverse Effects: None.

Practitioner Observations: Trying to keep her aware of her body with questions for feeling during the work.

12th session (11/01/18)

Complains: None

Main Treatment: In the supine position: Leg Jue Yin Liver, Leg Tai Yin Spleen, Leg Yang Ming Stomach, stretching, mobilisations, palming, three fingers. Neck, head.

Feeling / Comments: Relaxing, no problem after last treatment. Worries expressed about what is going to happen now that the trail ends.

Inquired Adverse Effects: None.

Practitioner Observations: Easy to “open” the channels worked with multiple palming passing.

Appendix 4. Semi-Structured Interview Verbatim Transcript

Researcher (R): So, I would like to begin by thanking you for agreeing to take part in this study and for accepting this interview.

Participant (P): You are welcome.

R: I remind again that you can interrupt the interview whenever you want, or you can say that you don't want to give an answer and that you are free to say whatever you want and this is not going to have any effect to your treatment and your care.

So, I would like to begin by asking you to share your experience of including shiatsu as part of your care during the last period.

P: Ok, well, well, it has been very relaxing in general, and of course it has... with my usual care it has been quit... mmm... so it has complete it, each other. Yeah... my usual care is quit much like physical care, and this one was more relaxing and maybe taking more care of those areas which were a little painful or hearting. Because actually they don't take care in the usually physical treatment.

R: Do you mean it was physical aspects that are not taking usually in the daily care or was non-physical aspects that was now addressed by shiatsu?

P: More like those hm... local things like local pain in my lower back and my hand and those things. They were more carefully taking care of... like... shiatsu.

R: Was anything that was quite bad about shiatsu?

P: No, everything was great. I liked it, yeah. There were many aspects which were good, firstly the one that I didn't... I didn't have to take off my cloths. That was very

nice, because it's so exhausting to take of your cloths and put them back again and such things, yeah...hm.... What was I saying?

R: So, I have asked if there was something very bad about shiatsu but... if see the question from the other side, was something very good about shiatsu? If you have to choose something...

P: And also there were relaxing point, it was very relaxing, well, I feel asleep most of the time so, you can tell from that, and... well yeah, it releases my spasticity, temporarily, so it came back after a while but... maybe if I get shiatsu each week it would be more permanent. Maybe, I don't know. And especially my right hand has been better after shiatsu, much better. Sometimes my legs have been maybe too, too relaxed so it's hard to stand up if I don't have spasticity in them. Because I need it when I change from the chair to the toilet seat or to bed.

R: So, would you say that this was some kind of adverse event?

P: What did you mean?

R: That there was not enough spasticity sometimes in your legs, that makes things to be more difficult afterwards?

P: Yeah, actually yes, yes. But otherwise than standing up and changing from chair to bed or toilet seat it has been very nice feeling when they are not so spastic.

R: Were there any other adverse events after the treatment?

P: No... no, no, and there the other good thing that was also that my stomach was very... working very well when I got this shiatsu often in the middle of this... this treatment time, yeah... it has never work so well.

R: By stomach you mean?

P: Constipation was released.

R: And, in the middle of the treatment period, based on the schedule of the study, you mean during the periods when you receive also shiatsu?

P: Yeah.

R: Ok, was shiatsu experience... first of all you haven't receive shiatsu before?

P: No

R: Was the experience of shiatsu what you were expecting from?

P: I didn't expect anything, actually. I didn't know about shiatsu anything. I haven't read about it anything. So, I didn't actually know what to expect. I didn't expect much, actually, so there wasn't any placebo effect, but... so, it was actually more than what I expected, yeah... I was actually quite astonished that it releases my spasticity so well and my stomach worked and, yeah...

R: So, if you wanted to speak about or to write about the possible contribution of shiatsu in the care of people with MS, what would be your opinion?

P: It would be that it helps in some extend, mostly temporally, for the spasticity and also for the constipation and it releases your pain areas, yeah, and, I would recommend it.

R: You will recommend it as a supplement to usual care...

P: Yeah, yeah...

R: Ok, and do you think that those aspects that was addressed are aspects that are not so often addressed from the usual care that people with MS receive?

P: Yes, I believe so, yes, because in the usual care I usually work my muscles, more, so strength for my muscles, like in gym. Yeah, and well, there are also quite a lot of stretching, they stretch my legs and... but mostly it's muscle work what we do there.

R: Could you imagine why?

P: Because I need it. I need muscles in my legs so that I can stand up and so... I think that's... well maybe also that's what I want to do there, because I can't do it at home...

R: So, possibly it would be also available help on those other domains if, for example if you ask from those that are involved in your usual care.

P: Well, yeah, sometimes I tell them that my lower back is aching and they give me massage and sometimes they give me a normal massage for my upper body and... if I ask for that. I have quite a lot of that usual care, I have 95 times a year, so there is much possibilities, much time to do different things. But I usually have to ask. Otherwise we do just the muscle work and stretching of the legs.

R: Ok, then, what if we take a look in the influence that this specific trial might had in your life, do you think that during the trial have been covered important domains for your life, that this trial succeeds to cover important domains for you?

P: What I can say... well, let's say the sleeping, I have slept better because my legs have been not so spastic... so they have not been so... they have been more relaxed during the nights, let's say. That's quite big thing because I always sleep so badly, so little things make the difference. And of course also my lower back has been better... I don't actually suffer of that much because I don't feel it when I'm sitting, but when I have to do something then I feel it, the pain, and it's so stiff

and aching... Maybe during night also that has been better. So that I have slept better.

R: So sleep is an important aspect for your life.

P: Yeah, that's true.

R: What else would you said that should be covered?

P: Also the constipation is great thing if it releases that, but otherwise I don't know.

R: So, as a treatment and as a trial, as a research study, was it enough flexible to your needs, according to your needs?

P: You mean the treatment as such?

R: The treatment as such and the trial itself.

P: Yeah, it was ok. There was no complains, it was great, it was great that you were coming to my house and... yeah, no complains.

R: And then, was there, if there was no complains, was there at least some difficulties to follow the study?

P: No...

R: I mean, for example, there was a full month that you have to have twice per week treatment...

P: It was ok, well, I have time, so it was ok. It was nice.

R: So, if see it like a "free-talking" now, is it something that you would like to add to what you have already speak about? Any concern, any idea...

P: Actually, not about the treatment itself but... well, I think that you were very professional, I like your style... but otherwise, I don't know anything else to say... Everything went well and smoothly.

R: In the previous treatment you have mention fear, or worry, I don't remember the exact word, because we try to speak also Finnish during the treatment but... regarding what is happening when the treatment stops.

P: Well, yeah...

R: Is it something that during the study period, when you have to get the breaks of the treatment, is it something that occur that cause the fear, or was it also worry at that time or how it was, how it was this experience for you?

P: The breaks you mean?

R: Yes.

P: Well, I didn't like the breaks... because this was so relaxing and... and pleasant. So I actually... I would like to have the treatments every week it was so nice.

R: Is it something that can contribute in getting worst period, the periods that are like without treatment? So... if I rephrase it... if you were going to take part in a similar study again, would the long break, there was two periods of break so four weeks continuously without treatment, would this be something that would make you think that "hm... maybe I would not take part on this study because this period"?

P: No, if you mean about the break that there was not pleasant, no, no, well, well the breaks were ok, but I would like to have treatment also all the time, yeah, because I liked it.

R: If there is not something else that you would like to add, maybe we can close this short interview here.

P: Yeah.

R: Thank you very much again.

P: Thank you.

Appendix 5. Publications Inspired from this Study

a) [Published] Safety and risks of shiatsu: Protocol for a systematic review (Tsiormpatzis, 2019)

European Journal of Integrative Medicine Volume 28, June 2019, Pages 20-26

<https://doi.org/10.1016/j.eujim.2019.03.006>

Abstract

Introduction: People use shiatsu for health maintenance and help with illness. Shiatsu is often considered safe, but there has been no published systematic review of its possible risks. The review aims to assess the evidence of safety and risk of harm for shiatsu.

Methods: All types of studies, independent of control and with any style of shiatsu are eligible. Reports in any language will be included. Peer-reviewed studies and non-peer-reviewed literature will be handled in separate parts of the review. Electronic databases (including among others MEDLINE, AMED, Alt HealthWatch, Web of Science, CiNii) will be searched for identification of peer-reviewed publications. Hand-search will be used for non-peer-reviewed literature. Risk of bias will be assessed using RoB 2.0 in conjunction with McHarm (randomised trials), ROBINS:I in conjunction with McHarm (non-randomised studies), a modified PHARMA checklist (adverse reports). When appropriate, reporting bias will be assessed using ORBIT. The relevance of the described intervention to shiatsu will be based on clinical experience, using CARE for massage and bodywork and TIDieR. Root cause analysis of adverse events will consider Bradford Hill's criteria in the light of clinical experience.

Results: Meta-analysis is not planned. Results for each study will be presented in tables. Relationships within and between studies will be explored. A theory about the safety profile of shiatsu will be developed. Identified incidents will be presented in a narrative way and tabular categories.

Discussion: The discussion will highlight the relevance to various stakeholders and will explore issues that occurred from the review.

b) [Published] Effects of shiatsu on the health-related quality of life of a person with secondary progressive multiple sclerosis: A mixed methods N-of-1 trial within a whole systems research case study

European Journal of Integrative Medicine Volume 32, December 2019, 101006

<https://doi.org/10.1016/j.eujim.2019.101006>

Abstract

Introduction: Multiple Sclerosis (MS) is a chronic neurological disorder with high prevalence in Finland. Most people with MS will develop Secondary-Progressive MS (SPMS) over time. People with MS report lower than the average Health-Related Quality of Life (HRQoL) and use Complementary and Alternative Medicine (CAM) for their symptoms. Personalised interventions such as shiatsu have an insufficient evidence base. The n-of-1 trial is a promising study design for personalised interventions in chronic conditions but has not little used in CAM research. The aim was to investigate if shiatsu affects the HRQoL of a person with SPMS.

Methods: Six-periods counterbalanced mixed-methods n-of-1 trial within a Whole Systems Research (WSR) case study was used. The short version of the MSQLI, data collected from a semi-structured interview and case notes were used to assess the effect of the treatment. The collected data analysed quantitatively and qualitatively and synthesised as a descriptive case study.

Results: The study was able to document improvements in spasticity, bowel function, fatigue, pain, sleep and relaxation. No adverse events occurred. Preliminary estimations of the onset and wash-out of shiatsu effects were inferred. Advantages and drawbacks of the design are discussed to improve future applicability.

Conclusions: Shiatsu was able to improve some domains of the HRQoL of the specific person with SPMS. It was a safe treatment with no adverse events. Mixed methods n-of-1 trial within a WSR case study was an appropriate design for the study.

c) [Working Title] A trial as a pilot: Are n-of-1 designs applicable to research in Non-Pharmacological Touch-Based Modalities (NPTBM)?

d) [Working Title] How Much is Enough? The “Half-Life” of Shiatsu, Preliminary Results and Methodological Considerations