

1 **Title**

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

5

6 **(Corresponding) Author**

7 Stergios Tsiormpatzis^a, MSc

8 Tuohilammentie 388, 03300, Otalampi, Finland

9 +358401650278

10 stergios.tsiormpatzis@gmail.com, stgio@orientalmedicine.eu

11 ^a Northern College of Acupuncture / Middlesex University London

12

13 **NOTE:** This is the accepted manuscript (authors version) of the article.

14 For the final version, please refer to the:

15 [European Journal of Integrative Medicine](#), [Volume 32](#), December 2019, 101006

16 or the address: <https://doi.org/10.1016/j.eujim.2019.101006>

17



18 © 2019. This manuscript version is made available under the CC-BY-NC-ND 4.0

19 license <http://creativecommons.org/licenses/by-nc-nd/4.0/>, according to the

20 publishers [article sharing policies](#).

21 **Abstract**

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

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

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

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

42 **Keywords**

43 multiple sclerosis, quality of life, shiatsu, n-of-1, mixed methods, whole system research

44

45

46 **1. Introduction**

47 *1.1. Background*

48 Multiple Sclerosis (MS) is a complex neurological disorder affecting physically,
49 psychologically, and socially [1] more than 2.2 million people worldwide, with
50 average sex ratio 2/1 female/male and significant association between latitude and
51 prevalence [2], putting Finland in the high-risk region. Most Persons with MS (PwMS)
52 initially diagnosed with Relapsing-Remitting MS. After an average period of 20 years,
53 the majority develop Secondary Progressive MS (SPMS) [3], which is characterised
54 by irreversible disease progression [4].

55 PwMS experience a lower level of Health-Related Quality of Life (HRQoL) compared
56 to the general population or other chronic disease populations [5–7]. HRQoL in MS
57 correlates with the function of the nervous system, mental and social complications
58 [8], fatigue, pain, sleep disturbances, emotional issues, physical disability, disease
59 progression [9], and comorbidities [10]. There is conflicting evidence for the effect
60 that the commonly used Disease-Modifying Treatments have on the HRQoL for
61 PwMS [11,12], while medicines used by PwMS may also lower their HRQoL, as
62 have been found for drug-related sleep disorders [13].

63 HRQoL might be the most relevant care outcome for PwMS [14]. Its improvement is
64 an unmet need for many [15]. A multidisciplinary approach combining medical
65 treatment with rehabilitation [16] following individualised, patient-centred principles
66 [17] could be an efficient HRQoL enhancing approach, minimising the impact of the
67 disease [18]. Such programs are offered in specialised rehabilitation centres across
68 Europe [19] with a small part of interventions being of Oriental Medicine (OM) origin
69 [20]. PwMS use Complementary and Alternative Medicine (CAM) [21,22] not only to

70 help themselves with symptom management but as part of a keen interest in
71 wellness [23,24]. The situation is similar in the Nordic countries despite the well-
72 established public healthcare systems [25], with over half of PwMS using CAM
73 during a year [26].

74 Shiatsu is an east-Asian bodywork form of CAM which took unique characteristics
75 while developing by integrating the culture and contemporary realities of 20th century
76 Japan [27]. In Japanese translates to “finger pressure”. European practitioners use
77 various approaches in their treatment [28,29], but they share at least the following
78 characteristics with the original Japanese style: a) diagnosis and therapy are
79 combined, b) the body is the only tool used, c) treat the whole body [30].

80 A recent definition of shiatsu reads as:

81 “Shiatsu is a manual therapy applied by leaning forward in a relaxed manner with the
82 weight of one’s body to an optimum point, and the correct use of fingers, palms, etc.,
83 in order to apply sustained, stationary pressure on different parts of the body for the
84 purpose of correcting the imbalances of the body, and for maintaining and promoting
85 health. It is a holistic therapy that aims to treat most of the body in each session.”
86 [31]

87 The receiver lies fully clothed on a futon, bed, massage couch or wheelchair and the
88 practitioner applies pressure to the body, while other techniques (e.g., stretches, joint
89 mobilisations, gentle touch) could be included. A typical session lasts about an hour,
90 and the practitioner might suggest exercise or dietary and lifestyle changes [32].

91 There has been some evidence for its effects on various health conditions [28] and
92 physiological effects in humans [33]. The mechanisms of its action are not yet

93 scientifically accessible, but it has been hypothesized that shiatsu may act, or at
94 least influence, the hypothalamus-pituitary-adrenocortical axis functioning [34]. One
95 of the conclusions of the biggest shiatsu study ever conducted [35] is that shiatsu,
96 when performed by qualified practitioners, is a safe therapy with no lasting adverse
97 effects [36], while a systematic safety review is ongoing [37].

98 As a personalised, whole system of healthcare, shiatsu approaches the receiver as
99 an organic whole with interconnected physical, emotional, and psychosocial aspects
100 [38]. Following a Whole Systems Research (WSR) [39] approach with mixed-
101 methods and single-subject design could be an appropriate methodology for its
102 investigation [40]. Single-subject research designs are carefully designed studies
103 where the sole unit of observation is an individual patient who acts as his/her own
104 control [41]. They are undertaken using a protocol involving multiple measurements
105 of the desired outcome across time [42]. They are used in medical and rehabilitation
106 research [43,44] and they are methodologically well established in those fields [45].
107 While not yet well integrated in CAM research, they have the potential to contribute
108 to the evaluation of CAM [46]. They are considered a feasible research approach for
109 the practitioners and a useful tool both for clinical research and for pilot studies while
110 developing bigger and more expensive trials [47].

111 N-of-1 trials belong to the family of single-subject research designs, and this
112 methodology has been proposed as very appropriate for trials in the contemporary era
113 of personalised medicine [48]. They are considered ideal to evaluate the effectiveness
114 of a treatment of chronic conditions [49].

115 *1.2. Rationale, Aims, and Objectives*

116 Personalised interventions like shiatsu might be possible to contribute to improving
117 HRQoL for patients with complex diseases such as SPMS. The aim was to
118 investigate if shiatsu affects the HRQoL of a person with SPMS. To achieve it, a
119 mixed-methods n-of-1 trial within a WSR case study designed and implemented.

120

121

122

123

124

125

126

127

128

129

130

131

132

133

134

135

EUJIM_2019_101006-Accepted_Manuscript

136 **2. Methods**

137 Ethical approvals were given by The Northern College of Acupuncture (NCA)
138 Research Ethics Committee (11/09/2017) and by the Helsinki and Uusimaa Hospital
139 District Coordinating Ethics Committee (HUS/648/2017, 8/8/2017). No identification
140 data were collected at any stage of the study, and a data processing diary was kept,
141 following all the requirements of the regulation 2016/679 (General Data Protection
142 Regulation) of the European Union. The study was supervised by a Medical Doctor,
143 two PhD (of which one was a physical therapist with expertise in rehabilitation of
144 PwMS) and a PhD candidate with expertise in shiatsu and multiple sclerosis.

145 The study was a mixed-methods six periods single-subject crossover experiment (n-
146 of-1 clinical trial), using a minimally optimal [50] counterbalanced design within a
147 WSR case study. Theoretical estimation of the number and length of crossovers, as
148 well as the number of data collection points, that could permit a statistically or
149 visually meaningful quantitative analysis were not performed, since the NCA
150 Research Ethics Committee required the absolute minimal approach that was used.
151 The clinical part took place between 11/2017 and 01/2018.

152 The practitioner-researcher was fully qualified shiatsu practitioner, having completed
153 three years shiatsu and OM training, one-year postgraduate shiatsu diploma and
154 continuous nursing education for MS care. He had seven years of clinical practice, of
155 which the last five focused on PwMS.

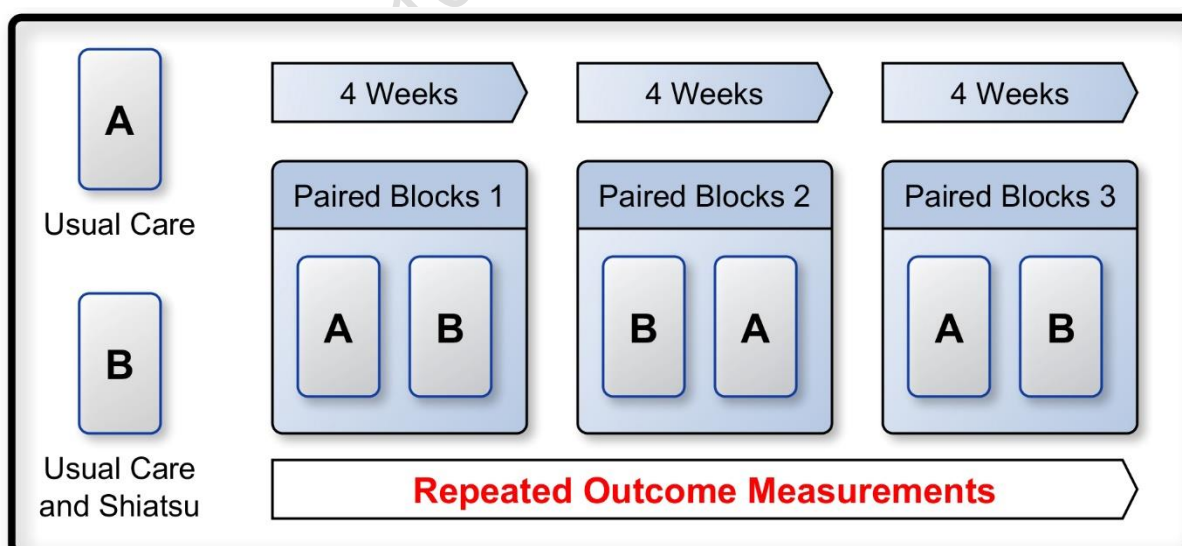
156 An invitation shared to former practitioner's patients, to inform possible participants
157 from the PwMS belonging to their social circles. The first responder screened and
158 satisfied the eligibility criteria (Table 1).

159

Eligibility Criteria	Exclusion Criteria
SPMS patient	Suffering from chronic or excessive fatigue
Between 35 and 65 years old	Receiving shiatsu, acupuncture or another form of OM during the last six months
Leaving in the central Uusimaa area	Inability to complete short questionnaires without assistance
Speaking good English	
Agrees to the study protocol	

160 *Table 1: Eligibility / Exclusion Criteria*

161 An information sheet and consent form were provided electronically, while a face-to-
 162 face meeting arranged between the patient and the researcher-practitioner. During
 163 this initial meeting all participant's concerns discussed, the consent form signed and
 164 the scheduling of the trial agreed to take place in six periods of paired two-week
 165 blocks of standard care (A) followed by intervention plus standard care (B) (AB BA
 166 AB) (Figure 1). The period (A) includes whatever care the patient normally receives
 167 (see §3.1. for a detailed description). In the period (B), two weekly shiatsu sessions
 168 were added.



169

170 *Figure 1: N-of-1 trial design*

171 Details required to form the natural history of the patient's MS and to provide a clinically
172 useful initial picture collected with the intake notes. Also, inquiries were made into the
173 patient's expectations from the trial, and the initial questionnaire (see below) was
174 completed.

175 The short version of the Multiple Sclerosis Quality of Life Inventory (MSQLI) [51] was
176 the HRQoL questionnaire, chosen due to its coverage of multiple domains in a way
177 that could be possible to complete in a reasonable amount of time. The MSQLI is a
178 validated measure [52] consisted of 10 questionnaires with multiple scales that the
179 patient can complete without help from the researcher. Each of the included scales
180 and the included averages gets a separate score, following a process described in its
181 manual [51]. In order to accommodate the biweekly blocks, it was modified to be
182 completed every two (instead of four) weeks: with the intake notes and at the end of
183 each period, seven times in total.

184 A semi-structured interview with the patient was made at the end of the trial to explore
185 the experience of the treatment, the influence of the trial in the patient's life, and
186 possible adverse events. The interview was recorded after obtaining the participant's
187 consent, with verbatim transcription and thematic analysis to follow. The transcript was
188 checked for accuracy by the participant.

189 The case records were kept by the practitioner and includes reporting of adverse
190 events as inquired into the patient after each session.

191 *2.1. Analysis*

192 A descriptive case study analytic strategy was used to outline the case. It began with
193 a familiarisation phase covering all types of collected data. Then the clinical case

194 was described, followed by a quantitative analysis of the questionnaires, and the
195 interview's thematic analysis.

196 Due to ethical concerns related to the possible burden to a patient that is considered
197 vulnerable, limited data collection points were included. Having only three pairs of
198 data, the statistical tests used for the analysis of n-of-1 trials [53–55] were not
199 applicable. Even the Wilcoxon Signed-rank test [56,57] that could be considered
200 theoretically appropriate, has no power with less than 5 pairs of data [58,59], since
201 with just simple enumerations is possible to calculate the exact frequencies of the sum
202 of the ranks, that provides a picture of the exact distribution of the Wilcoxon Signed-
203 rank statistic [60]. Thus no statistical test could answer a hypothesis for the study. The
204 scores are presented tabular and visually, as suggested by the CONSORT-CENT
205 extension for reporting N-of-1 trials [61]. For easier processing and interpretation, data
206 values were transformed in a directional scale 0-100 using the POMP formula [62,63].
207 A table compares the baseline with end scores. All calculations were made using the
208 LibreOffice 6.0.2.

209 The thematic analysis follows the six-step Braun and Clarke [64] approach flexibly.
210 Due to the single, short interview included in the thematic analysis, steps 3 (themes
211 searching) and 4 (themes reviewing) were compacted in one, while step 6 (writing
212 up) was completed in the synthesis of the findings.

213

214

215

216

217 **3. Results**

218 *3.1. Description of the Clinical Case and Usual Care*

219 The participant was a 57 years old woman with SPMS. Her first symptoms appeared
220 when she was 20, but remained undiagnosed until age 32. Six years after diagnosis,
221 she reached a stage where she could walk alone for a kilometre (EDSS 3.5-4) while
222 four years later, at 42, she was already in the SPMS stage. One year later, she had
223 to use a wheelchair for most of her movements, and at age 47, she was essentially
224 restricted to a wheelchair (EDSS 7.5). At that time, her perimenopause began and
225 continued for about four years. At age 49, the MS-related medication (Interferon-beta
226 (IFN- β)) was interrupted, and a year later, she had Chronic Cerebrospinal Venous
227 Insufficiency approach surgery, which helps with her fatigue but no other symptoms.

228 At the time of recruitment in the trial, she was restricted to a wheelchair, and retains
229 many self-care functions with effective use of arms, needing help to move from bed
230 to wheelchair (EDSS 8). Following an OM-based MS staging approach [65], she was
231 at the last, fourth stage where deficiency dominates with tiredness, urinary issues,
232 and considerably stiff and spastic muscles. Due to her restriction to a wheelchair,
233 she does not move a lot and experiences back and buttocks pain, stiffness and
234 spasticity in her legs and her right hand. There is no nerve pain and does not need
235 painkillers. She uses daily spasticity medication (Baclofen & Phenobarb-Hyoscy-
236 Atropine-Scop). Neurogenic bladder symptoms with chronic repeated inflammation
237 controlled with daily antibiotic medication (Nitrofurantoin-Ascorbic Acid). She suffers
238 from chronic constipation and sleep problems; frequently waking at night. In the early
239 morning, she wakes up with a sense that everything feels bad without knowing why.
240 She has a balance problem, heat makes her worse, and often she finds it difficult to

241 express herself in words. Receiving disability pension since age 46, today she feels
242 her retirement is a gift. In her diet, she avoids meat products.

243 After the interruption of the MS medication, she had neurologist appointments every
244 three years and 95 physiotherapy sessions per year (25 in a pool and 70 in health
245 care centre physiotherapist). She enjoys most the pool and feels satisfied with the
246 amount of care she receives.

247 Inquiring about her expectations from the trial, she expresses disbelief in any
248 possible benefit from shiatsu. Questioned about which symptom she would like to be
249 primarily addressed, she chooses spasticity.

250 *3.2. Shiatsu Treatments*

251 Treatments offered in the participant's house to a schedule agreed weekly. Due to
252 her mobility difficulties, she suggested having the sessions in a hard bed, which was
253 at the right height for her to move from and to the wheelchair with the practitioner's
254 help. Family members were present in the same big, open room but not focused on
255 the treatments. All 12 treatments included in the trial's plan completed successfully.
256 Sessions varied between 60-90 minutes, according to the practitioner's judgment. In
257 the beginning of each treatment after the first, and at the interview, the participant
258 was asked for her feelings, possible adverse events, or effects from the previous
259 treatment. A therapeutic relationship established without strong rapport.
260 Communication remained mostly focused on health. The treatment was focused on
261 the primary complaint (spasticity) and to issues raised before each session. A
262 general OM-based understanding of the participant's condition informed the
263 principles of treatment. The method of treatment specified by incorporating body

264 palpation during each session. Description of the sessions, as documented in the
 265 case notes, are available in Appendix A.

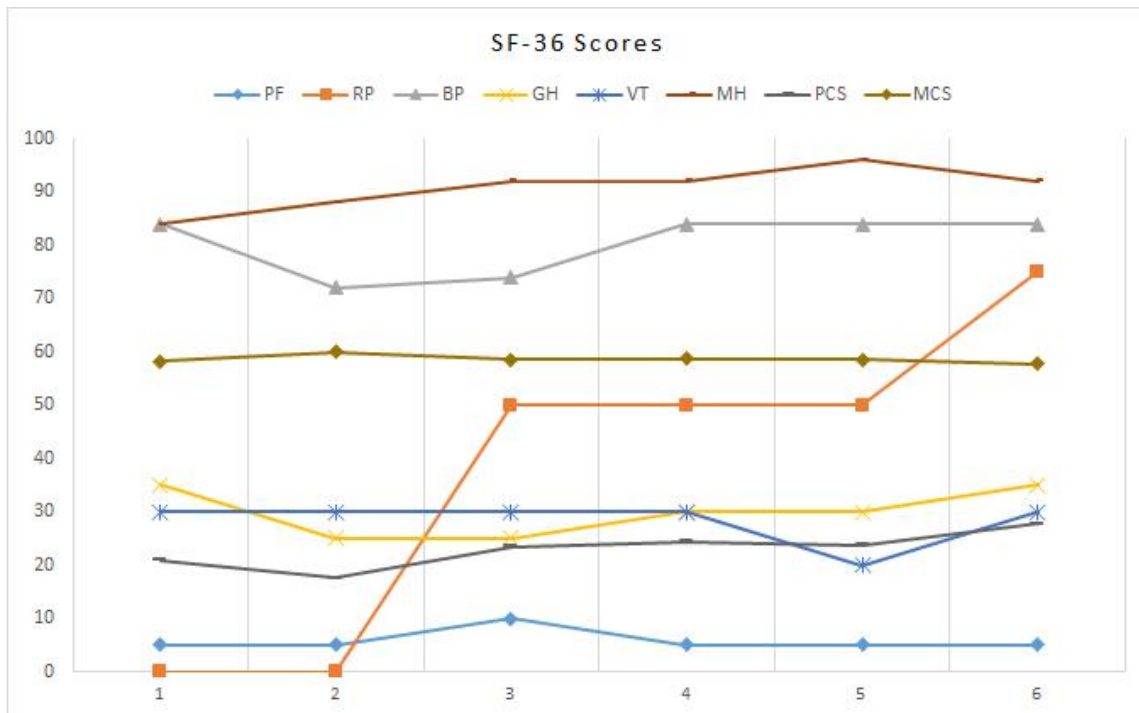
266 *3.3. Questionnaire Scores*

267 MSQLI scores (transformed when needed in 0-100 scale with 0=worst, 100=best
 268 possible score) are presented in Table 2, showing that the initial period established a
 269 stable baseline of two weeks, while Social Functioning Scale (SF), Role-Emotional
 270 Scale (RE) and Impact of Visual Impairment Scale (IVIS) remained stable during the
 271 trial. Changing scores during the time are visually presented in Figure 2. Table 3
 272 summarises scores comparison between baseline and the end of the trial.

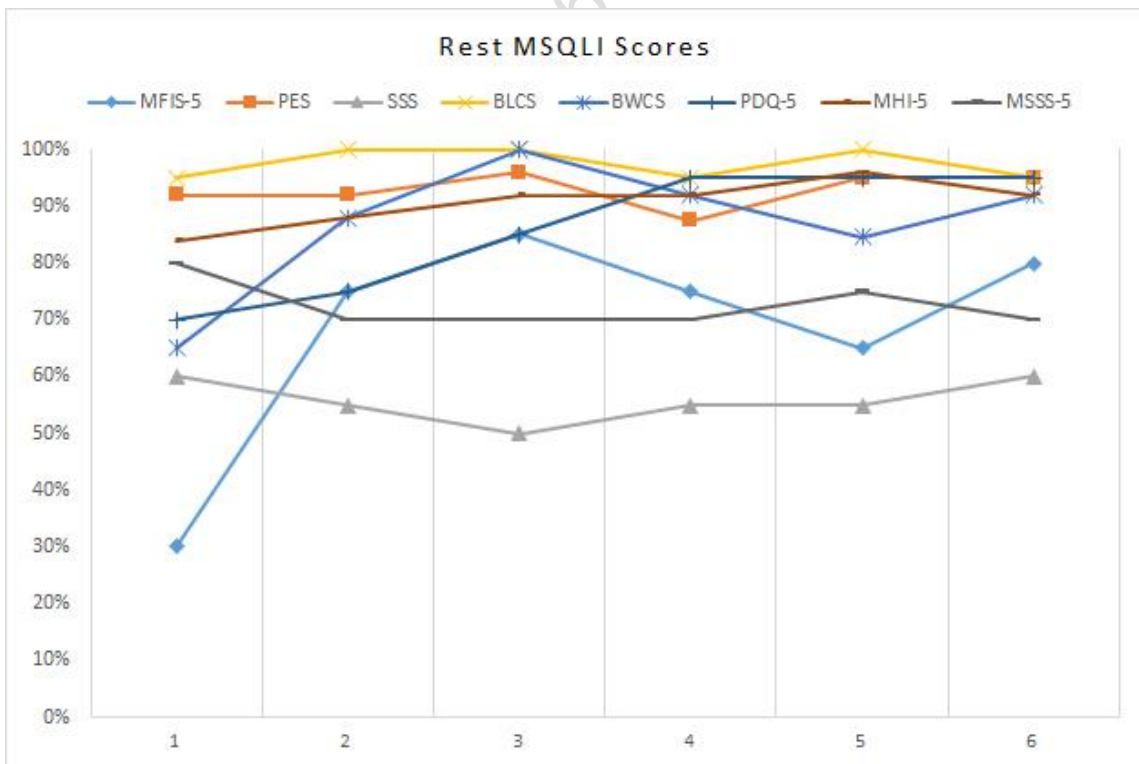
		A	B	B	A	A	B
	Initial	1st Block	2nd Block	3rd Block	4th Block	5th Block	6th Block
Health Transition Item* (1-5 scale)	3	3	3	2	3	3	3
Physical Functioning Scale (PF)	5	5	5	10	5	5	5
Role-Physical Scale (RP)	0	0	0	50	50	50	75
Bodily Pain Scale (BP)	84	84	72	74	84	84	84
General Health Scale (GH)	35	35	25	25	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)	58.28	58.28	59.933	58.603	58.653	58.604	57.702
Modified Fatigue Impact Scale - 5 Item Version (MFIS-5)	30	30	75	85	75	65	80
MOS Pain Effects Scale (PES)	91.67	91.67	91.67	95.83	87.5	95.83	95.83
Sexual Satisfaction Scale (SSS)	60	60	55	50	55	55	60
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	70	75	85	95	95	95
Mental Health Inventory - 5 Item Version (MHI-5)	84	84	88	92	92	96	92

MOS Modified Social Support Survey - 5 Item Version (MSSS-5)	80	80	70	70	70	75	70
--	----	----	----	----	----	----	----

273 Table 2: MSQLI scores in 0-100 scale



274



275

276 Figure 2: a) SF-36 scores, b) Rest of MSQLI scores

	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)

277 *Table 3: Pre-Post Comparison of all domains*

278 *3.4. Thematic Analysis of the Interview*

279 The verbatim transcript of the interview is available in Appendix B. Since the
 280 interview aimed to explore the experience of the treatment, the influence of the trial
 281 in the patient's life and possible adverse events, a theoretical approach was taken,
 282 coding relevant data [66]. Table 4 shows the themes that occurred with
 283 corresponding codes and frequency of occurrence.

284

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)				

285 *Table 4: Themes and Codes*

286 The definitions of the occurred themes (5th step) follow, omitting direct quotes due to
 287 space limitations:

- 288 - Treatment effects: The participant focuses a lot and continuously return to the
 289 effect of the treatment in her life, including relief from spasticity, constipation,
 290 local pains, improvement in sleep and function of her right hand, relaxation.
- 291 - Practical aspects of the trial: The participant considered the trial easy to
 292 follow, despite its length and intensity, with contributing aspects the lack of
 293 need to remove her clothes and the fact that the practitioner visited at her
 294 home. Contrarily, she expresses her dislike for the periods without shiatsu.
- 295 - Comparison with usual care: The participant thinks that shiatsu complements
 296 her usual care nicely by taking care of aspects not addressed during this care.

297 She is satisfied with the amount of the usual care, believing that it is focused
298 on muscle strengthening because she needs it. Inquired about the possibility
299 of covering more aspects during her usual care, she considers it possible and
300 sometimes, if she asks for, she receives massage.

301 - Adverse events: Inquired about adverse events, she reported none and
302 continued by mentioning positive effects. Considering legs spasticity, she
303 thinks that sometimes it was relieved too much, causing difficulties in standing
304 up.

305 - Expectations: Confirming her claim at the initial meeting, said she did not
306 expect anything and felt impressed by some effects that occurred. She would
307 recommend shiatsu as a complement to PwMS's usual care.

308 *3.5. Synthesis of Results*

309 The results of the study are to be considered based on triangulation of all types of
310 the collected data (raw scores, visual presentation, baseline-end comparison, case
311 notes, interview).

312 *3.5.1. Spasticity*

313 The primary symptom the patient wanted to address at the beginning of the trial was
314 spasticity, besides daily medication usage for it. Spasticity was also the major
315 complain during the first three sessions (period B1) and the three sessions after the
316 four weeks without shiatsu (period B3). MSQLI does not include spasticity domain,
317 an issue identified and commented on by the participant twice during B2 period, after
318 spasticity ceased to be the primary complaint, and the first MSQLI for a period with
319 shiatsu completed. Spasticity relief was a treatment effect the patient mentions as
320 very positive during the interview. She considers it one of the temporary benefits that

321 a PwMS could have from shiatsu, attributing to this the sleep improvement she
322 experienced. However, spasticity relief is also considered to cause difficulties in
323 changing from one place to another, since she had been used to have very spastic
324 legs that could statically support her weight.

325 3.5.2. Bowel Function, Bladder Control

326 Relief from constipation was the second important aspect mentioned in the interview
327 regarding treatment effects and as a reason to recommend shiatsu in PwMS. Case
328 notes indicate that after the 2nd session (B1 period) she reported relief from chronic
329 constipation, something confirmed again by her comments during fourth and eighth
330 sessions. Bowel Control Scale indicates improvement during shiatsu periods.

331 Looking at the scores over time we see an improvement of more than 23% during B1
332 period, which continued improving during B2 period reaching the best possible
333 score. During the A2 and A3 periods, there was a decline with a rhythm of about 8%
334 for each period. The improvement recovers about 8% during the last B3 period.

335 Bladder Control Scale scores suggest slight improvement during the first two shiatsu
336 periods, yet those were always inside the best 5% of the possible scores. Besides,
337 being on long-term daily medication for bladder issues that seems to work
338 effectively, the chances for real effect of shiatsu in her case could safely be
339 neglected.

340 3.5.3. Sleep and Relaxation

341 During the interview, the participant inquired about essential domains for her life that
342 were addressed by the trial. Improvement of sleep was a major one, attributed by her
343 mostly to spasticity improvement and lower back pain improvements. Case notes
344 indicate that during the treatments, the participant falls asleep at least four times.

345 The participant connects this with the relaxation she experiences from shiatsu,
346 something differing from her usual care.

347 3.5.4. Fatigue

348 Fatigue was not mentioned during the trial or in the interview. However, two of the
349 MSQLI scales showing improvement are fatigue-related. Modified Fatigue Impact
350 Scale assesses the effects of fatigue on physical, cognitive, and psychosocial
351 functioning [51]. By looking at the scores during the time, we see a sharp
352 improvement during B1 period that continues rising during B2 period (from 30% to
353 85%). During the usual care periods A2 and A3 there is some worsening stopping at
354 65%, to recover again at 80% at the end of the last B3 period. Vitality Scale
355 intending to measure energy levels and fatigue [67], suggest a mostly stable
356 situation. Only during the A3 period there was a slight worsening that recovers in the
357 previous value during the last B3 period.

358 3.5.5. Pain

359 During the intake, the pain was not indicated as a significant issue, and no pain
360 medication was used. Case records indicate that in the first session, some pain in
361 the sacrum was a major complaint together with spasticity. During the three first
362 treatments (B1 period), some pains occurred during the treatment, on the legs, and
363 in the neck area. During the fourth session (last of the B1 period) those pains had
364 already stopped appearing. Some pain in specific points was indicated again during
365 the seventh and eighth sessions (B2 period). However, the pain was not mentioned
366 in any of the post-treatment adverse effects inquires.

367 Bodily Pain Scale shows an interesting paradox. From the scores of each period and
368 their visual presentation, we see that the periods with shiatsu did worst. That is due

369 to a decrease in the score during the B1 and B2 periods which return to the original
370 levels afterwards, remaining until the end of the trial. On the contrary, the participant
371 in her interview indicates that the treatment offer relief from local pains, and this was
372 a reason to recommend shiatsu to a PwMS. MOS Pain Effects Scale assess the
373 degree to which pains affect mood, ambulation, sleep, work, recreation, and
374 enjoyment [51]. The scores from the beginning are very close to the best possible.
375 There is a slight improvement during B2 period followed by worsening and
376 improvement during the A2 and A3 period, to remain in the improved level during the
377 last B3 period. It worth to mention that the Bodily Pain Scale follows a different time-
378 trend, implying the idea that the pain caught in it does not correlate with effects
379 assessed by MOS Pain Effects Scale.

380 3.5.6. Mental and Cognitive Issues

381 During the intake, the participant mention waking up with an unexplained bad feeling
382 as well as that she finds it difficult to express herself with words. Role Emotional
383 Scale (mostly relevant to psychiatric conditions [67]) gets the highest possible score
384 during the whole study. Mental Components Summary Scale, offering standardized
385 distribution-based interpretations gained from US population with mean set to 50 and
386 standard deviation 10 [51,68] where scores above 50 indicate better health than the
387 mean of the general population and below 50 indicate worst health [68], seems to
388 have remained almost stable during the trial (57.7-59.9). Mental Health Scale (as
389 well as Mental Health Inventory which is derived from it) which covers four mental
390 health dimensions (anxiety, depression, loss of control, and psychological well-
391 being) [67] suggest complex interactions. During B1 and B2 periods, there is a slight
392 improvement that remains stable for A2 period, increasing slightly during A3 period,
393 to return to the B2 level at the last B3 period. Slight improvement appears comparing

394 before-after trial scores. In Perceived Deficits Questionnaire, covering cognitive
395 aspects (attention, retrospective and prospective memory, planning, and
396 organisation) [51], during B1 and B2 periods, there is an improvement that continues
397 during A2 period and remains stable till trial's end. In the interview, an overall
398 enthusiasm for the treatments was expressed, while at the last 12th session worries
399 regarding the trial's end were expressed. Finally, the Sexual Satisfaction Scale,
400 addressing the degree of satisfaction with aspects of sexual life both for the patient
401 and her partner [51], suggests stability, with no other indications for this domain in
402 other data sources.

403 3.5.7. Functioning and Roles

404 During the intake, the participant said that she feels her retirement is a gift. Social
405 Functioning Scale, indicating whether the social activities of the patients have been
406 affected by their health problems [67], remained unaffected during the trial. On the
407 contrary, Role-Physical Scale, referring to role limitations (problems with daily
408 activities) due to physical health [67], shows sharp improvement during the 3rd block.
409 From the worst possible score during baseline and period B1, rises to the middle of
410 the scale after period B2 and remains stable for the four weeks without treatment to
411 rise again in the three-quarters of the scale after the new introduction of shiatsu (B3
412 period).
413 Physical Functioning Scale assesses levels and kinds of physical limitations (lifting
414 and carrying groceries, climbing stairs, bending, kneeling, and walking moderate
415 distances as well as self-care activities). Considering most physical limitations as
416 chronic, estimates the severity of each limitation without considering its duration [67].

417 The score remained at a very low level. Minimum fluctuation occurs during the B2
418 period, that subsides to the original level in the A2 period and does not recover.

419 3.5.8. Social Support

420 In the intake, the participant expressed satisfaction with the amount of care she
421 regularly receives, even if in the interview, she indicates that with shiatsu areas not
422 usually addressed in her usual care were covered. MOS Modified Social Support
423 Survey, relevant to emotional, informational, tangible and affectional support as well
424 as with positive social interaction [51], suggests some worsening during period B1
425 that tends to remain until the end of the trial.

426 3.5.9. General Health and Expectations

427 During the intake, the participant's general health situation described as very
428 compromised, while she expressed her disbelief that the treatments could help her.
429 The interview indicates that her expectations change after the end of the trial. She
430 now expects to get temporary improvements by shiatsu, and she believed that
431 shiatsu complements her usual care nicely by addressing otherwise ignored aspects.
432 The areas discussed above shows that indeed there were improvements in some
433 domains of HRQoL. Health Transition Item, aiming to get information regarding
434 changes in health status during the year before the administration of the
435 questionnaire [67], remained mostly stable. General Health Scale, evaluating with
436 self-perceived questions the current health situation, resistance to illness and health
437 outlook [67], shows slight worsening during B1 and B2 periods, which take a positive
438 direction during A2 and A3 periods, to recover to its original score after B3 period.
439 Physical Components Summary Scale (similar to the Mental one described earlier)
440 shows slight worsening during B1 period to get slightly better during B2 period. Then

441 remained almost stable for the two usual care periods (A2-A3) and slightly improved
442 during the last B3 period. Impact of Visual Impairment Scale, related to difficulties
443 with simple visual recognition tasks that cannot be corrected by visual aids [51],
444 remained stable during the trial, getting the best possible score.

445 3.5.10. Summary of the Results

446 Summarising, the results of the study indicate possible improvement in some
447 domains, including spasticity, bowel function, fatigue, pain, sleep, and relaxation.
448 Similarly, there was an improvement in her expectations by the treatment. The
449 domains that are related to mental and cognitive issues, functioning and roles, social
450 support, the impact of visual impairment, bladder control as well as the general
451 health remained unaffected or showed a more complex picture (discussed in §4.1.).

452 3.6. Adverse Events

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

459

460

461

462

463

464 **4. Discussion**

465 *4.1. On the clinical results*

466 Minimal Clinically Important Difference (MCID) is defined as “the smallest difference
467 in score in the domain of interest which patients perceive as beneficial and which
468 would mandate, in the absence of troublesome side effects and excessive cost, a
469 change in the patient’s management” [69]. Summarising, the findings suggest that
470 the specific PwMS may have experience MCID in some HRQoL domains and
471 symptomatology (spasticity, bowel function, fatigue, pain, sleep, and relaxation).

472 Spasticity is a prevalent symptom that PwMS need to manage [70]. It influences their
473 HRQoL [71] and daily activities [72] negatively. It can have an impact on many
474 areas, including fatigue, depression, anxiety, pain, bladder function [73], bowel
475 function, and sleep [74]. Spasticity in MS cause substantial costs both regarding
476 HRQoL and economically [75,76] but is usually undertreated, since its
477 pharmacological management is not very efficient [77]. There are non-
478 pharmacological options for its management, with acupuncture and other CAM
479 playing a possibly positive role, besides the lack of adequate evidence [78]. In this
480 case, spasticity could be considered undertreated, despite the use of
481 pharmacological agents and physical therapy.

482 Additionally, the treatment influence fatigue, sleep problems, bowel function, and
483 possible mental issues suggested by the literature to be impacted by spasticity. The
484 participant herself attribute sleep improvement in the relief from leg spasticity.
485 However, a paradox accompanied the improvement. Even if spasticity was the
486 primary complain, the observed improvement seems to cause ambulation-related
487 difficulties. The participant used to have very spastic legs that could statically support

488 her weight during movement from wheelchair to bed or the toilet seat. The
489 improvement of her leg muscles seems to be the priority during her usual physical
490 therapy so that she has the possibility to stand-up. Leg spasticity is associated with
491 impaired ambulation [79], and the participant is mainly restricted to a wheelchair.
492 Thus possible future treatment for her spasticity should comprehensively consider
493 the sustainability of her basic ambulation.

494 The participant, during her interview, commented on sleep improvement, attributing it
495 mostly in spasticity and lower back pain improvement. Sleep disturbances in MS
496 remain mostly undiagnosed [80] even if they affect approximately 60% of the PwMS
497 [81] and can leave their marks in the routine MS neuroimaging [82]. Sleep problems
498 are associated with fatigue in PwMS [83–85] and the general population [85], while
499 diagnosed sleep disorder may be associated with reduced HRQoL in PwMS [86].
500 Treatment's effect on sleep supports previous evidence of a possible effect of
501 shiatsu in sleep disturbances [87–89].

502 Even if the pain was not a major complain and the participant considered shiatsu
503 offering local pains relief so that she would recommend it to PwMS, questionnaires
504 score and case notes show a complex picture. In Bodily Pain Scale, scores show
505 slight worsening during shiatsu periods. Case notes indicate that temporary pains
506 occurred during treatment, but those were not mentioned in post-treatment adverse
507 effects inquires. MOS Pain Effects Scale suggests that pain captured from the Bodily
508 Pain Scale did not lead to effects in the domains it assesses. Considering all sources
509 of data, it is suggested that the temporary pain occurrences during treatment as well
510 as the temporary worsening in Bodily Pain Scale were a form of theory and
511 experientially consistent “transitional effect”, according to the typology of negative
512 responses for shiatsu [36].

513 After the beginning of shiatsu treatments, participant's perception regarding her
514 health and social support begin to show signs of worsening. That is documented with
515 slight worsening in scores of General Health Scale and MOS Modified Social
516 Support Survey. Perceptions of health status and HRQoL of PwMS have been found
517 to differ significantly between the PwMS themselves and those of their neurologists
518 [90,91]. Physical activity correlates with a better health status perception [92] while
519 levels of social support, which includes supportive input received from the social
520 environment and can include almost any type of social interaction [93], are positively
521 associated with perceived health status in PwMS [94]. Considering the interview,
522 where the participant commented that shiatsu complements her usual care nicely by
523 addressing usually ignored aspects, it is possible to speculate that the worsening
524 documented in the relevant scales are related to realisations occurred due to shiatsu
525 effects. That could be attributed to the comparison with usual care together with the
526 expressed worries about not being able to continue the treatment after trial's end.
527 Those are elements that might have downgraded her perception about her general
528 health condition and the support she usually receives.

529 *4.2. Methodological issues*

530 The present study could take the role of a methodological pilot for the application of
531 n-of-1 trials designs in areas that traditionally are not considered appropriate for
532 them, manual therapies and bodywork. A detailed consideration of the study under
533 that perspective is attempted in a separate paper that is currently in the writing
534 stage, yet crucial issues that are related to the quality of the study and its clinical
535 relevance are discussed below.

536 4.2.1. Statistical analysis?

537 Due to ethical concerns, the number of data collection points were minimum, making
538 impossible any meaningful statistical analysis. Most of the published reports of n-of-1
539 trials use only visual comparisons, and of those reporting statistical analysis most
540 use simple statistical tests such as t-test [95]. When at least three data points per
541 period are included, visual inspection of data for changes of level (the average
542 performance of a period), trend (direction of change during a period), and variability
543 (scale of change during a period) is straightforward for substantial and fast changes
544 [96]. While visual inspections alone can provide evidence of large effects [97],
545 without enough data collection points, a useful visual analysis is not feasible. More
546 complex statistical approaches are required, with more treatment periods necessary
547 to minimise type I and II errors [98]. Overall, the more observations, the better.
548 Usage of daily diaries might help too. It is reminded that any statistical inferences of
549 this study could refer only to what occurred during the specific trial with the specific
550 PwMS. It is not possible to gain any valid inferences for other persons and situations.
551 This is the limit even when the most appropriate statistical analysis for single-subject
552 trials is used. Nevertheless, the purpose of applied research should be to discover
553 inferences with clinical meaning, not just statistical significance [97]. Any
554 generalisation could come only in a clinical context, relying on the common scientific
555 rationale that “similar” outcomes should occur in “similar” situations in the future [99].

556 4.2.2. Carry-over effects and the “half-life” of shiatsu. How much is enough?

557 The issue of the carry-over effects is discussed in the single-subject design literature
558 [100]. Carry-over effects could potentially distort the results of the periods following
559 the initial treatment [101], a problem usually solved in pharmacological studies by
560 including a wash-out period [102]. Statistical tests had been proposed to check for
561 pharmacological carry-over effects even if it had been argued that there is no benefit

562 by using them [100,103]. For non-pharmacological treatments, where the concepts
563 of pharmacokinetics and pharmacodynamics are not applicable, the solution of
564 including wash-out periods is not feasible [104]. Carry-over effects are difficult to
565 detect and the results difficult to interpret unless the researcher is confident about
566 their amplitude due to previous knowledge [105]. A way to address possible lack of
567 previous knowledge could be to use ideas proposed in different contexts. In the
568 study of pharmacodynamics, “Physiological Effect Models” are applied when the
569 effect of a drug in the organism is unknown quantitatively, using the physiological
570 results of its effect instead to measure its effect [106]. Additionally, “looking at the
571 data” could be a valuable way to address the issue, as long as this is supported by
572 rich description and transparent, open availability of the data for each period [107],
573 while using the baseline data from the period before the treatment could partially
574 remedy the situation [108].

575 In this study, a minimal approach was taken with six biweekly periods of twelve
576 treatments in total. While some change in the HRQoL was documented, the potential
577 of the methodology to address the carry-over issue and clarify the “half-life” or
578 “wash-out” period of shiatsu could be further exploited in a more protracted trial. Only
579 some of the MSQLI-assessed domains provides interesting clues towards this aim.
580 The Role-Physical scale suggests that two consecutive treatment periods (four
581 weeks) were necessary to document improvement that persists for two control
582 periods (four weeks) and continue improving during the last treatment period (two
583 weeks). Similar trends show the results of the Bowel Control and the Modified
584 Fatigue Impact scales, with improvement occurring after a treatment period (two
585 weeks) to maximise after the second consecutive treatment period (four weeks).
586 Then a partial reversal of the improvement occurs during the following two control

587 periods (four weeks) to improve again after the re-introduction of the last treatment
588 period (two weeks).

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

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

598 It should also be noted that in this study, for logistic reasons, there was no follow-up
599 period. Informal contact of the author with the participant four months after the
600 conclusion of the trial reveals that the effect had already reversed during that time.
601 The suggestion someone could get from this is in agreement with existing guidelines
602 on the field of Chinese and integrative medicine regarding the usefulness of
603 sufficient follow-up time [109].

604 Shiatsu in Europe is usually offered in weekly sessions, either for short periods of a
605 few treatments or as a long-term treatment that can continue for months or years.
606 Similar to concerns expressed about physical therapy [110], it is not known what
607 type of treatment and for how long it should be offered to optimise the results. To the
608 knowledge of the practitioner, the amount of physical therapy offered to PwMS in
609 Finland depends on the disability level and the needs of each patient. This can vary
610 during the years and according to the results, with weekly or biweekly physical

611 therapy sessions available. In a recent RCT pilot study for shiatsu as adjuvant
612 therapy for depression in patients with Alzheimer's disease [111], shiatsu was
613 offered once per week for ten consecutive months. In the Chinese context, bodywork
614 modalities such as tuina are often offered daily, similarly to acupuncture [112,113].
615 While such treatment schedules might seem strange in Europe, the author of the
616 study has positive clinical experience in offering daily shiatsu treatment for periods of
617 two months with PwMS. Such an intensive mode of treatment, even for a shorter
618 period, have been used earlier in the research context of acupuncture n-of-1 trials
619 [114]. Regarding shiatsu and considering the chronic nature of MS, an intensive and
620 long-term treatment perspective seems more appropriate.

621 4.2.3. What and how to measure

622 As indicated earlier, the MSQLI even if widely used in HRQoL research for PwMS
623 and covering a broad spectrum of HRQoL areas, it did not cover essential domains
624 for the specific patient. This issue is an integral part of the concept of outcome and
625 HRQoL measures as used in individualised trials of complex treatments, since the
626 underpinnings of outcomes are usually population-based and appropriate for
627 pharmaceutical trials but not so for complex interventions [115,116]. This study
628 strongly supports the need for richer methods to measure the effect of the treatment.
629 Without various data sources, the interpretations of the MSQLI would be challenging,
630 and important aspects could be lost. The mixing of data was able to provide some
631 conclusions, yet it is not known how stronger those could be if the design were able
632 to accommodate powerful statistical analysis and a more relevant questionnaire.
633 More qualitative and patient-specific measures, such as the interview-based SEIQoL
634 [117] or the MYMOP [118], could be used to offer more relevant and potentially more
635 robust conclusions.

636 4.2.4. The practitioner as a researcher

637 Issues related to the role of the practitioner as a researcher have concern
638 researchers before. The position of the researcher is unavoidably influencing the
639 research from its conception [119] and can affect the honesty of the participant's
640 interview responses [120]. Including external interviewer would not remedy the
641 situation since the participant would know that the practitioner-researcher will
642 analyse the data; thus, favourable feedback would be more expected [120]. This
643 dual-role probably means that the researcher has a positive attitude for the tested
644 modality, too [120].

645 Yet it should be noted that this applies to all kind of health practitioners and is not
646 necessarily something negative since this "belief system" of health professions are
647 integral to the clinical practice [121]. Even more, it has been suggested that
648 engaging practitioners in CAM research is essential to improve the validity and
649 ensure that the therapies are evaluated as they are used in practice [122]. To that
650 aim, the inclusion of Evidence Based Medicine and critical research reading courses
651 in the curriculum of CAM schools is encouraged [123] so that practitioners are better
652 prepared to participate in research projects.

653 Since the practitioner of the study is also the researcher, the following measures were
654 taken in order to help establish the credibility of the study:

655 a) Synthesis of data collected from various sources.

656 b) Supervision (see §2) and peer debriefing.

657 c) The interview transcript was checked for accuracy by the patient.

658 Besides, this study highlights a possible drawback of that approach, in terms of the
659 WSR approach. Due to the dual practitioner-researcher role, the methods applied in
660 practice were restricted, even if the study protocol poses no practice restrictions.
661 While the literature indicates that lifestyle consultation and nutritional advice could be
662 parts of shiatsu practice [32,124] the practitioner-researcher still sought to avoid
663 them during the study. Similarly, usage of other OM modalities like cupping was
664 avoided, even if they are often integrated into a shiatsu session [125]. This might be
665 due to the engagement with the designing of the study, that made the practitioner
666 more aware of possible methodological issues, such as that since lifestyle changes
667 are not easy to “switch off”, treatments that include lifestyle changes are usually
668 ruled out from candidates of n-of-1 trials evaluation [126].

669 4.2.5. Shiatsu in the specific context

670 In the context of the trial, the treatment offered was very close to the real-life practice
671 of the specific practitioner, besides the issues highlighted above. Yet this does not
672 mean that the shiatsu practised by the specific practitioner is representative of
673 shiatsu in general [127].

674 A general feature of the shiatsu offered in the study that deviates from the norm in
675 Europe is the fact that it was offered in a bed. While originally shiatsu was offered on
676 a futon on the floor, modern Japanese practitioners found more comfortable and safe
677 for the practitioner to work in a massage table or bed [128]. This way of work has
678 also been introduced in the US [129], but it has not flourished in Europe. To work on
679 a bed was proposed by the participant due to her movement difficulties. This is a
680 promising way to work for patients with disabilities, restricted to a bed or wheelchair.

681 Moreover, working at a table, bed or chair could make shiatsu more easily to offer in
682 a hospital or healthcare-centre setting, as a recent service evaluation of a cancer
683 centre where shiatsu as well a range of CAM were available shows [130]. Even if
684 many practitioners might not have training and experience of working on a table, it
685 should be their responsibility to adjust their practice in a way possible to
686 accommodate the needs of the receiver. Shiatsu schools from their side should offer
687 training to promote safe and effective ways to adjust a shiatsu session for table, bed
688 or chair.

689 Despite recent efforts by the practitioners association, Shiatsu in Finland is not yet
690 well-developed professionally [37] and is neither recognised as part of healthcare or
691 as a healthcare profession nor covered by health or patient insurance. Even if the
692 study shows possible MCID, currently there is no way shiatsu could be integrated
693 into the care and management plan of the participant. No social structure could
694 support her in receiving shiatsu, and thus there were no practitioners that the
695 researcher could suggest to her. It should be considered that all costs of the trial
696 were covered out-of-pocket by the practitioner-researcher who volunteered the
697 shiatsu treatments and all costs related to the study. This is very concerning since
698 the participant herself expresses her dislike of the periods that she did not receive
699 shiatsu, and she was concerned about how she could continue after the end of the
700 trial. It should be noted that the yearly cost of severe MS in Finland reaches 110.000
701 euros per PwMS, a cost that is “essentially due to the high requirement of
702 professional services and informal care in the advanced disease stage” [131].
703 Moreover, most patients would welcome a personalised trial if it can limit their out-of-
704 pocket costs [132].

705 *4.3. Implications for practice, training and policy*

706 The results of this study are not generalizable but refer to the specific participant in
707 the specific setting. Some indicative implications exist both for practice, training and
708 policy. For shiatsu in practice, it can be suggested that a denser treatment schedule,
709 compared to the commonly used once-weekly treatment, might be more effective in
710 chronic and severe conditions. The practitioners should be ready to adjust their
711 treatment in various settings and work in bed, table or chair. Shiatsu schools should
712 prepare future practitioners for work as healthcare providers in various setting and
713 assist current practitioners to this adjustment. Also, EBM and research skills courses
714 should be included in their curriculums. Professional shiatsu associations should
715 ensure that it is possible for patients to reach professionally competent practitioners.
716 The policy-makers should consider how shiatsu as a method that is not currently
717 considered healthcare could be integrated into the healthcare and management plan
718 of severely diseased chronic patients when found of being of help.

719 *4.4. Limitations of the study*

720 The study has some limitations that are integral to the nature of the examined modality
721 and the research design. The bodywork nature of shiatsu does not allow the
722 application of randomisation and blinding [133]. Yet, the n-of-1 trial crossover design
723 bypasses at least the concerns of selection bias that the lack of randomisation cause,
724 since the same person is at the same time the control of the trial. The design could
725 control better for the therapeutic relationship effect by including meetings without
726 treatment during the usual care periods. This is an issue that needs further
727 investigation, since it would change the nature of the control period from usual care to
728 therapeutic relationship.

729 It is reminded that since the study is a single subject trial, the results refer only to
730 what occurred during the specific trial with the specific PwMS and it is not possible to
731 infer relevance for other persons and situations. The study includes very few data
732 collection points, making statistical analysis impossible. The length of the periods
733 was not long enough to permit a full appreciation of the speed of effect and wash-out
734 of shiatsu. No follow-up evaluation was included. The questionnaire was not
735 personalised enough, missing essential domains for the participant. The dual
736 researcher-practitioner role downgraded the WSR approach and inserted potential
737 bias in the interview. The interview and the clinical interaction between the
738 participant and the practitioner-researcher were not optimal since they
739 communicated mostly in English, which is a second language for both of them.

740 *4.5. Suggestions for Future Studies*

741 A research program consisting of multiple studies following the fundamental design
742 principles and methodological concerns of this study is suggested to evaluate the
743 effect of shiatsu as a personalised treatment for PwMS. More flexible and rich design
744 is needed with the amount of data collection points per period calculated in order to
745 permit a useful visual and robust statistical analysis. A cost-effectiveness aspect
746 would be useful to be included in such a research program.

747

748

749

750

751

752 **5. Conclusion**

753 To the knowledge of the author, this is the first study to investigate if shiatsu affects
754 the HRQoL of a person with SPMS, by implementing a mixed methods n-of-1 trial
755 within a WSR case study. The study succeeds to show that in the specific setting
756 with the specific severely diseased patient who already receives physical therapy
757 according to her needs, shiatsu was able to improve the HRQoL of a person with
758 SPMS influencing spasticity, bowel function, sleep and relaxation, fatigue and pain.
759 Shiatsu was a safe treatment, and no adverse events occurred. In addition, to the
760 knowledge of the author, this is the first study that attempted and partially succeeded
761 to exploit the advantages of the employed design in order to systematically
762 determine the speed of shiatsu's effect onset and wash-out. It is suggested that an
763 improved version of the design that considers the findings and methodological
764 limitations of this study could be promising as part of a research program to
765 investigate the effect of CAM bodywork systems of care (such as shiatsu) on chronic
766 conditions (such as SPMS).

767

768

769

770

771

772

773

774

775 **Appendix A. Description of Treatments – Case Records**

776 ***Period B1***

777 **1st session (6/11/17)**

778 Complains: Spasticity, pain in the sacrum

779 Main Treatment: In the prone position (inquired): Leg Tai Yang Bladder, HuaTuoJiaJi
780 points, Du Mai, sacrum, scapula's, stretching, mobilizations, palming, three fingers,
781 thumb pressure.

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

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

785 Inquired Adverse Effects: None, everything fine

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

791 **2nd session (9/11/17)**

792 Complains: Spasticity

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

797 In chair: hands, shoulders, neck

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

799 Inquired Adverse Effects: None, everything fine

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

802 **3rd session (16/11/17)**

803 Complains: Spasticity

804 Main Treatment: In the supine position: right Arm Tai Yin Lung very Jitsu,
805 mobilizations, stretching. Mobilizations, stretching, palming, three fingers, thumbs,
806 Leg Jue Yin Liver, Leg Shao Yang Gall Bladder, Leg Yang Ming Stomach, Leg Shao
807 Yin Kidney. Upper back release with palms. Neck, head.

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

811 Inquired Adverse Effects: None, everything fine

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

814 **4th session (19/11/17)**

815 Complains: Stiff back

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

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

820 Inquired Adverse Effects: None, everything fine

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

822 **Period B2**

823 **5th session (20/11/17)**

824 Complains: None

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

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

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

832 Inquired Adverse Effects: None.

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

835 **6th session (23/11/17)**

836 Complains: Legs

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

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

842 Inquired Adverse Effects: None.

843 Practitioner Observations: None

844 **7th session (28/11/17)**

845 Complains: Urination difficulties

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

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

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

851 Inquired Adverse Effects: None.

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

854 **8th session (01/12/17)**

855 Complains: None

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

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

862 Inquired Adverse Effects: None.

863 Practitioner Observations: None

864 **BREAK**

865 ***Period B3***

866 **9th session (02/01/18)**

867 Complains: Spasticity

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

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

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

875 Inquired Adverse Effects: None.

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

877 **10th session (04/01/18)**

878 Complains: Spasticity

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

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

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

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

886 Inquired Adverse Effects: None.

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

889 **11th session (08/01/18)**

890 Complains: Leg spasticity

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

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

896 Inquired Adverse Effects: None.

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

899 **12th session (11/01/18)**

900 Complains: None

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

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

905 Inquired Adverse Effects: None.

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

908

909

910

911

912

913

914

915

916

917

918

919

920

921

922

923

924

EUJIM_2019_101006-Accepted_Manuscript

925 **Appendix B. Semi-structured interview verbatim transcript**

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

928 Participant (P): You are welcome.

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

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

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

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

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

943 R: Was anything that was quite bad about shiatsu?

944 P: No, everything was great. I liked it, yeah. There were many aspects which were
945 good, firstly the one that I didn't... I didn't have to take off my cloths. That was very
946 nice, because it's so exhausting to take of your cloths and put them back again and
947 such things, yeah...hm.... What was I saying?

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

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

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

959 P: What did you mean?

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

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

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

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

968 R: By stomach you mean?

969 P: Constipation was released.

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

972 P: Yeah.

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

974 P: No

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

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

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

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

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

987 P: Yeah, yeah...

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

990 P: Yes, I believe so, yes, because in the usual care I usually work my muscles,
991 more, so strength for my muscles, like in gym. Yeah, and well, there are also quite a

992 lot of stretching, they stretch my legs and... but mostly it's muscle work what we do
993 there.

994 R: Could you imagine why?

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

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

1000 P: Well, yeah, sometimes I tell them that my lower back is aching and they give me
1001 massage and sometimes they give me a normal massage for my upper body and...
1002 if I ask for that. I have quite a lot of that usual care, I have 95 times a year, so there
1003 is much possibilities, much time to do different things. But I usually have to ask.
1004 Otherwise we do just the muscle work and stretching of the legs.

1005 R: Ok, then, what if we take a look in the influence that this specific trial might had in
1006 your life, do you think that during the trial have been covered important domains for
1007 your life, that this trial succeeds to cover important domains for you?

1008 P: What I can say... well, let's say the sleeping, I have slept better because my legs
1009 have been not so spastic... so they have not been so... they have been more
1010 relaxed during the nights, let's say. That's quite big thing because I always sleep so
1011 badly, so little things make the difference. And of course also my lower back has
1012 been better... I don't actually suffer of that much because I don't feel it when I'm
1013 sitting, but when I have to do something then I feel it, the pain, and it's so stiff and
1014 aching... Maybe during night also that has been better. So that I have slept better.

1015 R: So sleep is an important aspect for your life.

1016 P: Yeah, that's true.

1017 R: What else would you said that should be covered?

1018 P: Also the constipation is great thing if it releases that, but otherwise I don't know.

1019 R: So, as a treatment and as a trial, as a research study, was it enough flexible to
1020 your needs, according to your needs?

1021 P: You mean the treatment as such?

1022 R: The treatment as such and the trial itself.

1023 P: Yeah, it was ok. There was no complains, it was great, it was great that you were
1024 coming to my house and... yeah, no complains.

1025 R: And then, was there, if there was no complains, was there at least some
1026 difficulties to follow the study?

1027 P: No...

1028 R: I mean, for example, there was a full month that you have to have twice per week
1029 treatment...

1030 P: It was ok, well, I have time, so it was ok. It was nice.

1031 R: So, if see it like a "free-talking" now, is it something that you would like to add to
1032 what you have already speak about? Any concern, any idea...

1033 P: Actually, not about the treatment itself but... well, I think that you were very
1034 professional, I like your style... but otherwise, I don't know anything else to say...
1035 Everything went well and smoothly.

1036 R: In the previous treatment you have mention fear, or worry, I don't remember the
1037 exact word, because we try to speak also Finnish during the treatment but...
1038 regarding what is happening when the treatment stops.

1039 P: Well, yeah...

1040 R: Is it something that during the study period, when you have to get the breaks of
1041 the treatment, is it something that occur that cause the fear, or was it also worry at
1042 that time or how it was, how it was this experience for you?

1043 P: The breaks you mean?

1044 R: Yes.

1045 P: Well, I didn't like the breaks... because this was so relaxing and... and pleasant.
1046 So I actually... I would like to have the treatments every week it was so nice.

1047 R: Is it something that can contribute in getting worst period, the periods that are like
1048 without treatment? So... if I rephrase it... if you were going to take part in a similar
1049 study again, would the long break, there was two periods of break so four weeks
1050 continuously without treatment, would this be something that would make you think
1051 that "hm... maybe I would not take part on this study because this period"?

1052 P: No, if you mean about the break that there was not pleasant, no, no, well, well the
1053 breaks were ok, but I would like to have treatment also all the time, yeah, because I
1054 liked it.

1055 R: If there is not something else that you would like to add, maybe we can close this
1056 short interview here.

1057 P: Yeah.

1058 R: Thank you very much again.

1059 P: Thank you.

1060

1061

1062

1063

1064

1065

1066

1067

1068

1069

1070

1071

1072

1073

1074

1075

1076

1077

EUJIM_2019_101006-Accepted_Manuscript

1078 **Authors**

1079 All research done by the author

1080

1081 **Financial support**

1082 This study was supported by a grant of 400 € for specific translation costs from the
1083 Foundation for Research into Traditional Chinese Medicine via the Northern College
1084 of Acupuncture.

1085

1086 **Conflict of interest**

1087 The author is himself a shiatsu practitioner, working as a personal assistant of
1088 PwMS.

1089

1090 **Acknowledgements**

1091 The author would like to thank Trina Ward and Lisa Esmonde for their generous
1092 comments during the study. Anders Romberg, Karen Charlesworth, Richard
1093 Blackwell and Kathryn Murphy for their help with the regional ethical approval
1094 process. The anonymous participant of this study for her willingness to participate
1095 and complete it according to the schedule. The anonymous reviewers for their
1096 constructive comments that help in improving the quality of this paper.

1097

1098

1099

1100 **References**

- 1101 [1] S.F. Hunter, Overview and Diagnosis of Multiple Sclerosis, *The American Journal of Managed*
1102 *Care*. 22 (2016) s141-150. <http://www.ncbi.nlm.nih.gov/pubmed/27356023>.
- 1103 [2] M.T. Wallin, W.J. Culpepper, E. Nichols, Z.A. Bhutta, T.T. Gebrehiwot, S.I. Hay, I.A. Khalil,
1104 K.J. Krohn, X. Liang, M. Naghavi, A.H. Mokdad, M.R. Nixon, R.C. Reiner, B. Sartorius, M.
1105 Smith, R. Topor-Madry, A. Werdecker, T. Vos, V.L. Feigin, C.J.L. Murray, Global, regional, and
1106 national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden
1107 of Disease Study 2016, *The Lancet Neurology*. 18 (2019) 269–285. doi:10.1016/S1474-
1108 4422(18)30443-5.
- 1109 [3] M. Koch, E. Kingwell, P. Rieckmann, H. Tremlett, The Natural History of Secondary
1110 Progressive Multiple Sclerosis, *Journal of Neurology, Neurosurgery & Psychiatry*. 81 (2010)
1111 1039–1043. doi:10.1136/jnnp.2010.208173.
- 1112 [4] F.D. Lublin, S.C. Reingold, J.A. Cohen, G.R. Cutter, P.S. Sorensen, A.J. Thompson, J.S.
1113 Wolinsky, L.J. Balcer, B. Banwell, F. Barkhof, B. Bebo, P.A. Calabresi, M. Clanet, G. Comi,
1114 R.J. Fox, M.S. Freedman, A.D. Goodman, M. Inglese, L. Kappos, B.C. Kieseier, J.A. Lincoln,
1115 C. Lubetzki, A.E. Miller, X. Montalban, P.W. O'Connor, J. Petkau, C. Pozzilli, R.A. Rudick,
1116 M.P. Sormani, O. Stuve, E. Waubant, C.H. Polman, Defining the Clinical Course of Multiple
1117 Sclerosis: The 2013 Revisions, *Neurology*. 83 (2014) 278–286.
1118 doi:10.1212/WNL.0000000000000560.
- 1119 [5] M.P. McCabe, S. McKern, Quality of Life and Multiple Sclerosis: Comparison Between People
1120 with Multiple Sclerosis and People from the General Population, *Journal of Clinical Psychology*
1121 *in Medical Settings*. 9 (2002) 287–295. doi:10.1023/A:1020734901150.
- 1122 [6] B.P. Hermann, B. Vickrey, R.D. Hays, J. Cramer, O. Devinsky, K. Meador, K. Perrine, L.W.
1123 Myers, G.W. Ellison, A Comparison of Health-Related Quality of Life in Patients with Epilepsy,
1124 Diabetes and Multiple Sclerosis, *Epilepsy Research*. 25 (1996) 113–118. doi:10.1016/0920-
1125 1211(96)00024-1.
- 1126 [7] R.A. Rudick, Quality of Life in Multiple Sclerosis, *Archives of Neurology*. 49 (1992) 1237–1242.
1127 doi:10.1001/archneur.1992.00530360035014.

- 1128 [8] J. Benito-León, J. Manuel Morales, J. Rivera-Navarro, A.J. Mitchell, A Review About the
1129 Impact of Multiple Sclerosis on Health-Related Quality of Life, Disability and Rehabilitation. 25
1130 (2003) 1291–1303. doi:10.1080/09638280310001608591.
- 1131 [9] A.G. Beiske, H. Naess, J.H. Aarseth, O. Andersen, I. Elovaara, M. Farkkila, H.J. Hansen, S.I.
1132 Mellgren, M. Sandberg-Wollheim, P.S. Sorensen, K.M. Myhr, Health-Related Quality of Life in
1133 Secondary Progressive Multiple Sclerosis, *Multiple Sclerosis*. 13 (2007) 386–392.
1134 doi:10.1177/13524585070130030101.
- 1135 [10] L.I. Berrigan, J.D. Fisk, S.B. Patten, H. Tremlett, C. Wolfson, S. Warren, K.M. Fiest, K.A.
1136 McKay, R.A. Marrie, Health-Related Quality of Life in Multiple Sclerosis, *Neurology*. 86 (2016)
1137 1417–1424. doi:10.1212/WNL.0000000000002564.
- 1138 [11] P.J. Jongen, Health-Related Quality of Life in Patients with Multiple Sclerosis: Impact of
1139 Disease-Modifying Drugs, *CNS Drugs*. 31 (2017) 585–602. doi:10.1007/s40263-017-0444-x.
- 1140 [12] P. Grossman, L. Kappos, H. Gensicke, M. D’Souza, D.C. Mohr, I.K. Penner, C. Steiner, MS
1141 Quality of Life, Depression, and Fatigue Improve after Mindfulness Training: A Randomized
1142 Trial, *Neurology*. 75 (2010) 1141–1149. doi:10.1212/WNL.0b013e3181f4d80d.
- 1143 [13] G. Lanza, R. Ferri, R. Bella, L. Ferini-Strambi, The impact of drugs for multiple sclerosis on
1144 sleep, *Multiple Sclerosis Journal*. 23 (2017) 5–13. doi:10.1177/1352458516664034.
- 1145 [14] A.P. Lysandropoulos, E. Havrdova, “Hidden” Factors Influencing Quality of Life in Patients with
1146 Multiple Sclerosis, *European Journal of Neurology*. 22 (2015) 28–33. doi:10.1111/ene.12801.
- 1147 [15] H.L. Zwibel, J. Smrtka, Improving Quality of Life in Multiple Sclerosis: An Unmet Need, *The*
1148 *American Journal of Managed Care*. 17 (2011) S139–S145.
- 1149 [16] R.P. di Fabio, T. Choi, J. Soderberg, C.R. Hansen, Health-Related Quality of Life for Patients
1150 with Progressive Multiple Sclerosis: Influence of Rehabilitation., *Physical Therapy*. 77 (1997)
1151 1704–1716. <http://www.ncbi.nlm.nih.gov/pubmed/9413449>.
- 1152 [17] M.E. Vore, S. Elgelid, S. Bolger, C. Parsons, R. Quashnoc, J. Raymor, Impact of a 10-Week
1153 Individualized Exercise Program on Physical Function and Fatigue of People with Multiple
1154 Sclerosis, *International Journal of MS Care*. 13 (2011) 121–126. doi:10.7224/1537-2073-

- 1155 13.3.121.
- 1156 [18] A.J. Thompson, S.E. Baranzini, J. Geurts, B. Hemmer, O. Ciccarelli, Multiple Sclerosis, The
1157 Lancet. 391 (2018) 1622–1636. doi:10.1016/S0140-6736(18)30481-1.
- 1158 [19] K. Rasova, J. Freeman, P. Martinkova, M. Pavlikova, D. Cattaneo, J. Jonsdottir, T. Henze, I.
1159 Baert, P. Van Asch, C. Santoyo, T. Smedal, A.G. Beiske, M. Stachowiak, M. Kovalewski, U.
1160 Nedeljkovic, D. Bakalidou, J.M.A. Guerreiro, Y. Nilsagård, E.N. Dimitrova, M. Habek, K.
1161 Armutlu, C. Donzé, E. Ross, A.M. Ilie, A. Martić, A. Romberg, P. Feys, The Organisation of
1162 Physiotherapy for People with Multiple Sclerosis Across Europe: A Multicentre Questionnaire
1163 Survey, BMC Health Services Research. 16 (2016). doi:10.1186/s12913-016-1750-6.
- 1164 [20] P. Martinková, J. Freeman, A. Drabinová, E. Erosheva, D. Cattaneo, J. Jonsdottir, I. Baert, T.
1165 Smedal, A. Romberg, P. Feys, J. Alves-Guerreiro, M. Habek, T. Henze, C.S. Medina, A.
1166 Beiske, P. Van Asch, D. Bakalidou, Y. Salcı, E.N. Dimitrova, M. Pavlíková, K. Řasová,
1167 Physiotherapeutic Interventions in Multiple Sclerosis Across Europe: Regions and Other
1168 Factors that Matter, Multiple Sclerosis and Related Disorders. 22 (2018) 59–67.
1169 doi:10.1016/j.msard.2018.03.005.
- 1170 [21] M. Gotta, C.A. Mayer, J. Huebner, Use of Complementary and Alternative Medicine in Patients
1171 with Multiple Sclerosis in Germany, Complementary Therapies in Medicine. 36 (2018) 113–
1172 117. doi:10.1016/j.ctim.2017.12.006.
- 1173 [22] L. Esmonde, A.F. Long, Complementary Therapy use by Persons with Multiple Sclerosis:
1174 Benefits and Research Priorities, Complementary Therapies in Clinical Practice. 14 (2008)
1175 176–184. doi:10.1016/j.ctcp.2008.03.001.
- 1176 [23] R.W. Motl, E.M. Mowry, D.M. Ehde, N.G. LaRocca, K.E. Smith, K. Costello, L. Shinto, A. V Ng,
1177 A.B. Sullivan, B. Giesser, K.K. McCully, B. Fernhall, M. Bishop, M. Plow, P. Casaccia, N.D.
1178 Chiaravalloti, Wellness and Multiple Sclerosis: The National MS Society Establishes a
1179 Wellness Research Working Group and Research Priorities, Multiple Sclerosis Journal. 24
1180 (2018) 262–267. doi:10.1177/1352458516687404.
- 1181 [24] M. Dunn, P. Bhargava, R. Kalb, Your Patients with Multiple Sclerosis have Set Wellness as a
1182 High Priority—And the National Multiple Sclerosis Society is Responding, US Neurology. 11

- 1183 (2015) 80–86. doi:10.17925/USN.2015.11.02.80.
- 1184 [25] A. Salamonsen, Use of Complementary and Alternative Medicine in Patients with Cancer or
1185 Multiple Sclerosis: Possible Public Health Implications, *The European Journal of Public Health*.
1186 26 (2016) 225–229. doi:10.1093/eurpub/ckv184.
- 1187 [26] L. Skovgaard, P.H. Nicolajsen, E. Pedersen, M. Kant, S. Fredrikson, M. Verhoef, D.W.
1188 Meyrowitsch, Use of Complementary and Alternative Medicine among People with Multiple
1189 Sclerosis in the Nordic Countries, *Autoimmune Diseases*. 2012 (2012).
1190 doi:10.1155/2012/841085.
- 1191 [27] H.-L. Park, H.-S. Lee, B.-C. Shin, J.-P. Liu, Q. Shang, H. Yamashita, B. Lim, Traditional
1192 Medicine in China, Korea, and Japan: A Brief Introduction and Comparison, *Evidence-Based
1193 Complementary and Alternative Medicine*. 2012 (2012). doi:10.1155/2012/429103.
- 1194 [28] N. Robinson, A. Lorenc, X. Liao, The evidence for Shiatsu: a systematic review of Shiatsu and
1195 acupuncture., *BMC Complementary and Alternative Medicine*. 11 (2011) 88.
1196 doi:10.1186/1472-6882-11-88.
- 1197 [29] A.F. Long, *The Practitioners within the Cross- European Shiatsu Study. Their Characteristics
1198 and an Insight into Their Practice*, School of Healthcare, University of Leeds, Leeds, UK, 2007.
1199 <http://eprints.whiterose.ac.uk/42958/>.
- 1200 [30] T. Namikoshi, *The Complete Book of Shiatsu Therapy*, 6th ed., Health Harmony, New Delhi,
1201 2013.
- 1202 [31] F. Cabo, A. Baskwill, I. Aguaristi, S. Christophe-tchakaloff, J. Guichard, Shiatsu and
1203 Acupressure: Two Different and Distinct Techniques, *International Journal of Therapeutic
1204 Massage and Bodywork*. 11 (2018) 4–10. <http://www.ncbi.nlm.nih.gov/pubmed/29881477>
1205 (accessed January 8, 2019).
- 1206 [32] Z.M. Pirie, N.J. Fox, N.J. Mathers, Delivering shiatsu in a primary care setting: Benefits and
1207 challenges, *Complementary Therapies in Clinical Practice*. 18 (2012) 37–42.
1208 doi:10.1016/j.ctcp.2011.07.001.
- 1209 [33] Japan Shiatsu College, *Collected Reports of the Shiatsu Research Lab: 1998-2012*, The

- 1210 Japan Shiatsu College, Tokyo, 2013.
- 1211 [34] G. Lanza, S.S. Centonze, G. Destro, V. Vella, M. Bellomo, M. Pennisi, R. Bella, D. Ciavardelli,
1212 Comment on “Shiatsu as an Adjuvant Therapy for Depression in Patients With Alzheimer’s
1213 Disease: A Pilot Study,” *Journal of Evidence-Based Integrative Medicine*. 24 (2019).
1214 doi:10.1177/2515690X18825105.
- 1215 [35] A.F. Long, *The Effects and Experience of Shiatsu: A Cross-European Study. Final Report*,
1216 School of Healthcare, University of Leeds, Leeds, UK, 2007.
1217 <http://eprints.whiterose.ac.uk/42957/>.
- 1218 [36] A.F. Long, L. Esmonde, S. Connolly, A Typology of Negative Responses: A Case Study of
1219 Shiatsu, *Complementary Therapies in Medicine*. 17 (2009) 168–175.
1220 doi:10.1016/j.ctim.2008.09.004.
- 1221 [37] S. Tsiormpatzis, Safety and risks of shiatsu: Protocol for a systematic review, *European*
1222 *Journal of Integrative Medicine*. 28 (2019) 20–26. doi:10.1016/j.eujim.2019.03.006.
- 1223 [38] A.F. Long, The Potential of Complementary and Alternative Medicine in Promoting Well-Being
1224 and Critical Health Literacy: A Prospective, Observational Study of Shiatsu, *BMC*
1225 *Complementary and Alternative Medicine*. 9 (2009). doi:10.1186/1472-6882-9-19.
- 1226 [39] C. Ritenbaugh, M. Verhoef, S. Fleishman, H. Boon, A. Leis, Whole Systems Research: A
1227 Discipline for Studying Complementary and Alternative Medicine, *Alternative Therapies in*
1228 *Health and Medicine*. 9 (2003) 32–36. <http://www.ncbi.nlm.nih.gov/pubmed/12868250>.
- 1229 [40] M.J. Verhoef, G. Lewith, C. Ritenbaugh, H. Boon, S. Fleishman, A. Leis, Complementary and
1230 Alternative Medicine Whole Systems Research: Beyond Identification of Inadequacies of the
1231 RCT, *Complementary Therapies in Medicine*. 13 (2005) 206–212.
1232 doi:10.1016/j.ctim.2005.05.001.
- 1233 [41] E.O. Lillie, B. Patay, J. Diamant, B. Issell, E.J. Topol, N.J. Schork, The N-of-1 Clinical Trial:
1234 The Ultimate Strategy for Individualizing Medicine?, *Personalized Medicine*. 8 (2011) 161–173.
1235 doi:10.2217/pme.11.7.
- 1236 [42] A. Porcino, *Not Birds of a Feather: Case Reports, Case Studies, and Single-Subject Research*,

- 1237 International Journal of Therapeutic Massage & Bodywork. 9 (2016) 1–2.
1238 doi:10.3822/ijtmb.v9i3.334.
- 1239 [43] A.M. Germain, A.M. Blackmore, N. Gibson, B. Newell, S.A. Williams, Effects of Adaptive
1240 Bungee Trampolining for Children With Cerebral Palsy, *Pediatric Physical Therapy*. 31 (2019)
1241 165–174. doi:10.1097/PEP.0000000000000584.
- 1242 [44] K. Koseki, H. Mutsuzaki, K. Yoshikawa, Y. Endo, T. Maezawa, H. Takano, A. Yozu, Y. Kohno,
1243 Gait Training Using the Honda Walking Assistive Device® in a Patient Who Underwent Total
1244 Hip Arthroplasty: A Single-Subject Study, *Medicina*. 55 (2019).
1245 doi:10.3390/medicina55030069.
- 1246 [45] J.A. Haegele, S.R. Hodge, The Applied Behavior Analysis Research Paradigm and Single-
1247 Subject Designs in Adapted Physical Activity Research, *Adapted Physical Activity Quarterly*.
1248 32 (2015) 285–301. doi:10.1123/APAQ.2014-0211.
- 1249 [46] M. Teut, K. Linde, Scientific Case Research in Complementary and Alternative Medicine - A
1250 Review, *Complementary Therapies in Medicine*. 21 (2013) 388–395.
1251 doi:10.1016/j.ctim.2013.04.006.
- 1252 [47] B.C. Johnston, E. Mills, N-of-1 Randomized Controlled Trials: An Opportunity for
1253 Complementary and Alternative Medicine Evaluation, *The Journal of Alternative and*
1254 *Complementary Medicine*. 10 (2004) 979–984. doi:10.1089/acm.2004.10.979.
- 1255 [48] N.J. Schork, Personalized Medicine: Time for One-Person Trials, *Nature*. 520 (2015) 609–611.
1256 doi:10.1038/520609a.
- 1257 [49] S. Vohra, N-of-1 Trials to Enhance Patient Outcomes: Identifying Effective Therapies and
1258 Reducing Harms, One Patient at a Time, *Journal of Clinical Epidemiology*. 76 (2016) 6–8.
1259 doi:10.1016/j.jclinepi.2016.03.028.
- 1260 [50] K.C. Carriere, Y. Li, G. Mitchell, H. Senior, Methodological Considerations for N-of-1 Trials, in:
1261 J. Nikles, G. Mitchell (Eds.), *The Essential Guide to N-of-1 Trials in Health*, Springer
1262 Netherlands, Dordrecht, 2015: pp. 67–80. doi:10.1007/978-94-017-7200-6_6.
- 1263 [51] The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee,

- 1264 Multiple Sclerosis Quality of Life Inventory: A User's Manual, National Multiple Sclerosis
1265 Society, New York, 1997.
1266 https://web.archive.org/web/20170828231242/http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/MSQLI_-A-User-s-Manual.pdf.
1267
- 1268 [52] J.S. Fischer, N.G. LaRocca, D.M. Miller, P.G. Ritvo, H. Andrews, D. Paty, Recent
1269 Developments in the Assessment of Quality of Life in Multiple Sclerosis (MS), Multiple
1270 Sclerosis. 5 (1999) 251–259. doi:10.1177/135245859900500410.
- 1271 [53] K. Mengersen, J.M. McGree, C.H. Schmid, Statistical Analysis of N-of-1 Trials, in: J. Nikles, G.
1272 Mitchell (Eds.), The Essential Guide to N-of-1 Trials in Health, 1st ed., Springer Science &
1273 Business Media, Dordrecht, 2015: pp. 135–153.
- 1274 [54] X. Chen, P. Chen, A Comparison of Four Methods for the Analysis of N-of-1 Trials, PLoS
1275 ONE. 9 (2014). doi:10.1371/journal.pone.0087752.
- 1276 [55] C.H. Schmid, N. Duan, The DEClDE Methods Center N-of-1 Guidance Panel, Statistical
1277 Design and Analytic Considerations for N-of-1 Trials, in: R. Kravitz, N. Duan, The DEClDE
1278 Methods Center N-of-1 Guidance Panel (Eds.), Design and Implementation of N-of-1 Trials: A
1279 User's Guide, 1st ed., Agency for Healthcare Research and Quality, Rockville, MD, 2014: pp.
1280 33–53. <https://effectivehealthcare.ahrq.gov/topics/n-1-trials/research-2014-1>.
- 1281 [56] F. Wilcoxon, Individual Comparisons by Ranking Methods, Biometrics Bulletin. 1 (1945) 80–
1282 83. doi:10.2307/3001968.
- 1283 [57] F. Wilcoxon, Some Rapid Approximate Statistical Procedures, Annals of the New York
1284 Academy of Sciences. 52 (1950) 808–814. doi:10.1111/j.1749-6632.1950.tb53974.x.
- 1285 [58] R.L. McCornack, Extended Tables of the Wilcoxon Matched Pair Signed Rank Statistic,
1286 Journal of the American Statistical Association. 60 (1965) 864–871. doi:10.2307/2283253.
- 1287 [59] P.K. Sen, P.R. Krishnaiah, 37 Selected tables for nonparametric statistics, in: Handbook of
1288 Statistics, 1984: pp. 937–958. doi:10.1016/S0169-7161(84)04039-6.
- 1289 [60] C.A. Bellera, M. Julien, J.A. Hanley, Normal Approximations to the Distributions of the
1290 Wilcoxon Statistics: Accurate to what N? Graphical Insights, Journal of Statistics Education. 18

- 1291 (2010). doi:10.1080/10691898.2010.11889486.
- 1292 [61] S. Vohra, L. Shamseer, M. Sampson, C. Bukutu, C.H. Schmid, R. Tate, J. Nikles, D.R. Zucker,
1293 R. Kravitz, G. Guyatt, D.G. Altman, D. Moher, CONSORT Extension for Reporting N-of-1 Trials
1294 (CENT) 2015 Statement, *BMJ*. 350 (2015). doi:10.1136/bmj.h1738.
- 1295 [62] J. Moeller, A Word on Standardization in Longitudinal Studies: Don't, *Frontiers in Psychology*.
1296 6 (2015). doi:10.3389/fpsyg.2015.01389.
- 1297 [63] P. Cohen, J. Cohen, L.S. Aiken, S.G. West, The Problem of Units and the Circumstance for
1298 POMP, *Multivariate Behavioral Research*. 34 (1999) 315–346.
1299 doi:10.1207/S15327906MBR3403_2.
- 1300 [64] V. Braun, V. Clarke, Using Thematic Analysis in Psychology, *Qualitative Research in*
1301 *Psychology*. 3 (2006) 77–101. doi:10.1191/1478088706qp0630a.
- 1302 [65] R. Blackwell, H. MacPherson, Multiple Sclerosis Staging and Patient Management, *Journal of*
1303 *Chinese Medicine*. (2000) 5–12.
- 1304 [66] B. Maguire, M., & Delahunt, Doing a Thematic Analysis: A Practical, Step-by-Step Guide for
1305 Learning and Teaching Scholars., *AISHE-J: The All Ireland Journal of Teaching and Learning*
1306 *in Higher Education*. 9 (2017). doi:10.1109/TIA.2014.2306979.
- 1307 [67] J.E.J. Ware, K.K. Snow, M. Kosinski, G. Barbara, SF-36 Health Survey: Manual and
1308 Interpretation Guide, The Health Institute, New England Medical Center, Boston, 1993.
- 1309 [68] C. Jenkinson, The SF-36 Physical and Mental Health Summary Measures: An Example of
1310 How to Interpret Scores, *Journal of Health Services Research & Policy*. 3 (1998) 92–96.
1311 doi:10.1177/135581969800300206.
- 1312 [69] R. Jaeschke, J. Singer, G.H. Guyatt, Measurement of Health Status: Ascertaining the Minimal
1313 Clinically Important Difference, *Controlled Clinical Trials*. 10 (1989) 407–415.
1314 doi:10.1016/0197-2456(89)90005-6.
- 1315 [70] D.A. Gelber, P.B. Jozefczyk, The Management of Spasticity in Multiple Sclerosis, *International*
1316 *Journal of MS Care*. 1 (1999) 35–49. doi:10.7224/1537-2073-1.1.35.
- 1317 [71] H.L. Zwibel, Contribution of Impaired Mobility and General Symptoms to the Burden of Multiple

- 1318 Sclerosis, *Advances in Therapy*. 26 (2009) 1043–1057. doi:10.1007/s12325-009-0082-x.
- 1319 [72] F. Bethoux, R.A. Marrie, A Cross-Sectional Study of the Impact of Spasticity on Daily Activities
1320 in Multiple Sclerosis, *The Patient - Patient-Centered Outcomes Research*. 9 (2016) 537–546.
1321 doi:10.1007/s40271-016-0173-0.
- 1322 [73] K. Milinis, A. Tennant, C.A. Young, Spasticity in Multiple Sclerosis: Associations with
1323 Impairments and Overall Quality of Life, *Multiple Sclerosis and Related Disorders*. 5 (2016)
1324 34–39. doi:10.1016Z/j.msard.2015.10.007.
- 1325 [74] C. Pozzilli, Overview of MS Spasticity, *European Neurology*. 71 (2014) 1–3.
1326 doi:10.1159/000357739.
- 1327 [75] V. Stevenson, A. Gras, J. Bárdos, J. Broughton, The High Cost of Spasticity in Multiple
1328 Sclerosis to Individuals and Society, *Multiple Sclerosis Journal*. 21 (2015) 1583–1592.
1329 doi:10.1177/1352458514566416.
- 1330 [76] J. Svensson, S. Borg, P. Nilsson, Costs and Quality of Life in Multiple Sclerosis Patients with
1331 Spasticity, *Acta Neurologica Scandinavica*. 129 (2014) 13–20. doi:10.1111/ane.12139.
- 1332 [77] T. Berger, Multiple Sclerosis Spasticity Daily Management: Retrospective Data from Europe,
1333 Expert Review of Neurotherapeutics. 13 (2013) 3–7. doi:10.1586/ern.13.3.
- 1334 [78] C. Hughes, I.M. Howard, Spasticity Management in Multiple Sclerosis, *Physical Medicine and
1335 Rehabilitation Clinics of North America*. 24 (2013) 593–604. doi:10.1016/j.pmr.2013.07.003.
- 1336 [79] S. Balantrapu, J.J. Sosnoff, J.H. Pula, B.M. Sandroff, R.W. Motl, Leg Spasticity and
1337 Ambulation in Multiple Sclerosis, *Multiple Sclerosis International*. 2014 (2014).
1338 doi:10.1155/2014/649390.
- 1339 [80] S.D. Brass, C.-S. Li, S. Auerbach, The Underdiagnosis of Sleep Disorders in Patients with
1340 Multiple Sclerosis, *Journal of Clinical Sleep Medicine*. 10 (2014) 1025–1031.
1341 doi:10.5664/jcsm.4044.
- 1342 [81] G.K. Sakkas, C.D. Giannaki, C. Karatzaferi, M. Manconi, Sleep Abnormalities in Multiple
1343 Sclerosis, *Current Treatment Options in Neurology*. 21 (2019). doi:10.1007/s11940-019-0544-
1344 7.

- 1345 [82] M. Foschi, G. Rizzo, R. Liguori, P. Avoni, L. Mancinelli, A. Lugaesi, L. Ferini-Strambi, Sleep-
1346 Related Disorders and their Relationship with MRI Findings in Multiple Sclerosis, *Sleep*
1347 *Medicine*. (2019). doi:10.1016/j.sleep.2019.01.010.
- 1348 [83] C. Veauthier, F. Paul, Sleep Disorders in Multiple Sclerosis and their Relationship to Fatigue,
1349 *Sleep Medicine*. 15 (2014) 5–14. doi:10.1016/j.sleep.2013.08.791.
- 1350 [84] M. Kaminska, R.J. Kimoff, K. Schwartzman, D.A. Trojan, Sleep Disorders and Fatigue in
1351 Multiple Sclerosis: Evidence for Association and Interaction, *Journal of the Neurological*
1352 *Sciences*. 302 (2011) 7–13. doi:10.1016/j.jns.2010.12.008.
- 1353 [85] B.R. Stanton, F. Barnes, E. Silber, Sleep and Fatigue in Multiple Sclerosis, *Multiple Sclerosis*
1354 *Journal*. 12 (2006) 481–486. doi:10.1191/135248506ms1320oa.
- 1355 [86] E.K. White, A.B. Sullivan, M. Drerup, Short Report: Impact of Sleep Disorders on Depression
1356 and Patient-Perceived Health-Related Quality of Life in Multiple Sclerosis, *International Journal*
1357 *of MS Care*. 21 (2019) 10–14. doi:10.7224/1537-2073.2017-068.
- 1358 [87] P. Qin, B.D. Dick, A. Leung, C.A. Brown, Effectiveness of Hand Self-Shiatsu to Improve Sleep
1359 Following Sport-Related Concussion in Young Athletes: A Proof-of-Concept Study, *Journal of*
1360 *Integrative Medicine*. 17 (2019) 24–29. doi:10.1016/j.joim.2018.11.002.
- 1361 [88] S.L.K.K. Yuan, A.A. Berssaneti, A.P. Marques, Effects of Shiatsu in the Management of
1362 Fibromyalgia Symptoms: A Controlled Pilot Study, *Journal of Manipulative and Physiological*
1363 *Therapeutics*. 36 (2013) 436–443. doi:10.1016/j.jmpt.2013.05.019.
- 1364 [89] C.A. Brown, G. Bostick, L. Bellmore, D. Kumanayaka, Hand self-Shiatsu for sleep problems in
1365 persons with chronic pain: a pilot study., *Journal of Integrative Medicine*. 12 (2014) 94–101.
1366 doi:10.1016/S2095-4964(14)60010-8.
- 1367 [90] M.C. Ysraelit, M.P. Fiol, M.I. Gaitán, J. Correale, Quality of Life Assessment in Multiple
1368 Sclerosis: Different Perception between Patients and Neurologists, *Frontiers in Neurology*. 8
1369 (2018). doi:10.3389/fneur.2017.00729.
- 1370 [91] M. Kremenutzky, L. Walt, Perceptions of Health Status in Multiple Sclerosis Patients and
1371 Their Doctors, *The Canadian Journal of Neurological Sciences*. 40 (2013) 210–218.

- 1372 doi:10.1017/S0317167100013755.
- 1373 [92] A.K. Stuifbergen, Physical activity and perceived health status in persons with multiple
1374 sclerosis, *Journal of Neuroscience Nursing*. 29 (1997) 238–244.
- 1375 [93] V.S. Helgeson, Social Support and Quality of Life, *Quality of Life Research*. 12 (2003) 25–31.
1376 doi:10.1023/A:1023509117524.
- 1377 [94] M. Krokavcova, J.P. van Dijk, I. Nagyova, J. Rosenberger, M. Gavelova, B. Middel, Z.
1378 Gdovinova, J.W. Groothoff, Social Support as a Predictor of Perceived Health Status in
1379 Patients with Multiple Sclerosis, *Patient Education and Counseling*. 73 (2008) 159–165.
1380 doi:10.1016/j.pec.2008.03.019.
- 1381 [95] N.B. Gabler, N. Duan, S. Vohra, R.L. Kravitz, N-of-1 Trials in the Medical Literature, *Medical
1382 Care*. 49 (2011) 761–768. doi:10.1097/MLR.0b013e318215d90d.
- 1383 [96] A. Sunderland, Single-Case Experiments in Neurological Rehabilitation, *Clinical Rehabilitation*.
1384 4 (1990) 181–192. doi:10.1177/026921559000400301.
- 1385 [97] B.J. Byiers, J. Reichle, F.J. Symons, Single-Subject Experimental Design for Evidence-Based
1386 Practice, *American Journal of Speech-Language Pathology*. 21 (2012) 397–414.
1387 doi:10.1044/1058-0360(2012/11-0036).
- 1388 [98] E. Ernst, Single-Case Studies in Complementary/Alternative Medicine Research,
1389 *Complementary Therapies in Medicine*. 6 (1998) 75–78. doi:10.1016/S0965-2299(98)80079-4.
- 1390 [99] E.S. Edgington, Randomized Single-Subject Experimental Designs, *Behaviour Research and
1391 Therapy*. 34 (1996) 567–574. doi:10.1016/0005-7967(96)00012-5.
- 1392 [100] S. Senn, *Cross-Over Trials In Clinical Research*, 2nd ed., John Wiley & Sons, Chichester, UK,
1393 2002.
- 1394 [101] E.J. Mills, A.-W. Chan, P. Wu, A. Vail, G.H. Guyatt, D.G. Altman, Design, Analysis, and
1395 Presentation of Crossover Trials, *Trials*. 10 (2009). doi:10.1186/1745-6215-10-27.
- 1396 [102] G. D'Angelo, D. Potvin, J. Turgeon, Carry-Over Effects in Bioequivalence Studies, *Journal of
1397 Biopharmaceutical Statistics*. 11 (2001) 35–43. doi:10.1081/BIP-100104196.

- 1398 [103] S.J. Senn, Cross-Over Trials, Carry-Over Effects and the Art of Self-Delusion, *Statistics in*
1399 *Medicine*. 7 (1988) 1099–1101. doi:10.1002/sim.4780071010.
- 1400 [104] M. Chen, H. Zheng, J. Li, D. Huang, Q. Chen, J. Fang, Non-Pharmacological Treatments for
1401 Adult Patients with Functional Constipation: A Systematic Review Protocol, *BMJ Open*. 2014
1402 (2014). doi:10.1136/bmjopen-2014-004982.
- 1403 [105] M. Hills, P. Armitage, The Two-Period Cross-Over Clinical Trial, *British Journal of Clinical*
1404 *Pharmacology*. 8 (1979) 7–20. doi:10.1111/j.1365-2125.1979.tb05903.x.
- 1405 [106] N.H.G. Holford, L.B. Sheiner, Understanding the Dose-Effect Relationship: Clinical Application
1406 of Pharmacokinetic-Pharmacodynamic Models, *Clinical Pharmacokinetics*. 6 (1981) 429–453.
1407 doi:10.2165/00003088-198106060-00002.
- 1408 [107] T.J.M. Cleophas, A Simple Method for the Estimation of Interaction Bias in Crossover Studies,
1409 *The Journal of Clinical Pharmacology*. 30 (1990) 1036–1040. doi:10.1002/j.1552-
1410 4604.1990.tb03591.x.
- 1411 [108] P. Armitage, Should we Cross Off the Crossover?, *British Journal of Clinical Pharmacology*. 32
1412 (1991) 1–2. doi:10.1111/j.1365-2125.1991.tb05604.x.
- 1413 [109] J.-P. Liu, K.-J. Chen, The Guideline Development Team, Methodology Guideline for Clinical
1414 Studies Investigating Traditional Chinese Medicine and Integrative Medicine, *Complementary*
1415 *Therapies in Medicine*. 23 (2015) 751–756. doi:10.1016/j.ctim.2015.08.001.
- 1416 [110] J. Riddoch, S. Lennon, Single Subject Experimental Design: One Way Forward?,
1417 *Physiotherapy*. 80 (1994) 215–218. doi:10.1016/S0031-9406(10)61299-0.
- 1418 [111] G. Lanza, S.S. Centonze, G. Destro, V. Vella, M. Bellomo, M. Pennisi, R. Bella, D. Ciavardelli,
1419 Shiatsu as an Adjuvant Therapy for Depression in Patients with Alzheimer’s Disease: A Pilot
1420 Study, *Complementary Therapies in Medicine*. 38 (2018) 74–78.
1421 doi:10.1016/j.ctim.2018.04.013.
- 1422 [112] D. Ilic, A. Djurovic, Z. Brdareski, A. Vukomanovic, V. Pejovic, M. Grajic, The Position of the
1423 Chinese Massage (Tuina) in Clinical Medicine, *Military-Medical and Pharmaceutical Review =*
1424 *Vojnosanitetski Pregled*. 69 (2012) 999–1004. doi:10.2298/VSP110104013I.

- 1425 [113] L. Ming, L. Xiaoyan, Insomnia Due to Deficiency of Both the Heart and Spleen Treated by
1426 Acupuncture-Moxibustion and Chinese Tuina, *Journal of Traditional Chinese Medicine*. 28
1427 (2008) 10–12. doi:10.1016/S0254-6272(08)60004-7.
- 1428 [114] A. Jackson, H. MacPherson, S. Hahn, Acupuncture for Tinnitus: A Series of Six n=1 Controlled
1429 Trials, *Complementary Therapies in Medicine*. 14 (2006) 39–46.
1430 doi:10.1016/j.ctim.2005.07.005.
- 1431 [115] C. Paterson, C. Baarts, L. Launsø, M.J. Verhoef, Evaluating Complex Health Interventions: A
1432 Critical Analysis of the “Outcomes” Concept, *BMC Complementary and Alternative Medicine*. 9
1433 (2009). doi:10.1186/1472-6882-9-18.
- 1434 [116] A.J. Carr, I.J. Higginson, Measuring Quality of Life: Are Quality of Life Measures Patient
1435 Centred?, *BMJ*. 322 (2001) 1357–1360. doi:10.1136/bmj.322.7298.1357.
- 1436 [117] C.A. O’Boyle, The Schedule for the Evaluation of Individual Quality of Life (SEIQoL): The
1437 Concept of Quality of Life in Clinical Research, *International Journal of Mental Health*. 23
1438 (1994) 3–23. <http://www.jstor.org/stable/41344691>.
- 1439 [118] C. Paterson, Measuring Outcomes in Primary Care: a Patient Generated Measure, MYMOP,
1440 Compared with the SF-36 Health Survey, *BMJ*. 312 (1996) 1016–1020.
1441 doi:10.1136/bmj.312.7037.1016.
- 1442 [119] A. Broom, Using Qualitative Interviews in CAM Research: A Guide to Study Design, Data
1443 Collection and Data Analysis, *Complementary Therapies in Medicine*. 13 (2005) 65–73.
1444 doi:10.1016/j.ctim.2005.01.001.
- 1445 [120] Z. Pirie, *The Impact of Delivering Shiatsu in General Practice*, University of Sheffield, 2003.
1446 <http://etheses.whiterose.ac.uk/4214/> (accessed May 29, 2018).
- 1447 [121] G. Lewith, Can Practitioners be Researchers?, *Complementary Therapies in Medicine*. 12
1448 (2004) 2–5. doi:10.1016/j.ctim.2003.12.004.
- 1449 [122] J. Wardle, More Integrative Research is Needed: But Where will it Come From?, *Advances in*
1450 *Integrative Medicine*. 3 (2016) 1–2. doi:10.1016/j.aimed.2016.07.005.
- 1451 [123] F. de A. Andrade, C.F.S. Portella, *Research Methods in Complementary and Alternative*

- 1452 Medicine: an Integrative Review, *Journal of Integrative Medicine*. 16 (2018) 6–13.
1453 doi:10.1016/j.joim.2017.12.001.
- 1454 [124] A.F. Long, S. Connolly, Advice Giving and Advice Taking: Potential Contribution of Shiatsu in
1455 Promoting Health and Well-Being, *European Journal of Integrative Medicine*. 1 (2008) 38.
1456 doi:10.1016/j.eujim.2008.08.073.
- 1457 [125] I.Z. Chirali, Complementary and Alternative Medicine (CAM) Therapies that Can Safely
1458 Introduce Cupping to their Treatment Protocol, in: *Traditional Chinese Medicine Cupping
1459 Therapy*, 3rd ed., Churchill Livingstone, Edinburgh, 2014: pp. 72–78. doi:10.1016/B978-0-
1460 7020-4352-9.00006-0.
- 1461 [126] A. Hart, C.J. Sutton, N-of-1 Trials and their Combination: Suitable Approaches for CAM
1462 Research?, *Complementary Therapies in Medicine*. 11 (2003) 213–214. doi:10.1016/S0965-
1463 2299(03)00139-0.
- 1464 [127] C. Beresford-Cooke, What is Shiatsu?, in: *Shiatsu Theory and Practice*, 3rd ed., Churchill
1465 Livingstone, Edinburgh, 2011: pp. 3–4.
- 1466 [128] G. Adams, Shiatsu in Britain and Japan: Personhood, Holism and Embodied Aesthetics,
1467 *Anthropology & Medicine*. 9 (2002) 245–265. doi:10.1080/13648470216334.
- 1468 [129] C. Dubitsky, At your Table, in: *Bodywork Shiatsu*, Healing Art Press, Rochester, 1997: pp.
1469 115–120.
- 1470 [130] N. Browne, P. Bush, F. Cabo, Relieving Pressure – An Evaluation of Shiatsu Treatments for
1471 Cancer and Palliative Care Patients in an NHS Setting, *European Journal of Integrative
1472 Medicine*. 21 (2018) 27–33. doi:10.1016/j.eujim.2018.06.002.
- 1473 [131] J. Ruutiainen, A.-M. Viita, J. Hahl, J. Sundell, H. Nissinen, Burden of Illness in Multiple
1474 Sclerosis (DEFENSE) Study: The Costs and Quality-of-Life of Finnish Patients with Multiple
1475 Sclerosis, *Journal of Medical Economics*. 19 (2016) 21–33.
1476 doi:10.3111/13696998.2015.1086362.
- 1477 [132] N. Moise, D. Wood, Y.K.K. Cheung, N. Duan, T. St. Onge, J. Duer-Hefele, T. Pu, K.W.
1478 Davidson, I.M. Kronish, C. Alcantara, P. Appelbaum, E. Carter, E. Cohn, R. Kravitz, S. Kelly, J.

- 1479 Luchsinger, T. Ridenour, M. Romandetto, J. Shaffer, S. Shea, Patient Preferences for
1480 Personalized (N-of-1) Trials: a Conjoint Analysis, *Journal of Clinical Epidemiology*. 102 (2018)
1481 12–22. doi:10.1016/j.jclinepi.2018.05.020.
- 1482 [133] W.E. Mehling, Z. DiBlasi, F. Hecht, Bias Control in Trials of Bodywork: A Review of
1483 Methodological Issues, *The Journal of Alternative and Complementary Medicine*. 11 (2005)
1484 333–342. doi:10.1089/acm.2005.11.333.
- 1485

EUJIM_2019_101006-Accepted_Manuscript