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**PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL
THERAPY IN PATIENTS WITH TEMPOROMANDIBULAR
DISORDERS:
A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY**

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**PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN
PATIENTS WITH TEMPOROMANDIBULAR DISORDERS:
A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY**

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3 **44 ABSTRACT**
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5 **45 Introduction**
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7
8 46 Temporomandibular Disorders (TMD) are principally characterised by pain in the
9
10 47 craniomandibular area and probable limitations of jaw opening. Manual therapy, like other
11
12 48 recommended conservative treatments included in clinical guidelines, is commonly used to
13
14 49 treat patients with TMD to reduce pain and improve function. However, outcomes may be
15
16 50 variable. In this study we will use a unique combination of patient-reported outcome
17
18 51 measures and clinical tests to identify predictors associated with pain reduction in patients
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20 52 with TMD following manual therapy. Such knowledge will support a more personalised
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22 53 management approach by facilitating clinical decision-making.
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26 **54 Methods/analysis**
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28 55 An observational prospective design will recruit a cohort of 100 adults with a diagnosis of
29
30 56 TMD (according to Axis I of the Diagnostic Criteria for TMD) at a Dental Hospital in Italy.
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32 57 Patients will be treated with four weekly sessions of manual
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34 58 therapy applied to craniomandibular structures. An array of
35
36 59 predictors has been chosen based on previous research on
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38 60 prognostic factors for TMD and altered pain modulation in
39
40 61 musculoskeletal disorders. Candidate predictors including
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42 62 demographic variables, general health variables, psychosocial
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44 63 features, TMD characteristics, and clinical tests of the
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46 64 temporomandibular joint and masticatory muscles will be
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48 65 collected at baseline. Definition of good outcome is a clinically
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50 66 significant reduction of pain intensity over the last week ($\geq 30\%$
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52 67 reduction Visual Analogue Scale) immediately following the 4-
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3 68 week intervention. Exploratory factor analysis will be applied to
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6 69 analyse factor loading of candidate predictors for good outcome at
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8
9 70 4 weeks. Subsequently, a logistic multivariable regression model
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11 71 will be performed to calculate low and high risk of good outcome.

12 13 72 **Ethics and dissemination**

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15
16 73 Ethical approval will be obtained from the “Fondazione IRCCS Ca’ Granda Ospedale
17
18 74 Maggiore Policlinico” and University of Birmingham Ethics Committee. The results will be
19
20
21 75 submitted for publication in a peer-reviewed journal and presented at conferences.

22
23
24 76 Keywords: Temporomandibular Disorders, Temporomandibular Joint Dysfunction
25 77 Syndrome, Pain, Prediction, Manual Therapy

26 78
27 79 Word count: 3322 [excluding references]
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33 81 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 34
35 82 ▪ This will be the first study to identify predictors associated with pain reduction
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38 83 following manual therapy interventions in patients with TMD
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40 84 ▪ The study will utilise a comprehensive array of candidate factors to predict clinically
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43 85 relevant pain reduction
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45 86 ▪ The implications from this study will facilitate clinical decision-making for manual
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47 87 therapists managing patients with TMD
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49 88 ▪ Alternative or additional predictors could be valuable to include but the candidate
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51 89 predictors have been prioritised as they are reliable and valid measures which have a
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53 90 relationship with pain
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55 91 ▪ The study could potentially generate a non-representative sample of patients as it will
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57 92 exclude people who have already received recent treatment for their TMD
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INTRODUCTION

Temporomandibular Disorders (TMD) affect approximately 10% of the adult population and, in the USA alone, are estimated to cost US\$4 billion per year on management (Lipton et al. 1993; NIDCR, 2014). TMD are principally characterised by pain and limitations of jaw opening (de Leeuw & Klasser, 2013) but many patients also complain of neck and back pain or pain at other sites (Plesh et al. 2011).

Physical therapy is one of the most common conservative interventions for the management of TMD (Calixtre et al., 2016) and given that the aetiology may be unclear (Slade et al., 2016), several therapeutic approaches have been described (Coskun Benlidayi et al., 2016). One approach is manual therapy applied to the craniomandibular structures with evidence suggesting a significant reduction in pain with manual therapy treatment (Armijo-Olivo et al., 2016), although responses are highly variable (Kalamir et al., 2013). In other musculoskeletal pain disorders, such as neck or back pain, pain reduction from manual therapy has been shown to be superior to other treatments (e.g. therapeutic exercise) when targeted towards patients with specific clinical features including the onset of symptoms within 30 days (Flynn et al., 2002; Cleland et al., 2007). Nevertheless, in TMD, no previous study has investigated patient factors associated with significant pain reduction following manual therapy. Such knowledge could be achieved by identifying potential predictors (e.g. pain characteristics, psychosocial features, TMD characteristics) of pain reduction following

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2
3 118 manual therapy interventions in patients with TMD to support a more personalised
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5 119 management approach.

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7
8 120 Very few studies have examined factors associated with pain reduction in patients
9
10 121 with TMD. Forssell et al. (2016) conducted a prospective cohort study with 263 primary care
11
12 122 patients with TMD pain. They analysed several potential predictors of persistent pain at one-
13
14 123 year follow-up including demographic, pain-related and psychosocial variables. It was
15
16 124 concluded that patients with TMD who have had numerous previous healthcare visits,
17
18 125 complained of high-intensity pain at other body sites and had a greater number of disability
19
20 126 days, were at greater risk of having pain one year after the initial assessment. Nevertheless,
21
22 127 this study did not examine predictors of pain reduction related to a therapeutic intervention
23
24 128 which could be useful to inform clinical practice. Kapos et al. (2018) investigated the
25
26 129 association of long-term pain intensity with baseline health-related quality of life and jaw
27
28 130 functional limitation in patients with TMD. Findings suggested that baseline health-related
29
30 131 quality of life is inversely proportional with pain intensity at an eight-year follow-up
31
32 132 regardless of the type of treatment that they received (e.g. surgery, drugs, physical therapy or
33
34 133 unconventional therapy). After adjusting for the type of treatments received, by clustering the
35
36 134 participants into three groups (medical/conventional management, alternative medicine, and
37
38 135 surgical intervention), each predictor analysed (demographic, pain-related and health-related
39
40 136 quality of life) maintained similar statistical significance. Notwithstanding, the group
41
42 137 classified as “medical/ conventional management” included participants receiving diverse
43
44 138 treatments ranging from physical therapy, pharmacology (Acetaminophen, Antidepressants,
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46 139 Anti-inflammatories) to the application of a mouth appliance. This previous work can
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48 140 facilitate clinicians to identify patients who are more challenging to treat by identifying
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50 141 clinical features associated with persistent pain in the long term regardless of the type of
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3 142 interventions applied. However, currently no study has examined predictive factors
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5 143 associated with pain reduction following manual therapy interventions in patients with TMD.
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8 144 In this study we will use a combination of: (1) demographical variables, (2) general
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10 145 health variables, (3) psychosocial features, (4) TMD characteristics, and (5) clinical tests of
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12 146 the temporomandibular joint and masticatory muscles to identify predictors associated with
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14 147 pain reduction in patients with TMD following manual therapy applied to craniomandibular
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16 148 structures. The knowledge gained from this study will facilitate clinical decision-making for
17
18 149 manual therapists managing patients with TMD by providing clinicians with key factors to
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20 150 evaluate, to determine whether or not the patient is likely to have a clinically relevant
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22 151 reduction in their pain immediately following four weekly applications of manual therapy.
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28 153 **METHODS AND ANALYSIS**

30 31 154 **Source of data**

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34 155 A prospective observational study will recruit a cohort of patients referred to the
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36 156 Italian Stomatologic Institute with a TMD diagnosis according to the Axis I of the Diagnostic
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38 157 Criteria for TMDs (DC/TMD) (Shiffman et al., 2014). This protocol is written according to
39
40 158 the Transparent Reporting of a multivariable prediction model for Individual Prognosis or
41
42 159 Diagnosis (TRIPOD) statement (Collins et al., 2015) in which recommendations are provided
43
44 160 about prediction model development and validation. Ethical clearance will be obtained from
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46 161 the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
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48 162 and the University of Birmingham Ethics Committee, and the study will be conducted in
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50 163 accordance with the Declaration of Helsinki.
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56 164 Patient reported and physical assessment data will be collected at baseline prior to
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58 165 commencing treatment. Outcome will be collected at the end of the fourth session of
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3 166 craniomandibular manual therapy (at one month). This timeline has been selected based on
4
5 167 previous studies investigating 1) the effects of manual therapy on pain (Bishop et al., 2015;
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7 168 Vigotsky et al., 2015); and 2) work confirming the effectiveness of manual therapy for TMD
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9 169 patients (Calixtre et al., 2015) and is believed to be reasonable for the purposes of this study.
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13 170 **Setting and Participants**

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15 171 Participant recruitment will be carried out at the TMJ Unit of the Italian Stomatological
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17 172 Institute (Dental Hospital) in Milan, Italy over a period of up to 12 months (planned start date
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19 173 July 2019). Consecutive eligible participants will be approached for recruitment until the
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21 174 sample size is reached.
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25 175 *Eligibility criteria*

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27 176 Inclusion criteria: (1) adults aged ≥ 18 years; (2) TMD diagnosis
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29 177 according to the Axis I of the Diagnostic Criteria for TMDs (DC/TMD)
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31 178 (Shiffman et al., 2014); (3) no therapeutic interventions reported
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33 179 (for their TMD) in the past six months (Wahlund et al., 2015); (4)
34
35 180 capacity to use and understand written and verbal Italian language;
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37 181 (5) mental capacity to provide informed consent.
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43 182 Exclusion criteria: (1) TMD pain related to rheumatoid/inflammatory arthritis (2) any
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45 183 physical or mental condition that could potentially influence the study. Additionally, patients
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47 184 will be excluded if (3) they commence another treatment for their TMD (pharmacology, oral
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49 185 appliance, others) throughout the duration of the study.
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54 187 **Recruitment**

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57 188 Based on feasibility data from the last 5 years of activity at the TMJ Unit of Italian
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59 189 Stomatologic Institute, it is estimated that at least 130 eligible participants will be available
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3 190 for recruitment over 13 months. According to previous observational studies on the
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5 191 prediction of outcomes in musculoskeletal disorders, it is estimated that 75% of eligible
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7 192 participants will consent to participation [100 participants] (Flynn et al., 2002; Cleland et al.,
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9 193 2007).

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12 194 All patients attending the TMJ Unit will be screened for the presence of a TMD. One
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14 195 expert dentist with >10 years' experience in the management of patients with TMD, will
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16 196 confirm the TMD diagnosis and, in accordance with the inclusion/exclusion criteria, will
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18 197 explain the study to the potential participant and provide the patient information sheet.
19
20 198 Participants will then give their written informed consent prior to inclusion in the study.
21
22 199 Afterwards, the participant will be referred to see a physiotherapist [independent assessor, >5
23
24 200 years' experience in managing patients with TMD] for the baseline assessments (summarised
25
26 201 in Table 1) and then treatment will commence within the same week. After the last session
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28 202 (i.e. one month from baseline), the participants will be assessed again by the assessing
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30 203 physiotherapist to measure outcome. Participant flow through the study is outlined in Figure
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40 [FIGURE 1]
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44 208 **Treatment**

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46 209 Participants will receive four sessions of manual therapy applied to craniomandibular
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48 210 structures over 4 weeks (Crockett et al., 1986; Guarda-Nardini et al., 2012; Nascimento et al.,
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50 211 2013). Two physiotherapists, each with >5 years' experience in manual therapy / TMD will
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52 212 perform the treatments. They will not be involved in participant recruitment, assessment or
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54 213 the collection of the outcome measure. Manual therapy techniques will be based on the
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56 214 clinical examination, and will be selected at the discretion of the treating physiotherapist
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3 215 according to their clinical reasoning of the individual case. Overall, the application of manual
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5 216 therapy aims to decrease pain by treating masticatory muscle trigger points, muscle tightness,
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7 217 and restricted temporomandibular joint movements. Several techniques will be considered
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9 218 including: (i) ventral and caudal anterior glide temporomandibular joint mobilization
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11 219 (Cleland et al. 2004); (ii) soft tissue interventions for the management of trigger points in
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13 220 masticatory muscles (Miernik et al. 2012); (iii) myofascial induction therapy [functional
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15 221 restoration of the fascial system] applied to craniomandibular structures (Fernández-de-la-
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17 222 Peñas et al. 2018).

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21 223 The structures targeted in the treatment sessions will be the temporomandibular joint,
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23 224 temporal muscles, masseter muscles, medial and lateral pterygoid muscles and suprahyoid
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25 225 muscles, applied at the discretion of the physiotherapist based on the patient's individual
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27 226 presentation. During the treatment sessions, the treating physiotherapists will provide
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29 227 explanations about the patient's condition and answer any participant questions by promoting
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31 228 general advice. The treatment sessions will last from 20 to 30 minutes duration. No other
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33 229 treatment (e.g. oral appliance) will be performed for the management of their TMD. If during
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35 230 the course of the four-week intervention, a patient seeks treatment for an acute episode of
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37 231 pain at another site (e.g. neck pain, low back pain, shoulder pain) they will be withdrawn
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39 232 from the study.
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47 234 **Outcome**

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49 235 The outcome being predicted by the prediction model is pain intensity since patients
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51 236 with TMD typically report pain to be their primary problem (de Leeuw & Klasser, 2013),
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53 237 manual therapy is largely known to be effective principally for pain modulation (Bialosky et
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55 238 al., 2009) and change in pain intensity has most commonly been the primary outcome of
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3 239 choice in several other studies of patients with TMD (Kalamir et al., 2010; Gomes et al.,
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5 240 2014; Tuncer et al., 2013; Von Piekartz et al., 2013).

7 241 Pain intensity will be calculated by averaging the ratings of current pain, average pain
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9 242 in the past week, and worst pain in the past week using the Visual Analogue Scale (VAS),
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11 243 consisting of a horizontal line measuring 10 cm (without marks), with “no pain” written at the
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13 244 left extremity, and “worst pain imaginable” at the right extremity (Haefeli et al., 2005). The
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15 245 VAS is a reliable and valid scale to assess pain intensity as an
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17 246 outcome measure in intervention studies (Dworkin et al. 2005).

18
19 247 Based on the Initiative on Methods, Measurement, and Pain
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21 248 Assessment in Clinical Trials (IMMPACT) recommendations about
22
23 249 TMD reviewed by Haythornthwaite (2010), a reduction of at least 30%
24
25 250 of the VAS score for pain intensity is considered clinically
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27 251 significant. Consequently, a reduction in the total VAS score [\geq
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29 252 30%] will be defined as a good outcome. The outcome measure will be
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31 253 evaluated by the same independent assessor to minimise detection bias (Higgins et al., 2011).

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33 254 To capture a potential change in function which may occur with a change in pain
34
35 255 intensity, patients will also complete the patient specific functional scale [PSFS] (Stratford et
36
37 256 al. 1995) pre and post treatment. The PSFS is a self-reported outcome measure assessing
38
39 257 functional change in patients with musculoskeletal disorders (Horn et al., 2012; Abbott et al.,
40
41 258 2014). It is responsive to clinically significant change over time (Maughan et al., 2010).
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43 259 Patients will be invited to rate, on an 11-point scale, their level of difficulty performing at least
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45 260 three different daily activities. Following the treatment, patients will be required to score again
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47 261 the activities previously rated. The PSFS is a valid, reliable, and responsive outcome measure
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262 with a high test-retest reliability in different musculoskeletal disorders such as low back and
 263 neck pain (Hefford et al., 2012; Westaway et al., 1998; Chatman et al., 1997).

264

265 **Candidate predictors**

266 The candidate predictors that have been chosen are reliable and valid measures which
 267 have a relationship with pain. The selection is based on previous research on prognostic factors
 268 for TMD and altered pain modulation in musculoskeletal disorders (Bair et al., 2016; Clark et
 269 al., 2017). Candidate predictors are summarised in Table 1, with further detail in
 270 Supplementary file S1. All data collection will be standardised through protocols and clinical
 271 report forms.

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275 **Table 1: Summary of candidate predictors.**

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| Domain / Candidate predictor | Measure / data item |
|---|---|
| Demographical variables | |
| Age | Years |
| Gender | Female / male |
| Education | Basic education, intermediate education and university-level education |
| General health variables | |
| Health-related quality of life | EuroQol EQ-5D-5L (Brooks et al., 1996) |
| Sleep quality | 11-point [0-10] Numerical Rating Scales, relating to current pain, from 'best possible sleep' to 'worst possible sleep' (Cappelleri et al., 2009) |
| Psychosocial features | |
| Coping strategies applied during a painful experience | Coping Strategies Questionnaire 27 [CSQ-27](Monticone et al., 2014) |

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|--|---|
| Anxiety and depression | Hospital Anxiety and Depression Scales [HADS] (Zigmond et al., 1983) |
| Treatment expectation | Positive / negative expectation (Puentedura et al., 2012) |
| TMD characteristics | |
| Pain duration | Days |
| Pain intensity | VAS: averaging ratings of current pain, average pain, and worst pain in the past week (Davis et al., 2014) |
| Pain location | Pain drawing as described by Shiffman et al. (2014) in the protocol of Diagnostic Criteria for TMD (DC/TMD) |
| Central sensitization | Central Sensitization Inventory (CSI) (Mayer et al., 2012) |
| Classification of TMD | In according to DC/TMD (Shiffman et al., 2014) Taxonomic Classification of TMD: TMJ Disorders, Masticatory Muscle Disorders, Mixed Disorders |
| Parafunction | Oral Behaviours Checklist [OBC] (Ohrbach et al., 2008) |
| Characteristic pain intensity and disability | RDC/TMD Axis II GCPS scores (Characteristic Pain Intensity (CPI) and disability points based on disability score and disability days) using the Italian version of the RDC/TMD questionnaire [www.rdc-tmdinternational.org] |
| Morning pain intensity after sleeping | VAS: average pain at morning after sleeping in the past month |
| TMJ and masticatory muscles clinical test | |
| TMJ range of motion | Maximal Mouth Opening (MMO) without pain measured in mm through a ruler as described by Shiffman et al. (2014) in the DC/TMD protocol |
| TMJ palpation pain | Dynamic TMJ lateral pole palpation [1 kg of palpation pressure] in according to DC/TMD protocol (Shiffman et al., 2014) Score range: 0-1 [no pain =0; pain = 1] |
| Muscle palpation pain | Palpation in the following 6 bilateral points: lateral pterygoid area [0.5 kg intraoral palpation], temporalis tendon [0.5 kg intraoral palpation], masseter muscle [1 kg extraoral palpation] as described by Shiffman et al. (2014) in the DC/TMD protocol. Score range: 0-1 [< 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain = 1] |
| JAw-test | Immediate effects of brief intraoral MT techniques on pain [VRS] and TMJ range of motion [MMO]. A standardised procedure is fully described in Supplementary file S1. Score range 0-2: [0 = no change; 1 = pain improvement or MMO improvement; 2 = improvement of both] |

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279 **Data handling**

280 Candidate predictors will be collected by independent physiotherapist assessor. All data
281 will be confidentially secured by storing it on a password-protected computer attainable only
282 by the principal investigators (GA). All individual details will be replaced with ID codes. At
283 the end of the data collection, all data stored on the principal investigator's computer will be
284 transferred securely to a server at the Centre of Precision Rehabilitation for Spinal Pain at
285 Birmingham University where the data will be analysed. All data will be stored on a secure
286 server at the University of Birmingham for a period of 10-years in line with Research
287 Governance procedures. Data will be analysed using IBM SPSS Statistics (Version 25, IBM).

288 **Sample Size**

289 Exploratory factor analysis will be utilised to reduce the number of predictors (Fabrigar
290 et al., 1999). This method will guarantee an adequate sample size (at least 10 cases per
291 candidate predictor) to power the final regression analysis (Peduzzi et al., 1996; Vittinghoff et
292 al., 2007). Data will be collected for a sample size of 100 participants so that, considering 10%
293 of potential drops out, final data are available for 90 participants.

294 **Statistical analysis methods**

295 A flow diagram will report eligible participants, examined for eligibility, confirmed
296 eligible, recruited into the study, completed follow-up and analysed. Reasons for non-
297 participation, exclusion, drop-outs and withdrawal will be fully documented and all missing
298 data of participants will be reported. Participant characteristics (candidate predictors - Table 1)
299 will be summarised with a descriptive method.

300 A primary phase of the exploratory data analysis will
301 summarise data to implement the predictive model (Shmueli, 2010).
302 Multicollinearity between candidate predictors will be assessed at

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3 303 baseline. Outcome [VAS pain intensity] will be split into good versus
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6 304 poor as described previously [good outcome: reduction in VAS score
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8 305 $\geq 30\%$] (Haythornthwaite, 2010). Exploratory factor analysis will be
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11 306 applied to analyse factor loading of candidate predictors (summary
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14 307 scores) on good outcome at one month. This process will reduce
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16 308 candidate predictors (supported by the cohort sample of 90) to enter
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19 309 into the final model.

20
21 310 The statistical model has been designed a priori. To investigate the impact of each
22
23 311 predictive factor on good outcome, a logistic multivariable regression model will be performed.
24
25 312 For each candidate predictor, the mean differences or the odds ratio with their 95% confidence
26
27 313 intervals will be calculated. A multiple imputation analysis (Sterne et al., 2009) will be applied
28
29 314 to manage possible missing data. The multivariable analysis will initially consider all candidate
30
31 315 predictors. In the case of a high correlation between candidate predictors, a reduced
32
33 316 multivariate analysis will be considered.
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40 318 **DISCUSSION**

41
42 319 There is a need to identify predictors for pain reduction in patients with TMD following
43
44 320 specific treatments in order to inform clinical decision-making. Several therapies are described
45
46 321 for patients with TMD such as the use of oral appliances, different types of physical therapy
47
48 322 modalities, pharmacology or temporomandibular joint arthrocentesis yet the amount of pain
49
50 323 relief that different people receive from each intervention is variable (Armijo-Olivo et al., 2016;
51
52 324 Calixtre et al., 2016). As shown by Forssell et al. (2016) and Kapos et al. (2018), many patients
53
54 325 continue to experience pain following such interventions. Investigating factors associated with
55
56 326 pain relief to such treatments can facilitate clinical assessment and treatment selection.
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3 327 Physical therapy is one of the most common conservative interventions to treat TMD
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5 328 (Calixtre et al., 2016). Among different physical therapy modalities, manual therapy can
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7
8 329 provide symptom and functional improvements (Armijo-Olivo et al., 2016) including pain
9
10 330 relief (Kalamir et al., 2013; Gomes et al., 2014). Knowledge of predictive factors associated
11
12 331 with good outcome to a specific intervention such as manual therapy applied to
13
14 332 craniomandibular structures will facilitate clinical decision making. Ultimately, such
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16
17 333 knowledge will lead to improved clinical and cost effectiveness of rehabilitation approaches.

18 19 334 **Quality assurance**

20
21 335 Only participants that have not received therapeutic intervention for their TMD in the
22
23 336 past six months will be included in the current study. It is possible that such eligibility criteria
24
25 337 could generate selection bias. To address this potential bias, the number of eligible and included
26
27 338 subjects with the reason for non-participation will be documented.

28 29 339 **Patient and Public Involvement**

30
31 340 The research question in this study was developed following consultations and
32
33 341 discussion with patients. Patients will not be involved in the analysis and data collection but
34
35 342 will contribute to data interpretation and production of a lay summary of the findings.

36 37 343 **Ethics and Dissemination**

38
39 344 The research protocol has been submitted to the Ethics Committee of the “Fondazione
40
41 345 IRCCS Ca’ Granda Ospedale Maggiore Policlinico” and subsequently will be submitted to the
42
43 346 University of Birmingham Ethics Committee for approval. Researchers will inform all
44
45 347 participants on the characteristics of the research and will obtain written consent. Participants
46
47 348 will be informed that they are free to withdraw from the study at any time, without needing to
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49 349 provide reason. Any concerns for a participant by the study team will be fed back to the primary
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51 350 investigator (GA). Baseline characteristics of withdrawn participants will be compared to those
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3 351 of retained participants to assess for any differences. In the event of any unlikely adverse
4
5 352 events, this will be immediately reported by the principal investigator to the ethics committee.
6
7

8 353 The results of this study will submitted for publication in a peer review journal and
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10 354 presented at conferences.
11

12 355

14 356 **Limitations**

16
17 357 The study could potentially generate a non-representative sample of patients with TMD
18
19 358 due to the exclusion of some participants, which may be more likely to commence other
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21 359 treatments thereby reducing the external validity and the generalisability of the results.
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23

24 360 **Conclusion**

25
26 361 This will be the first study to identify factors associated with pain reduction following
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28 362 manual therapy in patients with TMD and the knowledge gained from this study stands to
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30 363 facilitate clinical decision making for manual therapists managing patients with TMD.
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671 **Author Contributions**

672 GA, AEB and DF formulated the research question and study focus. GA drafted the initial
673 version of the manuscript with DF. All authors provided guidance on topic, methodology and

1
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3 674 analyses. All authors reviewed and commented on each draft of the protocol. All authors have
4
5 675 approved the final manuscript. DF is guarantor
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9

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11
12 678 or not-for-profit sectors.
13

14 679 **Competing Interests Statement**
15

16
17 680 The authors have no competing interests to report.
18

19 681 **Data sharing statement**
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21 682 No additional data are available.
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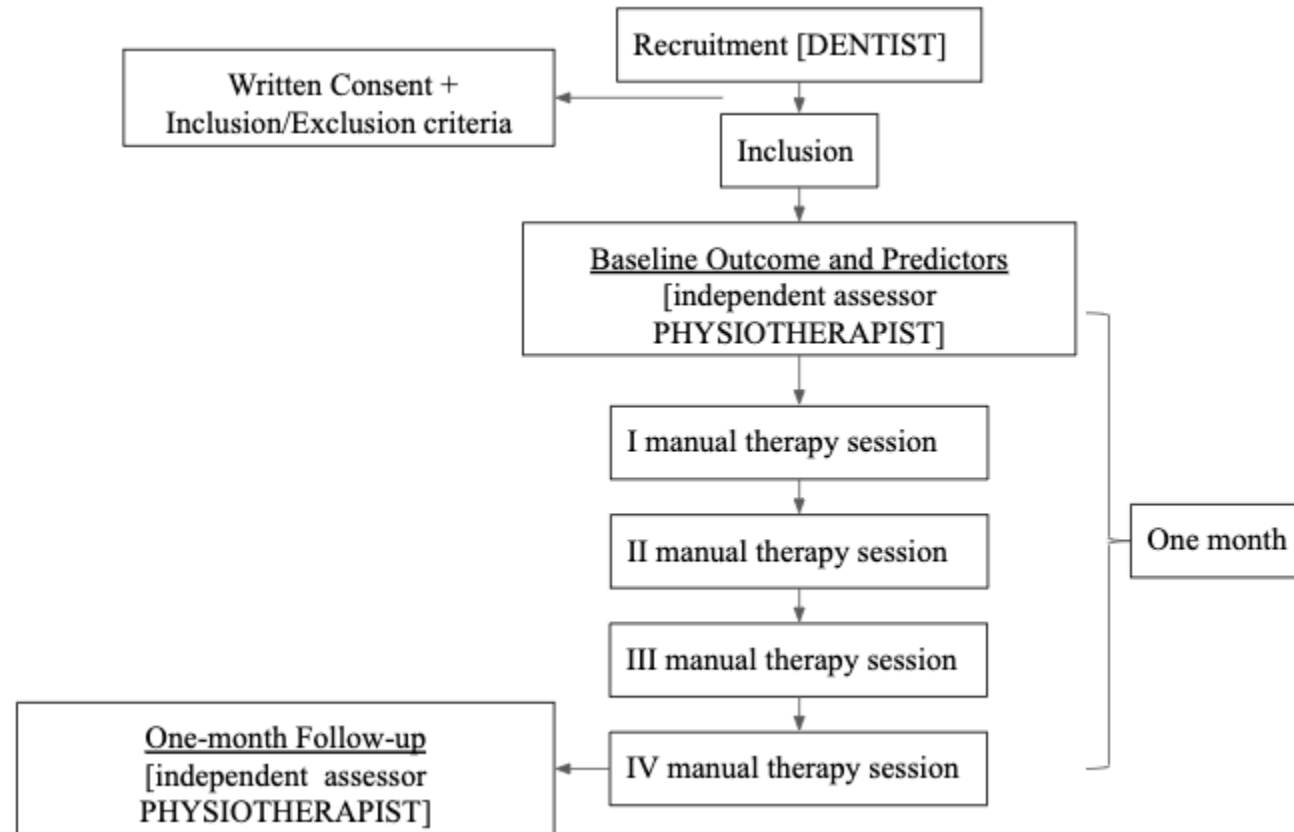
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42 692 **FIGURE LEGEND**
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46 694 **Figure 1:** Participant flow through the study
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3 **1 PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN**
4 **2 PATIENTS WITH TEMPOROMANDIBULAR DISORDERS:**
5 **3 A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY**
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11 **Supplementary file 1 - Candidate predictors**
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18 ***Demographical variables***
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22 10 Participants' demographic variables [age, gender, education] will be collected at baseline
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24 11 from open hospital records and patient interview.
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28 12 Age
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31 13 Age is a significant factor in TMD incidence and prevalence. Lipton et al. (1993) found
32
33 14 different age-specific prevalence for face/jaw pain: 6.5% in aged 18-34, 5.0% in 35-54 years old,
34
35 15 4.0% in 55-74 years old and 3.9% in people > 74 year old, showing a prevalence reduction across
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37
38 16 the lifetime. By contrast, data from the OPPERA study (Fillingim et al., 2011) showed a 40%
39
40 17 increased risk for TMD among individuals aged 25-34 years and a 50% increased risk for TMD
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42 18 among individuals aged 35-50 years.
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46 19 Gender
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50 20 Women are 1.5-2 times more likely to develop TMD than men (Helkimo, 1974; Von Korff
51
52 21 et al., 1988; Plesh et al., 2011). Currently, there is no study examining the extent of recovery from
53
54 22 TMD in men and women. Nevertheless, gender is a significant factor to be considered.
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23 Education

24 The National Centre of Health and Statistic (NCHS) found that the differences in jaw pain
25 prevalence among different educational groups are minimal. On the other hand, there is evidence
26 that people with lower levels of education adopt maladaptive coping strategies, including a
27 tendency to catastrophize about their pain (Roth et al., 2002). As a result, the education levels will
28 be collected as candidate predictor of outcome by classifying education into three categories: basic
29 education, intermediate education and university-level education.

30 *General health variable*

31 EuroQol Five Dimension Scale, 5-level [EQ-5D-5L]

32 According to Kapos et al. (2018), health-related quality of life can be a significant factor
33 influencing treatment outcome for TMD. The results showed that a higher health-related quality
34 of life predicted lower TMD pain intensity at an 8 year follow-up. Health-related quality of life
35 will be measured using the Italian version of the EQ-5D-5L [www.euroqol.org]. This instrument
36 transforms different health states into a single value with range 0-1 where 1 is perfect health, and
37 it measures the patient's own judgement about his/her health outcome through a visual analogue
38 scale range 0–100, representing respectively 'worst' to 'best' imaginable health state (Brooks,
39 1996). The EQ-5D-5L, with 5 possible responses to each item, has increased inter-observer [ICC
40 2,1 0.57] and test-retest [ICC 2,1 0.69] reliability compared to the previous EQ-5D-3L (Janssen et
41 al., 2008). Additionally, it has less ceiling effects [20.8% reduction] and adequate convergent
42 validity when compared with the WHO-5 [Spearman rank 0.38-0.51] (Janssen et al., 2013).

43

44 Sleep quality

45 It is known that chronic pain patients may suffer from poor sleep quality, even if it is
46 difficult to draw a causal relation (Sayar et al., 2002). Consequently, sleep quality will be assessed
47 as a candidate predictor because of its possible role among other factors in the transition from acute
48 to chronic pain. Sleep quality will be evaluated through an 11-point Numerical Rating Scale
49 [NRS], where 0 is 'the best possible sleep' and 10 is 'the worst possible sleep'. This scale owns
50 moderate psychometric properties in fibromyalgia patients to assess current sleep quality [over the
51 previous 24 hour period] with a symptom diary (Cappelleri et al., 2009). We will use the 0-10 NRS
52 to assess average sleep quality, related to the preceding 6-months at baseline (Rushton et al., 2018),
53 although no psychometric properties have previously been reported for this recall period.

54 *Psychosocial features*

55 Psychosocial factors are known to influence TMD onset and chronicity (Kight et al., 1999).
56 Psychological distress is significantly linked to a greater severity and persistence of TMD pain
57 (Dworkin et al., 1990). Moreover, depression and high levels of stress are significantly more
58 common in people with chronic TMD (Keefe et al., 2004; Gatchel et al., 2007). In addition, there
59 is agreement about the predictive strength of psychosocial factors in primary care among different
60 musculoskeletal pain conditions (Mallen et al., 2007; Artus et al., 2017).

61 The Hospital Anxiety and Depression Scales [HADS]

62 The Italian version of the HADS (Iani et al., 2014) will be utilised to investigate depression,
63 anxiety and manifestations of somatic symptoms (Zigmond et al. 1983). This scale consists of two
64 subscales [anxiety: HADS-A; depression: HADS-D] with 7 items and a total score from 0 to 21,

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3 65 with a higher score indicating elevated levels of anxiety and depression (Bjelland et al., 2002).
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6
7 66 HADS has been studied in different groups confirming adequate to excellent internal
8
9 67 consistency of HADS-A [0.68-0.93] and HADS-D [0.67-0.90] (Bjelland et al., 2002). In a
10
11 68 coronary heart disease sample, the standard measurement of error was 1.37 for anxiety and 1.44
12
13 69 for depression; the minimal detectable change was 3.80 for anxiety and 3.99 for depression (Wang
14
15
16 70 et al., 2009). The HADS has excellent concurrent validity in comparison to other
17
18 71 depression/anxiety scales (Bjelland et al., 2002).
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22 Coping Strategies Questionnaire 27 [CSQ-27] 23 24

25 73 Forssell et al. (2016) found that a low perceived ability to control pain increases the risk
26
27 74 for poor prognosis of TMD pain at one year regardless of the type of treatment. The Italian version
28
29 75 of the CSQ-27 (Monticone et al., 2014) will be used to provide an indication of coping strategies
30
31 76 used by participants when they are in pain. This 27-item questionnaire contains six domains to
32
33 77 assess the strategies for coping with pain: *Distraction*, *Catastrophizing*, *Ignoring pain sensations*,
34
35 78 *Distancing from pain*, *Coping self-statements*, and *Praying*. Patients rate the specific strategies for
36
37 79 coping with pain using a seven-point Likert scale [for each domain] ranging from 0 “Never do
38
39 80 that” to 6 “Always do that”, with higher scores indicating greater use (Robinson et al., 1997). A
40
41 81 recent study in a low back pain cohort (Campbell et al., 2013), in which individual items from
42
43 82 multiple questionnaires were factorised, suggested that diversion, reinterpreting and cognitive
44
45 83 coping clustered together as a single factor, representing coping cognitions; by contrast,
46
47 84 catastrophizing clustered with pain-related distress items. The original form was examined in
48
49 85 English-speaking subjects and revealed acceptable internal consistency [Cronbach’s alpha
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51 86 estimates ranging from 0.72 to 0.86] and satisfying construct validity (Robinson et al., 1997).
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87 Treatment expectation

88 A positive treatment expectation is considered as a treatment moderator because of its
89 influence on treatment outcome (Nicholas et al. 2011). A positive treatment expectation is
90 predictive of good outcome because the expectation of benefit (placebo) has a robust effect on pain
91 (Vase et al. 2009). In the current study we will investigate treatment expectation following the
92 same protocol used by Puentedura et al (2012). Participants will be asked whether they
93 “Completely disagree”, “Somewhat disagree”, “Neutral”, “Somewhat agree”, “Completely agree”
94 with the following statement: “I believe that *manual techniques applied to my jaw* will
95 significantly help to improve my pain”. If the participant chooses “completely disagree,”
96 “somewhat disagree,” or “neutral,” there is not a positive expectation that manual therapy applied
97 to craniomandibular structures will significantly help their temporomandibular disorder. If the
98 participant chooses “somewhat agree” or “completely agree,” there is a positive expectation that
99 manual therapy applied to craniomandibular structures will significantly help their
100 temporomandibular disorder.

101 ***TMD characteristics***

102 Based on previous studies on predictive factors of outcome in TMD patients (Forssell et
103 al., 2016; Grossman et al., 2017; Kapos et al., 2018), pain characteristics [e.g. pain duration, pain
104 intensity, pain location] are good predictors for pain change in the long-term. In addition, across a
105 variety of different conditions, pain features were reported to hold predictive value for pain
106 modulation (Clay et al., 2012; Clay et al., 2010; Kamaleri et al., 2009; Mallen et al., 2007).

107 Pain Duration

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2
3 108 According to Grossman et al. (2017), pain duration could be a significant factor influencing
4
5 109 the treatment outcome for TMD. Their results underline the fact that a longer pain duration is
6
7 110 associated with a more refractory therapeutic approach. Consequently, the pain duration [measured
8
9 111 in “days”] will be collected as candidate predictor of outcome from open hospital records and
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11 112 patient interview.
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15 16 113 Pain intensity 17

18
19 114 As shown in a previous study (Grossman et al., 2017), high levels of pain intensity at
20
21 115 baseline in people with TMD, can be associated with no-clinically significant results at a midterm
22
23 116 [3-4 months] follow up. Pain intensity will be calculated by averaging ratings of current pain,
24
25 117 average pain, and worst pain in the past week using the visual analogue scale (VAS), consisting
26
27 118 of a horizontal line measuring 10 cm (without marks), with “no pain” written at the left extremity,
28
29 119 and “unbearable pain” written at the right extremity (Wewers et al., 1990). Patients will be
30
31 120 educated to trace a perpendicular line on the horizontal line to intend the pain intensity. The
32
33 121 distance from the 0 points will be after measured in millimetres. The VAS is a reliable and valid
34
35 122 scale to assess pain intensity (Dworkin et al. 2005).
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41 123 Pain location and extent 42

43
44 124 Forssell et al. (2016) found that a high number of pain conditions increases the risk for
45
46 125 poor prognosis of TMD pain at one year regardless of the type of treatment. Comorbid painful
47
48 126 areas are common in patients with TMD pain (Velly et al., 2013). Therefore, the pain location and
49
50 127 the pain extent will be collected as a candidate predictor of outcome. This will be recorded as
51
52 128 described by Shiffman et al., (2014) in the DC/TMD protocol (Dworkin et al., 1990; Macfarlane
53
54 129 et al., 1996; Margolis et al., 1988; Ohrbach et al., 2011; Sanders et al., 2013; Ohrbach et al., 2013).
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3 130 Patients will be asked to complete a pain drawing symbolising the spatial distribution of the pain,
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5 131 over one chart with a frontal view of the body, one with a dorsal view and one with a dental setting
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7 132 (more specific for the jaw and teeth pain). Pain reported in different body areas (e.g., headache,
8
9 133 back pain, pelvic pain, neck pain) can be summarised as a count variable. The extent of pain will
10
11 134 be calculated as % of the body area by using an image scanning software (ImageJ: Image
12
13 135 Processing and Analysis in Java, <http://imagej.nih.gov/ij/>; Klong Image Measurement:
14
15 136 <http://www.imagemasurement.com/experience-image-measurement/pain-assessment-image->
16
17 137 measurement)

138 139 Central Sensitization Inventory (CSI) (Mayer et al., 2012)

140 Central sensitization can be present in different pain disorders including low back pain
141 (Roussel et al. , 2013), neck pain (Van Oosterwijck et al. , 2013), fibromyalgia (Desmeules et al. ,
142 2014), and TMD (Fernández-de Las-Peñas et al. , 2009). The Italian version of the Central
143 Sensitization Inventory (CSI) (Chiarotto et al., 2018) will be used. Part A consists of a 0-100 score
144 for 25 items on current health symptoms with five options ranging from ‘never’ (0) to ‘always’
145 (4). Part B examines previous physician diagnoses among seven different conditions (Mayer et al.,
146 2012). The CSI has significant test-retest reliability and internal consistency in subjects with and
147 without pain (Mayer et al., 2012). The Italian version of the CSI showed a satisfactory Cronbach’s
148 alpha [0.87] (Chiarotto et al., 2018).

149

150 Classification of TMD

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3 151 Manual therapy could potentially be beneficial for both myogenous and arthrogeous TMD
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5 152 (Armijo-Olivo et al., 2016). The TMD type will therefore be collected as a candidate predictor of
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7 153 outcome. As stated in the inclusion criteria, every patient included in the study will be diagnosed
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9 154 according to the Axis I of the Diagnostic Criteria for TMD DC/TMD (Shiffman et al., 2014). Based
10
11 155 on these criteria, Shiffman et al., (2014) reported different types of TMD. This Taxonomic
12
13 156 Classification of TMD includes four main domains: TMJ Disorders, Masticatory Muscle
14
15 157 Disorders, Headache and Associated Disorders. An additional domain, called Mixed TMD
16
17 158 (simultaneous presence of TMJ Disorders and Masticatory Muscle Disorders) will be included.
18
19 159 For every patient the type of TMD (total of 5 domains) will be collected as candidate predictors
20
21
22 160 from the patient medical records.
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27 161 Characteristic pain intensity and disability

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31 162 A greater number of disability days increases the risk of having clinically significant pain
32
33 163 one year after an initial assessment (Forssell et al., 2016). In this study we will use the Italian
34
35 164 version of the RDC/TMD questionnaire Axis II Graded Chronic Pain Scale [GCPS] version-2
36
37 165 [www.rdc-tmdinternational.org] (Von Korff et al., 1992; Von Korff et al., 2011) following the
38
39 166 DC/TMD protocol recommendations (Ohrbach et al., 2010; Shiffman et al. 2014; Ohrbach et al.,
40
41 167 2013). This scale has good internal consistency in temporomandibular pain [Cronbach's alpha of
42
43 168 0.84] (Von Korff et al. 1992). The GCPS measures the facial pain severity over the preceding 6-
44
45 169 months by unifying pain intensity and pain-related disability. The characteristic pain intensity
46
47 170 score [range: 0-100] is the mean of three pain intensity measurements: 'at the present time' and
48
49 171 'worst pain' and the 'average' pain over the preceding 6 months. The disability status is measured
50
51
52 172 with a 0-6 point score derived from a combination of the number of disability days and the
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54 173 disability level [range: 0-100; limitation given by pain in performing activities of daily living].
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3 174 Based on these scores, the participant's chronic pain and disability status can be classified into one
4
5 175 of the five ordinal categories of chronic pain severity (Von Korff et al. 1992).
6
7

8 176 Parafunction

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11 177 People with parafunctional behaviours with scores above 25 in the Oral Behaviours
12
13 178 Checklist [OBC] are 75% more likely to develop TMD than individuals with a score below 17
14
15 179 (Ohrbach et al., 2008; Ohrbach et al., 2012; Ohrbach et al., 2013). Parafunctional habits could play
16
17 180 a significant role in the development and the persistence of TMD pain (Glaros et al. 2016). In this
18
19 181 study we will use the Italian version of the RDC/TMD questionnaire Axis II Oral Behaviours
20
21 182 Checklist [www.rdc-tmdinternational.org] (Ohrbach et al., 2008; Ohrbach et al., 2012;) following
22
23 183 the DC/TMD protocol recommendations (Ohrbach et al., 2010; Shiffman et al. 2014). The OBC
24
25 184 measures the self-reported frequency over the preceding month of each of 21 activities involving
26
27 185 the jaw such as clenching the teeth or bracing the jaw (five ordinal response options, ranging from
28
29 186 "none of the time," coded 0, to "all of the time," coded 4). Psychometric properties of this
30
31 187 instrument suggest that it is valid, with patient behaviours matching those measured (Ohrbach et
32
33 188 al., 2008; Ohrbach et al., 2010; Markiewicz et al., 2006). Scoring is computed as the sum of the
34
35 189 number of items with non-zero response or as a weighted sum [e.g. the sum of the endorsed
36
37 190 frequencies of the respective items] (Ohrbach et al., 2008).
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45 192 **Clinical tests of the TMJ and masticatory muscles**

46 193 TMJ range of motion

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51 194 Mobility testing of the TMJ denotes an essential sign of TMD, it is one of the most reliable
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53 195 clinical measures (Shiffman et al., 2014). Grossman et al. (2017) examined the preoperative
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3 196 variables of TMD patients with articular disc displacement without reduction that may alter the
4
5 197 effects of arthrocentesis on joint effusion. They observed that small maximum interincisal distance
6
7 198 influences treatment outcome. As a result, we will use the Maximal Mouth Opening (MMO)
8
9
10 199 without pain as measure of TMJ range of motion. The measurements will be in millimeters and
11
12 200 will be taken with a ruler in a neutral craniocervical position [e.g. sitting or supine]. The distance
13
14 201 between the incisal edges of the maxillary and mandibular reference teeth, as described in the
15
16 202 DC/TMD protocol (Ohrbach et al., 2013), will be measured. Participants will be asked to open the
17
18 203 mouth as wide as they can without feeling any pain, or without increasing any present pain. The
19
20 204 tip of the ruler will be located against the incisal edge of the mandibular reference incisor, and the
21
22 205 distance to the mesial-distal center of the edge of the maxillary central incisor will be read. The
23
24 206 test will be repeated twice if the pain-free opening is less than 30mm (Ohrbach et al., 2013).
25
26 207 Assessment of mandibular ROM in a neutral craniocervical position obtained good inter- and intra-
27
28 208 rater reliability for MMO (Beltran-Alacreu et al. 2014).

29
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31 209 TMJ palpation pain:
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37 210 Pain induced in joints via palpation is a useful clinical test that allows to understand if the
38
39 211 provoked pain duplicates or replicates the patient's pain complaint by identifying potential joint
40
41 212 origin (Ohrbach et al., 2013). For this palpation, finger pressure is calibrated [1.0 kg], as described
42
43 213 in the DC/TMD protocol (Ohrbach et al., 2013), using a simple hand-held algometer prior to
44
45 214 palpation examination. While the participant mandible is in a comfortable position or in a slightly
46
47 215 protruded position, the examiner's index finger will be placed just anterior to the tragus of the ear
48
49 216 and dorsal to the TMJ with the participant in neutral craniocervical position e.g. sitting or supine.
50
51 217 The index finger will press while orbiting around the lateral pole in a circular fashion over the
52
53 218 superior aspect of the condyle and then anteriorly [from the 9:00 to the 3:00 position, and then
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3 219 continuing fully around the condyle]. Palpation will last 5 seconds for each pressed point (Ohrbach
4
5 220 et al., 2013). If a participant complains of familiar pain in at least one pressed point the point score
6
7 221 of this test will be 1; if there is no pain at any points the point score of this test will be 0 [range 0-
8
9 222 1: no pain =0; pain = 1]. Palpation will be performed in the left and right side. The interexaminer
10
11 223 reliability values of TMJ palpation in TMD patients is 0.59 and the specificity values is acceptable
12
13 224 [above 0.90] (Gomes et al. 2008).

14 15 16 17 18 225 Muscle palpation pain

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20
21 226 For this assessment, finger pressure is calibrated to 1.0 kg for masseter muscles and 0.5 kg
22
23 227 for lateral pterygoid area and temporalis tendons as described in the DC/TMD protocol (Ohrbach
24
25 228 et al., 2013), using a simple hand-held algometer prior to palpation examination. Pain induced in
26
27 229 muscles via palpation is a useful clinical test that allows to understand whether the provoked pain
28
29 230 duplicates or replicates the patient's pain complaint by identifying potential muscular origin
30
31 231 (Ohrbach et al., 2013). Palpation will be performed with the participant in a neutral craniocervical
32
33 232 position (e.g. sitting or supine), on the left and right side and will last 5 seconds for each testing
34
35 233 point (Ohrbach et al., 2013). The inter-examiner reliability values of palpation in TMD patients is
36
37 234 0.59 and the specificity values are acceptable [above 0.90] (Gomes et al. 2008).

38
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41
42 235 *Lateral pterygoid area:* palpation will be performed with a finger pressure calibrated at 0.5
43
44 236 kg (DC/TMD protocol - Ohrbach et al., 2013). The palpation will take place as described in FIG.1.
45
46 237 If a participant complains of familiar pain during palpation, then the lateral pterygoid area will be
47
48 238 considered as a painful site.

239

240 **FIG. 1 Lateral pterygoid area:** Palpation of the vestibule in a
 241 posterior-superior-medial direction while the mandible is
 242 omolaterally deviated.



244 *Masseter muscle:* masseter palpation consists of
 245 a sequence of three palpation sites with finger pressure calibrated to 1.0 kg (DC/TMD protocol -
 246 Ohrbach et al., 2013): origin zone [inferior to the bony margin of the zygomatic process], body
 247 zone [in front of ear lobe] and insertion zone [superior to the mandibular angle]. In each zone, the
 248 palpation continues until the anterior boundary of the muscle is reached (Ohrbach et al., 2013). If
 249 a participant complains of familiar pain in at least one location, then the masseter muscle will be
 250 considered as a painful site.

251 *Temporalis tendon area:* the palpation will be performed with a finger pressure calibrated
 252 to 0.5 kg (DC/TMD protocol - Ohrbach et al., 2013). The palpation will take place as described in
 253 FIG.2. If a participant complains of familiar pain during the palpation of the temporalis tendon,
 254 then this area will be considered as a painful site.

255

256 **FIG. 2 Temporalis tendon area:** Palpation against the ascending
 257 mandibular ramus while the mouth is slightly open. The palpation
 258 direction is superior as far as possible by following the bone surface.



259

260

261 *Total score:* if a participant complains of familiar pain in at least three of the six examined

1
2
3 262 sites the score will be 1, otherwise it will be 0 [score range 0–1: < 3 sites with familiar pain = 0; ≥
4
5 263 3 sites with familiar pain = 1] (Friction et al., 1988).

7
8
9 264 JAw-test

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11
12 265 The JAw-test is a clinical test that aims to investigate the immediate effects of four brief
13
14 266 intraoral manual therapy techniques on pain and on TMJ range of motion. The participant will be
15
16 267 positioned in supine. Before starting the test, the pain-free range of motion of the TMJ will be
17
18 268 measured [MMO - millimeters] with a ruler, as described above, according to the DC/TMD
19
20 269 protocol (Ohrbach et al., 2013). Then the participant will be asked to rate his/her pain through the
21
22 270 Verbal Rating Scale (VRS) “at rest”, “during clenching” and “during the maximal opening of the
23
24 271 mouth”; and the average of the three pain scores will be registered. For this test, finger pressure is
25
26 272 calibrated [1.0 kg], in the same way described in the DC/TMD protocol (Ohrbach et al., 2013),
27
28 273 using a simple hand-held algometer prior to palpation examination.

29
30
31
32 274 Participants will be informed with the following words: “*I am going to perform four manual*
33
34 275 *techniques on some muscles and joints in your jaw region. You may feel a little pain, if the pain*
35
36 276 *increases and becomes too intense, let me know, I will reduce the pressure until the pain returns*
37
38 277 *to acceptable levels*”.

39
40
41
42 278 *First technique: Lateral pterygoid area*

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44 279 This techniques will be performed on the most painful side. While one hand stabilizes the
45
46 280 participant’s head on the least painful side, the other hand will be used to apply pressure over the
47
48 281 lateral pterygoid area as described above and in accordance with the DC/TMD protocol (Ohrbach
49
50 282 et al., 2013). In this position, compression [1.0 kg] is applied for 30-60 seconds.

51
52
53 283 *Second technique: Temporalis tendon area*

54
55 284 This technique will be performed on the most painful side. While one hand stabilizes the

1
2
3 285 participant's head on the least painful side, the other hand (index finger) will be used to apply
4
5 286 pressure over the Temporalis tendon area as described above and in accordance with the DC/TMD
6
7 287 protocol (Ohrbach et al., 2013). In this position, compression [1.0 kg] is applied for 30-60 seconds.
8
9

10 288 *Third technique: Mylohyoid area*

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12 289 The participant will be instructed to open the mouth to let the examiner's finger reach the
13
14 290 mylohyoid area in a central position on the mylohyoid raphe. The other hand of the examiner will
15
16 291 reach the same area using a finger through an extraoral approach. In this position a combined
17
18 292 compression (1.0 kg) will be applied for 30-60 seconds.
19
20

21 293 *Fourth technique: TMJ mobilization*

22
23 294 An intraoral ventral and caudal anterior glide [mobilisation grades I and II] of both the
24
25 295 TMJs will be performed for 30 seconds as described by Cleland et al. (2004).
26
27

28 296 *Final scores:*

29
30 297 After the tests, the pain-free range of motion of the TMJ will be measured [MMO -
31
32 298 millimeters] with a ruler, as described above, according to DC/TMD protocol (Ohrbach et al.,
33
34 299 2013). Then the participant will be asked to rate his/her pain using the Verbal Rating Scale (VRS)
35
36 300 "at rest", "during clenching" and "during the maximal opening of the mouth"; an average of this
37
38 301 three pain scores will be registered. If a participant shows only an improvement in pain [average
39
40 302 score VRS pre-test > average score VRS post-test] the score will be 1; if a participant shows only
41
42 303 an improvement of TMJ mobility [MMO pre-test < MMO post-test at least 2 millimeters] the score
43
44 304 will be 1; if a participant shows improvements in both pain and TMJ mobility, the score will be 2;
45
46 305 if a participant shows no improvements the score will be 0 [Score range 0-2: 0 = no change; 1 =
47
48 306 VRS improvement or MMO improvement; 2 = improvement of both].
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For peer review only



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|-----------------------------------|---------|--|
| Administrative information | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – Page 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry – N/A |
| | 2b | All items from the World Health Organization Trial Registration Data Set – N/A |
| Protocol version | 3 | Date and version identifier – Page 1 |
| Funding | 4 | Sources and types of financial, material, and other support – Page 22 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors – Pages 1 and 22 |
| | 5b | Name and contact information for the trial sponsor – N/A |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities – N/A |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – N/A |
| Introduction | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – Pages 4-6 |
| | 6b | Explanation for choice of comparators – Supplementary file |
| Objectives | 7 | Specific objectives or hypotheses - Page 5-6 |

1
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) – N/A
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8 **Methods: Participants, interventions, and outcomes**
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10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained – Page 6
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) – Pages 7
17
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered – Pages 8-9
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease) – Page 9
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests) – N/A
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial – Pages 7 and 9
32
33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended – Page 9 and 10 (primary
40 outcome), Supplementary file (candidate predictors)
41
42

43 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
44 timeline washouts), assessments, and visits for participants. A schematic
45 diagram is highly recommended (see Figure) – Pages 7-8
46
47

48 Sample size 14 Estimated number of participants needed to achieve study objectives
49 and how it was determined, including clinical and statistical
50 assumptions supporting any sample size calculations – Page 12
51

52 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
53 target sample size – Pages 7
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56 **Methods: Assignment of interventions (for controlled trials)**
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58 Allocation:
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|----|----------------|-----|---|
| 1 | | | |
| 2 | Sequence | 16a | Method of generating the allocation sequence (eg, computer- |
| 3 | generation | | generated random numbers), and list of any factors for stratification. |
| 4 | | | To reduce predictability of a random sequence, details of any planned |
| 5 | | | restriction (eg, blocking) should be provided in a separate document |
| 6 | | | that is unavailable to those who enrol participants or assign |
| 7 | | | interventions – N/A |
| 8 | | | |
| 9 | | | |
| 10 | Allocation | 16b | Mechanism of implementing the allocation sequence (eg, central |
| 11 | concealment | | telephone; sequentially numbered, opaque, sealed envelopes), |
| 12 | mechanism | | describing any steps to conceal the sequence until interventions are |
| 13 | | | assigned – N/A |
| 14 | | | |
| 15 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, |
| 16 | | | and who will assign participants to interventions – N/A |
| 17 | | | |
| 18 | | | |
| 19 | Blinding | 17a | Who will be blinded after assignment to interventions (eg, trial |
| 20 | (masking) | | participants, care providers, outcome assessors, data analysts), and |
| 21 | | | how N/A |
| 22 | | | |
| 23 | | 17b | If blinded, circumstances under which unblinding is permissible, and |
| 24 | | | procedure for revealing a participant's allocated intervention during |
| 25 | | | the trial – N/A |
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Methods: Data collection, management, and analysis

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|----|-----------------|-----|--|
| 28 | | | |
| 29 | | | |
| 30 | Data collection | 18a | Plans for assessment and collection of outcome, baseline, and other |
| 31 | methods | | trial data, including any related processes to promote data quality (eg, |
| 32 | | | duplicate measurements, training of assessors) and a description of |
| 33 | | | study instruments (eg, questionnaires, laboratory tests) along with |
| 34 | | | their reliability and validity, if known. Reference to where data |
| 35 | | | collection forms can be found, if not in the protocol – Pages 9-11, |
| 36 | | | Supplementary file |
| 37 | | | |
| 38 | | | |
| 39 | | 18b | Plans to promote participant retention and complete follow-up, |
| 40 | | | including list of any outcome data to be collected for participants who |
| 41 | | | discontinue or deviate from intervention protocols – Page 12-13 |
| 42 | | | (withdrawals) |
| 43 | | | |
| 44 | | | |
| 45 | Data | 19 | Plans for data entry, coding, security, and storage, including any |
| 46 | management | | related processes to promote data quality (eg, double data entry; |
| 47 | | | range checks for data values). Reference to where details of data |
| 48 | | | management procedures can be found, if not in the protocol – Page |
| 49 | | | 12 |
| 50 | | | |
| 51 | | | |
| 52 | Statistical | 20a | Statistical methods for analysing primary and secondary outcomes. |
| 53 | methods | | Reference to where other details of the statistical analysis plan can be |
| 54 | | | found, if not in the protocol – Page 12-13 |
| 55 | | | |
| 56 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted |
| 57 | | | analyses) – n/A |
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- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – Page 12

Methods: Monitoring

- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed – N/A
- 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – N/A
- Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – Page 14
- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – N/A

Ethics and dissemination

- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – Pages 6 and 14
- Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – N/A
- Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – Page 7
- 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – N/A
- Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – Page 12
- Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site – Page 22
- Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – Not present
- Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – N/A

| | | | |
|--|-------------------------|-----|---|
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – N/A |
| 16 17 18 19 20 21 22 23 24 | | 31b | Authorship eligibility guidelines and any intended use of professional writers – N/A |
| 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – N/A |

Appendices

| | | | |
|--|-------------------------------|----|--|
| 17 18 19 20 21 22 23 24 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates – N/A |
| 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable – N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN PATIENTS WITH TEMPOROMANDIBULAR DISORDERS: A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2019-032113.R1 |
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**PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN
PATIENTS WITH TEMPOROMANDIBULAR DISORDERS:
A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY**

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ABSTRACT

Introduction

Temporomandibular Disorders (TMD) are principally characterised by pain in the craniomandibular area and probable limitations of jaw opening. Manual therapy, like other recommended conservative treatments included in clinical guidelines, is commonly used to treat patients with TMD to reduce pain and improve function. However, outcomes may be variable. The aim of this study is to identify predictors associated with pain reduction in patients with TMD following manual therapy by analysing a combination of patient-reported outcome measures and clinical tests. Such knowledge will support a more personalised management approach by facilitating clinical decision-making.

Methods/analysis

An observational prospective design will recruit a cohort of 100 adults with a diagnosis of TMD (according to Axis I of the Diagnostic Criteria for TMD) at a Dental Hospital in Italy. Patients will be treated with four weekly sessions of manual therapy applied to craniomandibular structures. An array of predictors has been chosen based on previous research on prognostic factors for TMD and altered pain modulation in musculoskeletal disorders. Candidate predictors including demographic variables, general health variables, psychosocial features, TMD characteristics, and clinical tests of the temporomandibular joint and masticatory muscles will be collected at baseline. Definition of good outcome is a clinically significant reduction of pain intensity over the last week ($\geq 30\%$ reduction Visual Analogue Scale) immediately following the 4-week intervention. Exploratory factor analysis will be applied to analyse factor loading of candidate predictors for good outcome at 4 weeks. Subsequently, a logistic multivariable regression model will be performed to calculate low and high risk of good outcome.

Ethics and dissemination

Ethical approval will be obtained from the “Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico” and University of Birmingham Ethics Committee. The results will be submitted for publication in a peer-reviewed journal and presented at conferences.

Keywords: Temporomandibular Disorders, Temporomandibular Joint Dysfunction Syndrome, Pain, Prediction, Manual Therapy

Word count: 3129 [excluding references]

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first study to identify predictors associated with pain reduction following manual therapy interventions in patients with TMD
- The study will utilise a comprehensive array of candidate factors to predict clinically relevant pain reduction
- The implications from this study will facilitate clinical decision-making for manual therapists managing patients with TMD
- Alternative or additional predictors could be valuable to include but the candidate predictors have been prioritised as they are reliable and valid measures which have a relationship with pain
- The study could potentially generate a non-representative sample of patients as it will exclude people who have already received recent treatment for their TMD

INTRODUCTION

Temporomandibular Disorders (TMD) affect approximately 10% of the adult population and, in the USA alone, are estimated to cost US\$4 billion per year on management¹⁻². In Spain, the incidence of TMD has significantly increased (from 8% in 1993 to 14% in 2015) despite a clear improvement in general oral health over the entire period³. Although some countries report less prevalence of TMD such as in Sweden (approximately 5%)⁴, TMD remains a public health-related challenge. TMD are principally characterised by pain and limitations of jaw opening⁵ but many patients also complain of neck and back pain or pain at other sites⁶.

Physical therapy is one of the most common conservative interventions for the management of TMD⁷ and given that the aetiology may be unclear⁸, several therapeutic approaches have been described⁹. One approach is manual therapy applied to the craniomandibular structures with evidence suggesting a significant reduction in pain with manual therapy treatment¹⁰, although responses are highly variable¹¹. In other musculoskeletal pain disorders, such as neck or back pain, pain reduction from manual therapy has been shown to be superior to other treatments (e.g. therapeutic exercise) when targeted towards patients with specific clinical features including the onset of symptoms within 30 days¹²⁻¹³. Nevertheless, in TMD, no previous study has investigated patient factors associated with significant pain reduction following manual therapy. Such knowledge could be achieved by identifying potential predictors (e.g. pain characteristics, psychosocial features, TMD characteristics) of pain reduction following manual therapy interventions in patients with TMD to support a more personalised management approach.

Very few studies have examined factors associated with pain reduction in patients with TMD. Forssell et al. conducted a prospective cohort study with 263 primary care

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2
3 patients with TMD pain¹⁴. They analysed several potential predictors of persistent pain at
4
5 one-year follow-up including demographic, pain-related and psychosocial variables. It was
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7 concluded that patients with TMD who have had numerous previous healthcare visits,
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9 complained of high-intensity pain at other body sites and had a greater number of disability
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11 days, were at greater risk of having pain one year after the initial assessment. Nevertheless,
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13 this study did not examine predictors of pain reduction related to a therapeutic intervention
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15 which could be useful to inform clinical practice. Kapos et al. investigated the association of
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17 long-term pain intensity with baseline health-related quality of life and jaw functional
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19 limitation in patients with TMD¹⁵. Findings suggested that baseline health-related quality of
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21 life is inversely proportional with pain intensity at an eight-year follow-up regardless of the
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23 type of treatment that they received (e.g. surgery, drugs, physical therapy or unconventional
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25 therapy). After adjusting for the type of treatments received, by clustering the participants
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27 into three groups (medical/conventional management, alternative medicine, and surgical
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29 intervention), each predictor analysed (demographic, pain-related and health-related quality
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31 of life) maintained similar statistical significance. Notwithstanding, the group classified as
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33 “medical/ conventional management” included participants receiving diverse treatments
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35 ranging from physical therapy, pharmacology (Acetaminophen, Antidepressants, Anti-
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37 inflammatory) to the application of a mouth appliance (e.g. Michigan splint). This previous
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39 work can facilitate clinicians to identify patients who are more challenging to treat by
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41 identifying clinical features associated with persistent pain in the long term regardless of the
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43 type of interventions applied. However, currently no study has examined predictive factors
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45 associated with pain reduction following manual therapy interventions in patients with TMD.
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54 The aim of this study is to identify predictors associated with pain reduction in
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56 patients with TMD following manual therapy applied to craniomandibular structures by
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58 analysing a combination of: (1) demographical variables, (2) general health variables, (3)
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3 psychosocial features, (4) TMD characteristics, and (5) clinical tests of the
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5 temporomandibular joint and masticatory muscles. The knowledge gained from this study
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7 will facilitate clinical decision-making for manual therapists managing patients with TMD by
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9 providing clinicians with key factors to evaluate, to determine whether or not the patient is
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11 likely to have a clinically relevant reduction in their pain immediately following four weekly
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13 applications of manual therapy.
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19 **METHODS AND ANALYSIS**

21 **Source of data**

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25 A prospective observational study will recruit a cohort of patients referred to the
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27 Italian Stomatologic Institute with a TMD diagnosis according to the Axis I of the Diagnostic
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29 Criteria for TMDs (DC/TMD)¹⁶. This protocol is written according to the Transparent
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31 Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis
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33 (TRIPOD) statement¹⁷ in which recommendations are provided about prediction model
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35 development and validation. Ethical clearance will be obtained from the Ethics Committee of
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37 the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and the University of
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39 Birmingham Ethics Committee, and the study will be conducted in accordance with the
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41 Declaration of Helsinki.
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47 Patient reported and physical assessment data will be collected at baseline prior to
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49 commencing treatment. Outcome will be collected at the end of the fourth session of
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51 craniomandibular manual therapy (at one month). This timeline has been selected based on
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53 previous studies investigating 1) the effects of manual therapy on pain¹⁸⁻¹⁹; and 2) work
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55 confirming the effectiveness of manual therapy for TMD patients²⁰ and is believed to be
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57 reasonable for the purposes of this study.
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Setting and Participants

Participant recruitment will be carried out at the TMJ Unit of the Italian Stomatological Institute (Dental Hospital) in Milan, Italy over a period of up to 12 months (planned start date July 2019). Consecutive eligible participants will be approached for recruitment until the sample size is reached.

Eligibility criteria

Inclusion criteria: (1) adults aged ≥ 18 years; (2) TMD diagnosis according to the Diagnostic Criteria for TMDs (DC/TMD)¹⁶; (3) no therapeutic interventions reported (for their TMD) in the past six months²¹; (4) capacity to use and understand written and verbal Italian language; (5) mental capacity to provide informed consent.

Exclusion criteria: (1) TMD pain related to rheumatoid/inflammatory arthritis (2) any physical (e.g. facial paralysis, neurological disorders, neuropathic pain) or mental condition (e.g. cognitive deficit, mental illness and/or disorders) that could potentially influence the study results. Additionally, patients will be excluded if (3) they commence another treatment for their TMD (pharmacology, oral appliance, others) throughout the duration of the study.

Recruitment

Based on feasibility data from the last 5 years of activity at the TMJ Unit of Italian Stomatologic Institute, it is estimated that at least 130 eligible participants will be available for recruitment over 13 months. According to previous observational studies on the prediction of outcomes in musculoskeletal disorders¹²⁻¹³, it is estimated that 75% of eligible participants will consent to participation [100 participants].

All patients attending the TMJ Unit will be screened for the presence of a TMD. One expert dentist with >10 years' experience in the management of patients with TMD, will confirm the TMD diagnosis according to the DC/TMD using the Italian translation of the

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3 protocol²². Subsequently, in accordance with the inclusion/exclusion criteria, he will explain
4 the study to the potential participant and provide the patient information sheet. Participants
5 will then give their written informed consent prior to inclusion in the study. Afterwards, the
6 participant will be referred to see a physiotherapist [independent assessor, >5 years'
7 experience in managing patients with TMD] for the baseline assessments (summarised in
8 Table 1) and then treatment will commence within the same week. After the last session (i.e.
9 one month from baseline), the participants will be assessed again by the assessing
10 physiotherapist to measure outcome. Participant flow through the study is outlined in Figure
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26 [FIGURE 1]
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30 **Treatment**

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33 Participants will receive four sessions of manual therapy applied to craniomandibular
34 structures over 4 weeks²³⁻²⁵. Two physiotherapists, each with >5 years' experience in manual
35 therapy / TMD will perform the treatments. They will not be involved in participant
36 recruitment, assessment or the collection of the outcome measure. Manual therapy techniques
37 will be based on the clinical examination, and will be selected at the discretion of the treating
38 physiotherapist according to their clinical reasoning of the individual case. Overall, the
39 application of manual therapy aims to decrease pain by treating masticatory muscle trigger
40 points, muscle tightness, and restricted temporomandibular joint movements. Several
41 techniques will be considered including: (i) ventral and caudal anterior glide
42 temporomandibular joint mobilization²⁶; (ii) soft tissue interventions for the management of
43 trigger points in masticatory muscles²⁷; (iii) myofascial induction therapy [functional
44 restoration of the fascial system] applied to craniomandibular structures²⁸.
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3 The structures targeted in the treatment sessions will be the temporomandibular joint,
4 temporal muscles, masseter muscles, medial and lateral pterygoid muscles and suprahyoid
5 muscles, applied at the discretion of the physiotherapist based on the patient's individual
6 presentation. During the treatment sessions, the treating physiotherapists will provide
7 explanations about the patient's condition and answer any participant questions by promoting
8 general advice. The treatment sessions will last from 20 to 30 minutes duration. No other
9 treatment (e.g. oral appliance) will be performed for the management of their TMD. If during
10 the course of the four-week intervention, a patient seeks treatment for an acute episode of
11 pain at another site (e.g. neck pain, low back pain, shoulder pain) they will be withdrawn
12 from the study.
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28 **Outcome**

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30 The outcome being predicted by the prediction model is pain intensity since patients
31 with TMD typically report pain to be their primary problem⁵, manual therapy is largely
32 known to be effective principally for pain modulation²⁹ and change in pain intensity has most
33 commonly been the primary outcome of choice in several other studies of patients with
34 TMD³⁰⁻³³.
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42 Pain intensity will be calculated by averaging the ratings of current pain, average pain
43 in the past week, and worst pain in the past week using the Visual Analogue Scale (VAS),
44 consisting of a horizontal line measuring 10 cm (without marks), with "no pain" written at the
45 left extremity, and "worst pain imaginable" at the right extremity³⁴. The VAS is a reliable and
46 valid scale to assess pain intensity as an outcome measure in intervention studies³⁵. Based on
47 the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)
48 recommendations about TMD reviewed by Haythornthwaite³⁶, a reduction of at least 30% of
49 the VAS score for pain intensity is considered clinically significant. Consequently, a
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reduction in the total VAS score [$\geq 30\%$] will be defined as a good outcome. The outcome measure will be evaluated by the same independent assessor to minimise detection bias³⁷.

To capture a potential change in function which may occur with a change in pain intensity, patients will also complete the patient specific functional scale [PSFS]³⁸ pre and post treatment. The PSFS is a self-reported outcome measure assessing functional change in patients with musculoskeletal disorders³⁹⁻⁴⁰. It is responsive to clinically significant change over time⁴¹. Patients will be invited to rate, on an 11-point scale, their level of difficulty performing at least three different daily activities. Following the treatment, patients will be required to score again the activities previously rated. The PSFS is a valid, reliable, and responsive outcome measure with a high test-retest reliability in different musculoskeletal disorders such as low back and neck pain⁴²⁻⁴⁴.

Candidate predictors

The candidate predictors that have been chosen are reliable and valid measures which have a relationship with pain. The selection is based on previous research on prognostic factors for TMD and altered pain modulation in musculoskeletal disorders⁴⁵⁻⁴⁶. Candidate predictors are summarised in Table 1, with further detail in Supplementary file S1. All data collection will be standardised through protocols and clinical report forms.

Table 1: Summary of candidate predictors.

| Domain / Candidate predictor | Measure / data item |
|--------------------------------|--|
| Demographical variables | |
| Age | Years |
| Gender | Female / male |
| Education | Basic education, intermediate education and university-level education |

| General health variables | |
|---|--|
| Health-related quality of life | EuroQol EQ-5D-5L ⁴⁷ |
| Sleep quality | 11-point [0-10] Numerical Rating Scales, relating to current pain, from 'best possible sleep' to 'worst possible sleep' ⁴⁸ |
| Psychosocial features | |
| Coping strategies applied during a painful experience | Coping Strategies Questionnaire 27 [CSQ-27] ⁴⁹ |
| Anxiety and depression | Hospital Anxiety and Depression Scales [HADS] ⁵⁰ |
| Treatment expectation | Positive / negative expectation ⁵¹ |
| TMD characteristics | |
| Pain duration | Days |
| Pain intensity | VAS: averaging ratings of current pain, average pain, and worst pain in the past week ⁵² |
| Pain location | Pain drawing as described in the protocol of Diagnostic Criteria for TMD (DC/TMD) ¹⁶ |
| Central sensitization | Central Sensitization Inventory (CS) ⁵³ |
| Classification of TMD | In according to DC/TMD Taxonomy ⁵⁴ |
| Oral Behaviours | Oral Behaviours Checklist [OBC] ⁵⁵ |
| Characteristic pain intensity and disability | Graded Chronic Pain Scale (GCPS) version 2.0 [Italian version - www.rdc-tmdinternational.org] |
| TMJ and masticatory muscles clinical test | |
| TMJ range of motion | Maximal Mouth Opening (MMO) without pain measured in mm through a ruler as described in the DC/TMD protocol ¹⁶ |
| TMJ palpation pain | Dynamic TMJ lateral pole palpation [1 kg of palpation pressure] in according to DC/TMD protocol ¹⁶ Score range: 0-1 [no pain =0; pain = 1] |
| Muscle palpation pain | Palpation in the following 6 bilateral points: lateral pterygoid area [0.5 kg intraoral palpation], temporalis tendon [0.5 kg intraoral palpation], masseter muscle [1 kg extraoral palpation] as described in the DC/TMD protocol ¹⁶ . Score range: 0–1 [< 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain = 1] |
| JAw-test | Immediate effects of brief intraoral MT techniques on pain [VRS] and TMJ range of motion [MMO]. A standardised procedure is fully described in Supplementary file S1. Score range 0-2: [0 = no change; 1 = pain improvement or MMO improvement; 2 = improvement of both] |

Data handling

Candidate predictors will be collected by independent physiotherapist assessor. All data will be confidentially secured by storing it on a password-protected computer attainable only by the principal investigators (GA). All individual details will be replaced with ID codes. At the end of the data collection, all data stored on the principal investigator's computer will be transferred securely to a server at the Centre of Precision Rehabilitation for Spinal Pain at Birmingham University where the data will be analysed. All data will be stored on a secure server at the University of Birmingham for a period of 10-years in line with Research Governance procedures. Data will be analysed using IBM SPSS Statistics (Version 25, IBM).

Sample Size

Exploratory factor analysis will be utilised to reduce the number of predictors⁵⁶. This method will guarantee an adequate sample size (at least 10 cases per candidate predictor) to power the final regression analysis⁵⁷⁻⁵⁸. Data will be collected for a sample size of 100 participants so that, considering 10% of potential drops out, final data are available for 90 participants.

Statistical analysis methods

A flow diagram will report eligible participants, examined for eligibility, confirmed eligible, recruited into the study, completed follow-up and analysed. Reasons for non-participation, exclusion, drop-outs and withdrawal will be fully documented and all missing data of participants will be reported. Participant characteristics (candidate predictors - Table 1) will be summarised with a descriptive method.

A primary phase of the exploratory data analysis will summarise data to implement the predictive model⁵⁹. Multicollinearity between candidate predictors will be assessed at baseline. Outcome [VAS pain intensity] will be split into good versus poor as described previously [good outcome: reduction in VAS score $\geq 30\%$]³⁶. Exploratory factor analysis will be applied to

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3 analyse factor loading of candidate predictors (summary scores) on good outcome at one
4 month. This process will reduce candidate predictors (supported by the cohort sample of 90) to
5 enter into the final model.
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10 The statistical model has been designed a priori. To investigate the impact of each
11 predictive factor on good outcome, a logistic multivariable regression model will be performed.
12 For each candidate predictor, the mean differences or the odds ratio with their 95% confidence
13 intervals will be calculated. A multiple imputation analysis⁶⁰ will be applied to manage possible
14 missing data. The multivariable analysis will initially consider all candidate predictors. In the
15 case of a high correlation between candidate predictors, a reduced multivariate analysis will be
16 considered.
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28 **DISCUSSION**

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30 There is a need to identify predictors for pain reduction in patients with TMD following
31 specific treatments in order to inform clinical decision-making. Several therapies are described
32 for patients with TMD such as the use of oral appliances, different types of physical therapy
33 modalities, pharmacology or temporomandibular joint arthrocentesis yet the amount of pain
34 relief that different people receive from each intervention is variable^{7,10}. As shown by Forssell
35 et al.¹⁴ and Kapos et al.¹⁵, many patients continue to experience pain following such
36 interventions. Investigating factors associated with pain relief to such treatments can facilitate
37 clinical assessment and treatment selection.
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49 Physical therapy is one of the most common conservative interventions to treat TMD⁷.
50 Among different physical therapy modalities, manual therapy can provide symptom and
51 functional improvements¹⁰ including pain relief^{11,31}. Knowledge of predictive factors
52 associated with good outcome to a specific intervention such as manual therapy applied to
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3 craniomandibular structures will facilitate clinical decision making. Ultimately, such
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5 knowledge will lead to improved clinical and cost effectiveness of rehabilitation approaches.
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8 **Quality assurance**

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10 Only participants that have not received therapeutic intervention for their TMD in the
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12 past six months will be included in the current study. It is possible that such eligibility criteria
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14 could generate selection bias. To address this potential bias, the number of eligible and included
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16 subjects with the reason for non-participation will be documented.
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19 **Patient and Public Involvement**

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21 The research question in this study was developed following consultations and
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23 discussion with patients. Patients will not be involved in the analysis and data collection but
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25 will contribute to data interpretation and production of a lay summary of the findings.
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28 **Ethics and Dissemination**

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30 The research protocol has been submitted to the Ethics Committee of the “Fondazione
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32 IRCCS Ca’ Granda Ospedale Maggiore Policlinico” and subsequently will be submitted to the
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34 University of Birmingham Ethics Committee for approval. Researchers will inform all
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36 participants on the characteristics of the research and will obtain written consent. Participants
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38 will be informed that they are free to withdraw from the study at any time, without needing to
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40 provide reason. Any concerns for a participant by the study team will be fed back to the primary
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42 investigator (GA). Baseline characteristics of withdrawn participants will be compared to those
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44 of retained participants to assess for any differences. In the event of any unlikely adverse
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46 events, this will be immediately reported by the principal investigator to the ethics committee.
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51 The results of this study will submitted for publication in a peer review journal and
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53 presented at conferences.
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58 **Limitations**

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3 The study could potentially generate a non-representative sample of patients with TMD
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5 due to a possible selection bias. Subjects reporting other treatments before [6 months] and
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7 during the study will be excluded to minimise confounding bias and preserve internal validity.
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10 This could potentially generate a non representative sample of TMDs because of exclusion of
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12 patients with high levels of pain which seek additional treatment. This potential event,
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14 associated with the fact that this observational study will be performed at a single site only,
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16 could reduce the external validity and the generalisability of the results.
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19 **Conclusion**

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21 This will be the first study to identify factors associated with pain reduction following
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23 manual therapy in patients with TMD and the knowledge gained from this study stands to
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25 facilitate clinical decision making for manual therapists managing patients with TMD.
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Author Contributions

GA, AEB and DF formulated the research question and study focus. GA drafted the initial version of the manuscript with DF. NH, AR, GB and ML provided guidance on topic, methodology and analyses. All authors reviewed and commented on each draft of the protocol. All authors have approved the final manuscript. DF is guarantor

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Competing Interests Statement

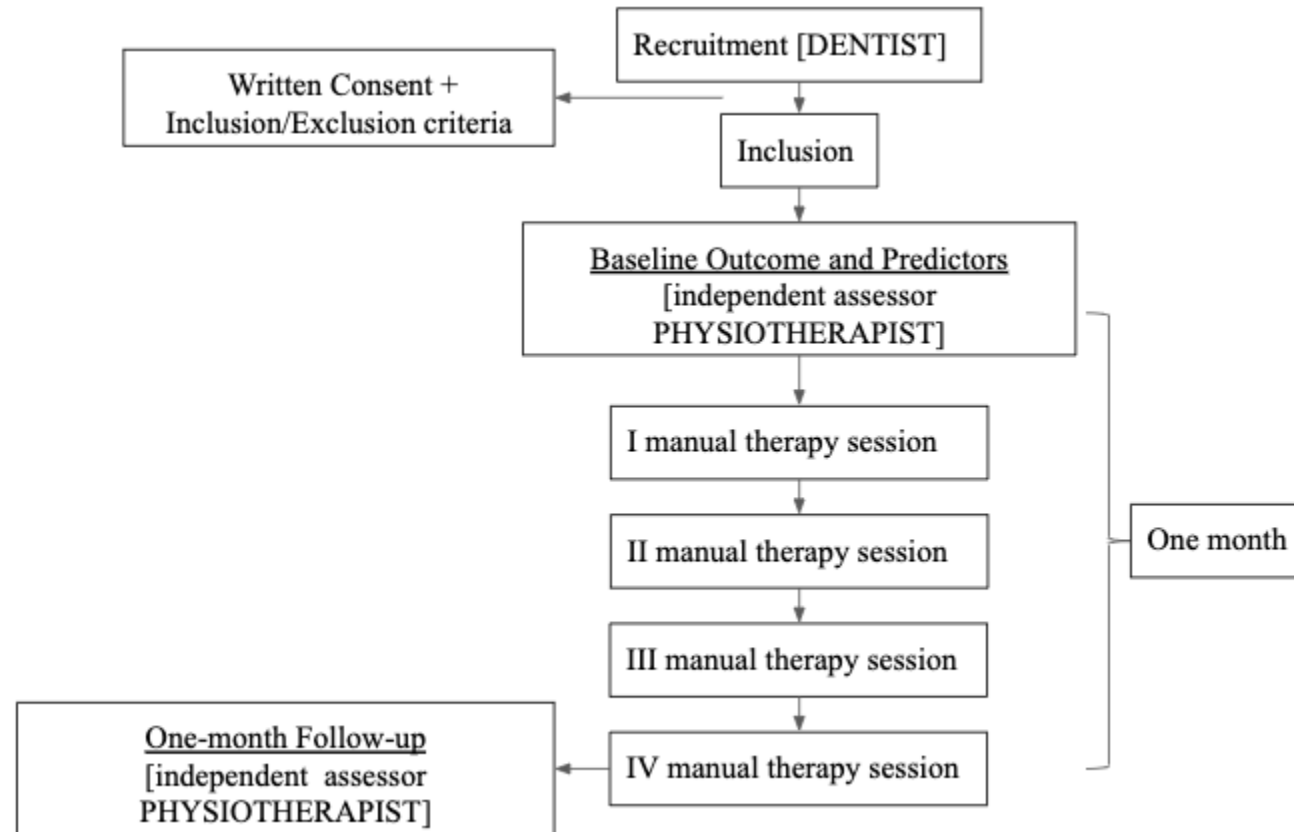
The authors have no competing interests to report.

Data sharing statement

No additional data are available.

FIGURE LEGEND

Figure 1: Participant flow through the study



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3 **PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN**
4 **PATIENTS WITH TEMPOROMANDIBULAR DISORDERS:**
5 **A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY**
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11 **Supplementary file 1 - Candidate predictors**
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18 ***Demographical variables***
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21 Participants' demographic variables [age, gender, education] will be collected at baseline
22 from open hospital records and patient interview.
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27 **Age**
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31 Age is a significant factor in TMD incidence and prevalence. Lipton et al. found different
32 age-specific prevalence for face/jaw pain: 6.5% in aged 18-34, 5.0% in 35-54 years old, 4.0% in
33 55-74 years old and 3.9% in people > 74 year old, showing a prevalence reduction across the
34 lifetime¹. By contrast, data from the OPPERA study² showed a 40% increased risk for TMD among
35 individuals aged 25-34 years and a 50% increased risk for TMD among individuals aged 35-50
36 years.
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46 **Gender**
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50 Women are 1.5-2 times more likely to develop TMD than men³⁻⁵. Currently, there is no
51 study examining the extent of recovery from TMD in men and women. Nevertheless, gender is a
52 significant factor to be considered.
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Education

The National Centre of Health and Statistic (NCHS)⁶ found that the differences in jaw pain prevalence among different educational groups are minimal. On the other hand, there is evidence that people with lower levels of education adopt maladaptive coping strategies, including a tendency to catastrophize about their pain⁷. As a result, the education levels will be collected as candidate predictor of outcome by classifying education into three categories: basic education, intermediate education and university-level education.

General health variable

EuroQol Five Dimension Scale, 5-level [EQ-5D-5L]

According to Kapos et al.⁸, health-related quality of life can be a significant factor influencing treatment outcome for TMD. The results showed that a higher health-related quality of life predicted lower TMD pain intensity at an 8 year follow-up. Health-related quality of life will be measured using the Italian version of the EQ-5D-5L [www.euroqol.org]. This instrument transforms different health states into a single value with range 0-1 where 1 is perfect health, and it measures the patient's own judgement about his/her health outcome through a visual analogue scale range 0–100, representing respectively 'worst' to 'best' imaginable health state⁹. The EQ-5D-5L, with 5 possible responses to each item, has increased inter-observer [ICC 2,1 0.57] and test-retest [ICC 2,1 0.69] reliability compared to the previous EQ-5D-3L¹⁰. Additionally, it has less ceiling effects [20.8% reduction] and adequate convergent validity when compared with the WHO-5 [Spearman rank 0.38-0.51]¹¹.

Sleep quality

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3 It is known that chronic pain patients may suffer from poor sleep quality, even if it is
4 difficult to draw a causal relation¹². Consequently, sleep quality will be assessed as a candidate
5 predictor because of its possible role among other factors in the transition from acute to chronic
6 pain. Sleep quality will be evaluated through an 11-point Numerical Rating Scale [NRS], where 0
7 is 'the best possible sleep' and 10 is 'the worst possible sleep'. This scale owns moderate
8 psychometric properties in fibromyalgia patients to assess current sleep quality [over the previous
9 24 hour period] with a symptom diary¹³. We will use the 0-10 NRS to assess average sleep quality,
10 related to the preceding 6-months at baseline¹⁴, although no psychometric properties have
11 previously been reported for this recall period.
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24 *Psychosocial features*

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29 Psychosocial factors are known to influence TMD onset and chronicity¹⁵. Psychological
30 distress is significantly linked to a greater severity and persistence of TMD pain¹⁶. Moreover,
31 depression and high levels of stress are significantly more common in people with chronic TMD¹⁷⁻
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18. In addition, there is agreement about the predictive strength of psychosocial factors in primary
care among different musculoskeletal pain conditions¹⁹⁻²⁰.

The Hospital Anxiety and Depression Scales [HADS]

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The Italian version of the HAD²¹ will be utilised to investigate depression, anxiety and
manifestations of somatic symptoms²². This scale consists of two subscales [anxiety: HADS-A;
depression: HADS-D] with 7 items and a total score from 0 to 21, with a higher score indicating
elevated levels of anxiety and depression²³.

HADS has been studied in different groups confirming adequate to excellent internal

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3 consistency of HADS-A [0.68-0.93] and HADS-D [0.67-0.90]²³. In a coronary heart disease
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5 sample, the standard measurement of error was 1.37 for anxiety and 1.44 for depression; the
6
7 minimal detectable change was 3.80 for anxiety and 3.99 for depression²⁴. The HADS has
8
9 excellent concurrent validity in comparison to other depression/anxiety scales²³.
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13 Coping Strategies Questionnaire 27 [CSQ-27]

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17 Forssell et al.²⁵ found that a low perceived ability to control pain increases the risk for poor
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19 prognosis of TMD pain at one year regardless of the type of treatment. The Italian version of the
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21 CSQ-27²⁶ will be used to provide an indication of coping strategies used by participants when they
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23 are in pain. This 27-item questionnaire contains six domains to assess the strategies for coping
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25 with pain: *Distraction*, *Catastrophizing*, *Ignoring pain sensations*, *Distancing from pain*, *Coping*
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27 *self-statements*, and *Praying*. Patients rate the specific strategies for coping with pain using a
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29 seven-point Likert scale [for each domain] ranging from 0 “Never do that” to 6 “Always do that”,
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31 with higher scores indicating greater use²⁷. A recent study in a low back pain cohort²⁸, in which
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33 individual items from multiple questionnaires were factorised, suggested that diversion,
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35 reinterpreting and cognitive coping clustered together as a single factor, representing coping
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37 cognitions; by contrast, catastrophizing clustered with pain-related distress items. The original
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39 form was examined in English-speaking subjects and revealed acceptable internal consistency
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41 [Cronbach’s alpha estimates ranging from 0.72 to 0.86] and satisfying construct validity²⁷.
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48 Treatment expectation

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52 A positive treatment expectation is considered as a treatment moderator because of its
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54 influence on treatment outcome²⁹. A positive treatment expectation is predictive of good outcome
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3 because the expectation of benefit (placebo) has a robust effect on pain³⁰. In the current study we
4 will investigate treatment expectation following the same protocol used by Puentedura et al³¹.
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6 Participants will be asked whether they “Completely disagree”, “Somewhat disagree”, “Neutral”,
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8 “Somewhat agree”, “Completely agree” with the following statement: “I believe that *manual*
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10 *techniques applied to my jaw* will significantly help to improve my pain”. If the participant chooses
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12 “completely disagree,” “somewhat disagree,” or “neutral,” there is not a positive expectation that
13
14 manual therapy applied to craniomandibular structures will significantly help their
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16 temporomandibular disorder. If the participant chooses “somewhat agree” or “completely agree,”
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18 there is a positive expectation that manual therapy applied to craniomandibular structures will
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20 significantly help their temporomandibular disorder.
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27 ***TMD characteristics***

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31 Based on previous studies on predictive factors of outcome in TMD patients^{8,25,32}, pain
32 characteristics [e.g. pain duration, pain intensity, pain location] are good predictors for pain change
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34 in the long-term. In addition, across a variety of different conditions, pain features were reported
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36 to hold predictive value for pain modulation^{19,33-35}.
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41 Pain Duration

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45 According to Grossman et al.³², pain duration could be a significant factor influencing the
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47 treatment outcome for TMD. Their results underline the fact that a longer pain duration is
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49 associated with a more refractory therapeutic approach. Consequently, the pain duration [measured
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51 in “days”] will be collected as candidate predictor of outcome from open hospital records and
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53 patient interview.
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Pain intensity

As shown in a previous study³², high levels of pain intensity at baseline in people with TMD, can be associated with no-clinically significant results at a midterm [3-4 months] follow up. Pain intensity will be calculated by averaging ratings of current pain, average pain, and worst pain in the past week using the visual analogue scale (VAS), consisting of a horizontal line measuring 10 cm (without marks), with “no pain” written at the left extremity, and “unbearable pain” written at the right extremity³⁶. Patients will be educated to trace a perpendicular line on the horizontal line to intend the pain intensity. The distance from the 0 points will be after measured in millimetres. The VAS is a reliable and valid scale to assess pain intensity³⁷.

Pain location and extent

Forssell et al.²⁵ found that a high number of pain conditions increases the risk for poor prognosis of TMD pain at one year regardless of the type of treatment. Comorbid painful areas are common in patients with TMD pain³⁸. Therefore, the pain location and the pain extent will be collected as a candidate predictor of outcome. This will be recorded as described in the DC/TMD protocol^{16,39-44}. Patients will be asked to complete a pain drawing symbolising the spatial distribution of the pain, over one chart with a frontal view of the body, one with a dorsal view and one with a dental setting (more specific for the jaw and teeth pain). Pain reported in different body areas (e.g., headache, back pain, pelvic pain, neck pain) can be summarised as a count variable. The extent of pain will be calculated as % of the body area by using an image scanning software (ImageJ: Image Processing and Analysis in Java, <http://imagej.nih.gov/ij/>; Klong Image Measurement: <http://www.imagemasurement.com/experience-image-measurement/pain-assessment-image-measurement>)

Central Sensitization Inventory (CSI)⁴⁵

Central sensitization can be present in different pain disorders including low back pain⁴⁶, neck pain⁴⁷, fibromyalgia⁴⁸, and TMD⁴⁹. The Italian version of the Central Sensitization Inventory (CSI)⁵⁰ will be used. Part A consists of a 0-100 score for 25 items on current health symptoms with five options ranging from ‘never’ (0) to ‘always’ (4). Part B examines previous physician diagnoses among seven different conditions⁴⁵. The CSI has significant test-retest reliability and internal consistency in subjects with and without pain⁴⁵. The Italian version of the CSI showed a satisfactory Cronbach’s alpha [0.87]⁵⁰.

Classification of TMD

Manual therapy could potentially be beneficial for both myogenous and arthrogenous TMD⁵¹. The TMD type will therefore be collected as a candidate predictor of outcome. As stated in the inclusion criteria, every patient included in the study will be diagnosed according to the Axis I of the Diagnostic Criteria for TMD DC/TMD³⁹. Based on these criteria, Peck et al.⁵² reported different types of TMD. This Taxonomic Classification of TMD includes four main domains: TMJ Disorders, Masticatory Muscle Disorders, Headache and Associated Disorders. An additional domain, called Mixed TMD (simultaneous presence of TMJ Disorders and Masticatory Muscle Disorders) will be included. For every patient the type of TMD (total of 5 domains) will be collected as candidate predictors from the patient medical records.

Characteristic pain intensity and disability

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3 A greater number of disability days increases the risk of having clinically significant pain
4 one year after an initial assessment²⁵. In this study we will use the Italian version of Graded
5 Chronic Pain Scale [GCPS] version 2.0 [www.rdc-tmdinternational.org]⁵³ following the DC/TMD
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10 protocol recommendations^{39,42,44}. This scale has good internal consistency in temporomandibular
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12 pain [Cronbach's alpha of 0.84]⁵⁴. The GCPS measures the facial pain severity over the preceding
13
14 6-months by unifying pain intensity and pain-related disability. The characteristic pain intensity
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16 score [range: 0-100] is the mean of three pain intensity measurements: 'at the present time' and
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18 'worst pain' and the 'average' pain over the preceding 6 months. The disability status is measured
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20 with a 0-6 point score derived from a combination of the number of disability days and the
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22 disability level [range: 0-100; limitation given by pain in performing activities of daily living].
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24 Based on these scores, the participant's chronic pain and disability status can be classified into one
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26 of the five ordinal categories of chronic pain severity⁵⁵.

31 Oral Behaviour

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35 People with abnormal oral behaviours with scores above 25 in the Oral Behaviours
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37 Checklist [OBC] are 75% more likely to develop TMD than individuals with a score below
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39 17^{42,44,56}. Parafunctional habits could play a significant role in the development and the persistence
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41 of TMD pain⁵⁸. In this study we will use the Italian version of the RDC/TMD questionnaire Axis
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43 II Oral Behaviours Checklist [www.rdc-tmdinternational.org]^{42,56} following the DC/TMD protocol
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45 recommendations^{39,56}. The OBC measures the self-reported frequency over the preceding month
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47 of each of 21 activities involving the jaw such as clenching the teeth or bracing the jaw (five ordinal
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49 response options, ranging from "none of the time," coded 0, to "all of the time," coded 4).
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51 Psychometric properties of this instrument suggest that it is valid, with patient behaviours
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53 matching those measured^{56,57,59}. Scoring is computed as the sum of the number of items with non-

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3 zero response or as a weighted sum [e.g. the sum of the endorsed frequencies of the respective
4
5 items]⁵⁶.
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8 9 10 **Clinical tests of the TMJ and masticatory muscles**

11 12 TMJ range of motion

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15 Mobility testing of the TMJ denotes an essential sign of TMD, it is one of the most reliable
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17 clinical measures³⁹. Grossman et al.⁸ examined the preoperative variables of TMD patients with
18
19 articular disc displacement without reduction that may alter the effects of arthrocentesis on joint
20
21 effusion. They observed that small maximum interincisal distance influences treatment outcome.
22
23 As a result, we will use the Maximal Mouth Opening (MMO) without pain as measure of TMJ
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25 range of motion. The measurements will be in millimeters and will be taken with a ruler in a
26
27 neutral craniocervical position [e.g. sitting or supine]. The distance between the incisal edges of
28
29 the maxillary and mandibular reference teeth, as described in the DC/TMD protocol⁴⁴, will be
30
31 measured. Participants will be asked to open the mouth as wide as they can without feeling any
32
33 pain, or without increasing any present pain. The tip of the ruler will be located against the incisal
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35 edge of the mandibular reference incisor, and the distance to the mesial-distal center of the edge
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37 of the maxillary central incisor will be read. The test will be repeated twice if the pain-free opening
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39 if less than 30mm⁴⁴. Assessment of mandibular ROM in a neutral craniocervical position obtained
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41 good inter- and intra-rater reliability for MMO⁶⁰.
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48 49 TMJ palpation pain:

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52 Pain induced in joints via palpation is a useful clinical test that allows to understand if the
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54 provoked pain duplicates or replicates the patient's pain complaint by identifying potential joint
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3 origin⁴⁴. For this palpation, finger pressure is calibrated [1.0 kg], as described in the DC/TMD
4 protocol⁴⁴, using a simple hand-held algometer prior to palpation examination. While the
5 participant mandible is in a comfortable position or in a slightly protruded position, the examiner's
6 index finger will be placed just anterior to the tragus of the ear and dorsal to the TMJ with the
7 participant in neutral craniocervical position e.g. sitting or supine. The index finger will press while
8 orbiting around the lateral pole in a circular fashion over the superior aspect of the condyle and
9 then anteriorly [from the 9:00 to the 3:00 position, and then continuing fully around the condyle].
10 Palpation will last 5 seconds for each pressed point⁴⁴. If a participant complains of familiar pain in
11 at least one pressed point the point score of this test will be 1; if there is no pain at any points the
12 point score of this test will be 0 [range 0-1: no pain =0; pain = 1]. Palpation will be performed in
13 the left and right side. The interexaminer reliability values of TMJ palpation in TMD patients is
14 0.59 and the specificity values is acceptable [above 0.90]⁶¹.

31 Muscle palpation pain

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34 For this assessment, finger pressure is calibrated to 1.0 kg for masseter muscles and 0.5 kg
35 for lateral pterygoid area and temporalis tendons as described in the DC/TMD protocol⁴⁴, using a
36 simple hand-held algometer prior to palpation examination. Pain induced in muscles via palpation
37 is a useful clinical test that allows to understand whether the provoked pain duplicates or replicates
38 the patient's pain complaint by identifying potential muscular origin⁴⁴. Palpation will be performed
39 with the participant in a neutral craniocervical position (e.g. sitting or supine), on the left and right
40 side and will last 5 seconds for each testing point⁴⁴. The inter-examiner reliability values of
41 palpation in TMD patients is 0.59 and the specificity values are acceptable [above 0.90]⁶¹. The
42 feasibility of the lateral pterygoid muscle palpation is controversial. Some authors defined it as a
43 feasible palpation technique⁶², and others considered this muscle inaccessible⁶³. Therefore, in this
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3 study, this parameter [pain at lateral pterygoid site] will not be considered alone but in combination
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5 with pain at other muscular sites.
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11 *Lateral pterygoid area:* palpation will be performed with a finger pressure calibrated at 0.5
12 kg (DC/TMD protocol⁴⁴). The palpation will take place as described in FIG.1. If a participant
13 complains of familiar pain during palpation the lateral pterygoid area will be considered as a
14 painful site.
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27 **FIG. 1 Lateral pterygoid area:** Finger is placed as
28 shown. Palpate the vestibule in posterior-superior-
29 medial direction while the mandible is omolaterally
30
31 medial direction while the mandible is omolaterally
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33 deviated.
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39 *Masseter muscle:* masseter palpation consists of a sequence of three palpation sites with
40 finger pressure calibrated to 1.0 kg (DC/TMD protocol⁴⁴): origin zone [inferior to the bony margin
41 of the zygomatic process], body zone [in front of ear lobe] and insertion zone [superior to the
42 mandibular angle]. In each zone, the palpation continues until the anterior boundary of the muscle
43 is reached⁴⁴. If a participant complains of familiar pain in at least one pressed point, the masseter
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45 muscle will be considered as a painful site.
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54 *Temporalis tendon area:* the palpation will be performed with a finger pressure calibrated
55 to 0.5 kg (DC/TMD protocol⁴⁴). The palpation will take place as described in FIG.2. If a participant
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3 complains of familiar pain during the palpation the temporalis tendon area will be considered as a
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5 painful site.
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11 **FIG. 2 Temporalis tendon area:** Finger is located against the ascending mandibular ramus
12 while the mouth is slightly open. The palpation direction is
13 superior as far as possible by following the bone surface.
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22 *Total score:* if a participant complains of familiar pain
23 in at least three of the six examined sites the score will be 1,
24 otherwise it will be 0 [score range 0–1: < 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain
25 = 1]⁶⁴.
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35 JAw-test

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38 The JAw-test is a clinical test that aims to investigate the immediate effects of four brief
39 intraoral manual therapy techniques on pain and on TMJ range of motion. The participant will be
40 positioned in supine position. Before starting the test, the TMJ range of motion without pain will
41 be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD
42 protocol⁴⁴. Then the participant will be asked to rate his/her pain through the Verbal Rating Scale
43 (VRS) “at rest”, “during clenching” and “during the maximal opening of the mouth”; an average
44 of the three pain scores will be registered. For this test, finger pressure is calibrated [1.0 kg], in the
45 same way described in the DC/TMD protocol⁴⁴, using a simple hand-held algometer prior to
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3 palpation examination.
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5 Participants will be informed with the following words: “*I am going to perform four manual*
6 *techniques on some muscles and joints in your jaw region. You may feel a little pain, if the pain*
7 *increases and becomes too intense, let me know, I will reduce the pressure until the pain returns*
8 *to acceptable levels*”.
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14 *First technique: Lateral pterygoid area*

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17 This techniques will be performed on the most painful side. While one hand stabilizes the
18 participant’s head on the least painful side, the other hand will be used to apply pressure over the
19 lateral pterygoid area as described above and in accordance with the DC/TMD protocol⁴⁴. In this
20 position, compression [1.0 kg] is applied for 30-60 seconds.
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26 *Second technique: Temporalis tendon area*

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28 This techniques will be performed on the most painful side. While one hand stabilizes the
29 participant’s head on the least painful side, the other hand (index finger) will be used to apply
30 pressure over the Temporalis tendon area as described above and in accordance with the DC/TMD
31 protocol⁴⁴. In this position, compression [1.0 kg] is applied for 30-60 seconds.
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38 *Third technique: Mylohyoid area*

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40 The participant will be instructed to open the mouth to let the examiner’s finger reach the
41 mylohyoid area in a central position on the mylohyoid raphe. The other hand of the examiner will
42 reach the same area using a finger through an extraoral approach. In this position a combined
43 compression (1.0 kg) will be applied for 30-60 seconds.
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49 *Fourth technique: TMJ mobilization*

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51 An intraoral ventral and caudal anterior glide [mobilisation grades I and II] of both the
52 TMJs will be performed for 30 seconds as described by Cleland et al.⁶⁵
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3 *Final scores:*
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5 After the tests, the TMJ range of motion without pain will be measured [MMO -
6 millimeters] with a ruler, as described above, according to DC/TMD protocol⁴⁴. Then the
7 participant will be asked to rate his/her pain using the Verbal Rating Scale (VRS) “at rest”, “during
8 clenching” and “during the maximal opening of the mouth”; an average of these three pain scores
9 will be registered. If a participant shows only an improvement in pain [average score VRS pre-test
10 > average score VRS post-test] the score will be 1; if a participant shows only an improvement of
11 TMJ mobility [MMO pre-test < MMO post-test at least 2 millimeters] the score will be 1; if a
12 participant shows improvements in both pain and TMJ mobility, the score will be 2; if a participant
13 shows no improvements the score will be 0 [Score range 0-2: 0 = no change; 1 = VRS improvement
14 or MMO improvement; 2 = improvement of both].
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|-----------------------------------|---------|--|
| Administrative information | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – Page 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry – N/A |
| | 2b | All items from the World Health Organization Trial Registration Data Set – N/A |
| Protocol version | 3 | Date and version identifier – Page 1 |
| Funding | 4 | Sources and types of financial, material, and other support – Page 22 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors – Pages 1 and 22 |
| | 5b | Name and contact information for the trial sponsor – N/A |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities – N/A |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – N/A |
| Introduction | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – Pages 4-6 |
| | 6b | Explanation for choice of comparators – Supplementary file |
| Objectives | 7 | Specific objectives or hypotheses - Page 5-6 |

1
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) – N/A
5
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7

8 **Methods: Participants, interventions, and outcomes**
9

10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained – Page 6
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) – Pages 7
17
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered – Pages 8-9
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease) – Page 9
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests) – N/A
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial – Pages 7 and 9
32
33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended – Page 9 and 10 (primary
40 outcome), Supplementary file (candidate predictors)
41
42

43 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
44 timeline washouts), assessments, and visits for participants. A schematic
45 diagram is highly recommended (see Figure) – Pages 7-8
46
47

48 Sample size 14 Estimated number of participants needed to achieve study objectives
49 and how it was determined, including clinical and statistical
50 assumptions supporting any sample size calculations – Page 12
51

52 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
53 target sample size – Pages 7
54
55

56 **Methods: Assignment of interventions (for controlled trials)**
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58 Allocation:
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|----|----------------|-----|---|
| 1 | | | |
| 2 | Sequence | 16a | Method of generating the allocation sequence (eg, computer- |
| 3 | generation | | generated random numbers), and list of any factors for stratification. |
| 4 | | | To reduce predictability of a random sequence, details of any planned |
| 5 | | | restriction (eg, blocking) should be provided in a separate document |
| 6 | | | that is unavailable to those who enrol participants or assign |
| 7 | | | interventions – N/A |
| 8 | | | |
| 9 | | | |
| 10 | Allocation | 16b | Mechanism of implementing the allocation sequence (eg, central |
| 11 | concealment | | telephone; sequentially numbered, opaque, sealed envelopes), |
| 12 | mechanism | | describing any steps to conceal the sequence until interventions are |
| 13 | | | assigned – N/A |
| 14 | | | |
| 15 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, |
| 16 | | | and who will assign participants to interventions – N/A |
| 17 | | | |
| 18 | | | |
| 19 | Blinding | 17a | Who will be blinded after assignment to interventions (eg, trial |
| 20 | (masking) | | participants, care providers, outcome assessors, data analysts), and |
| 21 | | | how N/A |
| 22 | | | |
| 23 | | 17b | If blinded, circumstances under which unblinding is permissible, and |
| 24 | | | procedure for revealing a participant's allocated intervention during |
| 25 | | | the trial – N/A |
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Methods: Data collection, management, and analysis

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|----|-----------------|-----|--|
| 28 | | | |
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| 30 | Data collection | 18a | Plans for assessment and collection of outcome, baseline, and other |
| 31 | methods | | trial data, including any related processes to promote data quality (eg, |
| 32 | | | duplicate measurements, training of assessors) and a description of |
| 33 | | | study instruments (eg, questionnaires, laboratory tests) along with |
| 34 | | | their reliability and validity, if known. Reference to where data |
| 35 | | | collection forms can be found, if not in the protocol – Pages 9-11, |
| 36 | | | Supplementary file |
| 37 | | | |
| 38 | | | |
| 39 | | 18b | Plans to promote participant retention and complete follow-up, |
| 40 | | | including list of any outcome data to be collected for participants who |
| 41 | | | discontinue or deviate from intervention protocols – Page 12-13 |
| 42 | | | (withdrawals) |
| 43 | | | |
| 44 | | | |
| 45 | Data | 19 | Plans for data entry, coding, security, and storage, including any |
| 46 | management | | related processes to promote data quality (eg, double data entry; |
| 47 | | | range checks for data values). Reference to where details of data |
| 48 | | | management procedures can be found, if not in the protocol – Page |
| 49 | | | 12 |
| 50 | | | |
| 51 | | | |
| 52 | Statistical | 20a | Statistical methods for analysing primary and secondary outcomes. |
| 53 | methods | | Reference to where other details of the statistical analysis plan can be |
| 54 | | | found, if not in the protocol – Page 12-13 |
| 55 | | | |
| 56 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted |
| 57 | | | analyses) – n/A |
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- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – Page 12

Methods: Monitoring

- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed – N/A
- 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – N/A
- Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – Page 14
- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – N/A

Ethics and dissemination

- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – Pages 6 and 14
- Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – N/A
- Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – Page 7
- 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – N/A
- Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – Page 12
- Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site – Page 22
- Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – Not present
- Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – N/A

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| 1 | | | |
| 2 | Dissemination | 31a | Plans for investigators and sponsor to communicate trial results to |
| 3 | policy | | participants, healthcare professionals, the public, and other relevant |
| 4 | | | groups (eg, via publication, reporting in results databases, or other |
| 5 | | | data sharing arrangements), including any publication restrictions – |
| 6 | | | N/A |
| 7 | | | |
| 8 | | 31b | Authorship eligibility guidelines and any intended use of professional |
| 9 | | | writers – N/A |
| 10 | | | |
| 11 | | 31c | Plans, if any, for granting public access to the full protocol, participant- |
| 12 | | | level dataset, and statistical code – N/A |
| 13 | | | |
| 14 | | | |

Appendices

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|----|------------------|----|--|
| 15 | | | |
| 16 | | | |
| 17 | Informed consent | 32 | Model consent form and other related documentation given to |
| 18 | materials | | participants and authorised surrogates – N/A |
| 19 | | | |
| 20 | Biological | 33 | Plans for collection, laboratory evaluation, and storage of biological |
| 21 | specimens | | specimens for genetic or molecular analysis in the current trial and for |
| 22 | | | future use in ancillary studies, if applicable – N/A |
| 23 | | | |
| 24 | | | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN PATIENTS WITH TEMPOROMANDIBULAR DISORDERS: A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY

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**PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN
PATIENTS WITH TEMPOROMANDIBULAR DISORDERS:
A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY**

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ABSTRACT

Introduction

Temporomandibular Disorders (TMD) are principally characterised by pain in the craniomandibular area and probable limitations of jaw opening. Manual therapy, like other recommended conservative treatments included in clinical guidelines, is commonly used to treat patients with TMD to reduce pain and improve function. However, outcomes may be variable. The aim of this study is to identify predictors associated with pain reduction in patients with TMD following manual therapy by analysing a combination of patient-reported outcome measures and clinical tests. Such knowledge will support a more personalised management approach by facilitating clinical decision-making.

Methods/analysis

An observational prospective design will recruit a cohort of 100 adults with a diagnosis of TMD (according to Axis I of the Diagnostic Criteria for TMD) at a Dental Hospital in Italy. Patients will be treated with four weekly sessions of manual therapy applied to craniomandibular structures. An array of predictors has been chosen based on previous research on prognostic factors for TMD and altered pain modulation in musculoskeletal disorders. Candidate predictors including demographic variables, general health variables, psychosocial features, TMD characteristics, and clinical tests of the temporomandibular joint and masticatory muscles will be collected at baseline. Definition of good outcome is a clinically significant reduction of pain intensity over the last week ($\geq 30\%$ reduction Visual Analogue Scale) immediately following the 4-week intervention. Exploratory factor analysis will be applied to analyse factor loading of candidate predictors for good outcome at 4 weeks. Subsequently, a logistic multivariable regression model will be performed to calculate low and high risk of good outcome.

Ethics and dissemination

Ethical approval will be obtained from the “Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico” and University of Birmingham Ethics Committee. The results will be submitted for publication in a peer-reviewed journal and presented at conferences.

Keywords: Temporomandibular Disorders, Temporomandibular Joint Dysfunction Syndrome, Pain, Prediction, Manual Therapy

Word count: 3129 [excluding references]

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first study to identify predictors associated with pain reduction following manual therapy interventions in patients with TMD
- The study will utilise a comprehensive array of candidate factors to predict clinically relevant pain reduction
- The implications from this study will facilitate clinical decision-making for manual therapists managing patients with TMD
- Alternative or additional predictors could be valuable to include but the candidate predictors have been prioritised as they are reliable and valid measures which have a relationship with pain
- The study could potentially generate a non-representative sample of patients as it will exclude people who have already received recent treatment for their TMD

INTRODUCTION

Temporomandibular Disorders (TMD) affect approximately 10% of the adult population and, in the USA alone, are estimated to cost US\$4 billion per year on management¹⁻². In Spain, the incidence of TMD has significantly increased (from 8% in 1993 to 14% in 2015) despite a clear improvement in general oral health over the entire period³. Although some countries report less prevalence of TMD such as in Sweden (approximately 5%)⁴, TMD remains a public health-related challenge. TMD are principally characterised by pain and limitations of jaw opening⁵ but many patients also complain of neck and back pain or pain at other sites⁶.

Physical therapy is one of the most common conservative interventions for the management of TMD⁷ and given that the aetiology may be unclear⁸, several therapeutic approaches have been described⁹. One approach is manual therapy applied to the craniomandibular structures with evidence suggesting a significant reduction in pain with manual therapy treatment¹⁰, although responses are highly variable¹¹. In other musculoskeletal pain disorders, such as neck or back pain, pain reduction from manual therapy has been shown to be superior to other treatments (e.g. therapeutic exercise) when targeted towards patients with specific clinical features including the onset of symptoms within 30 days¹²⁻¹³. Nevertheless, in TMD, no previous study has investigated patient factors associated with significant pain reduction following manual therapy. Such knowledge could be achieved by identifying potential predictors (e.g. pain characteristics, psychosocial features, TMD characteristics) of pain reduction following manual therapy interventions in patients with TMD to support a more personalised management approach.

Very few studies have examined factors associated with pain reduction in patients with TMD. Forssell et al. conducted a prospective cohort study with 263 primary care

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2
3 patients with TMD pain¹⁴. They analysed several potential predictors of persistent pain at
4
5 one-year follow-up including demographic, pain-related and psychosocial variables. It was
6
7 concluded that patients with TMD who have had numerous previous healthcare visits,
8
9 complained of high-intensity pain at other body sites and had a greater number of disability
10
11 days, were at greater risk of having pain one year after the initial assessment. Nevertheless,
12
13 this study did not examine predictors of pain reduction related to a therapeutic intervention
14
15 which could be useful to inform clinical practice. Kapos et al. investigated the association of
16
17 long-term pain intensity with baseline health-related quality of life and jaw functional
18
19 limitation in patients with TMD¹⁵. Findings suggested that baseline health-related quality of
20
21 life is inversely proportional with pain intensity at an eight-year follow-up regardless of the
22
23 type of treatment that they received (e.g. surgery, drugs, physical therapy or unconventional
24
25 therapy). After adjusting for the type of treatments received, by clustering the participants
26
27 into three groups (medical/conventional management, alternative medicine, and surgical
28
29 intervention), each predictor analysed (demographic, pain-related and health-related quality
30
31 of life) maintained similar statistical significance. Notwithstanding, the group classified as
32
33 “medical/ conventional management” included participants receiving diverse treatments
34
35 ranging from physical therapy, pharmacology (Acetaminophen, Antidepressants, Anti-
36
37 inflammatories) to the application of a mouth appliance (e.g. Michigan splint). This previous
38
39 work can facilitate clinicians to identify patients who are more challenging to treat by
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41 identifying clinical features associated with persistent pain in the long term regardless of the
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43 type of interventions applied. However, currently no study has examined predictive factors
44
45 associated with pain reduction following manual therapy interventions in patients with TMD.
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54 The aim of this study is to identify predictors associated with pain reduction in
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56 patients with TMD following manual therapy applied to craniomandibular structures by
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58 analysing a combination of: (1) demographical variables, (2) general health variables, (3)
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3 psychosocial features, (4) TMD characteristics, and (5) clinical tests of the
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5 temporomandibular joint and masticatory muscles. The knowledge gained from this study
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7 will facilitate clinical decision-making for manual therapists managing patients with TMD by
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9 providing clinicians with key factors to evaluate, to determine whether or not the patient is
10
11 likely to have a clinically relevant reduction in their pain immediately following four weekly
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13 applications of manual therapy.
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18 19 **METHODS AND ANALYSIS**

20 21 **Source of data**

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24
25 A prospective observational study will recruit a cohort of patients referred to the
26
27 Italian Stomatologic Institute with a TMD diagnosis according to the Axis I of the Diagnostic
28
29 Criteria for TMDs (DC/TMD)¹⁶. This protocol is written according to the Transparent
30
31 Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis
32
33 (TRIPOD) statement¹⁷ in which recommendations are provided about prediction model
34
35 development and validation. Ethical clearance will be obtained from the Ethics Committee of
36
37 the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and the University of
38
39 Birmingham Ethics Committee, and the study will be conducted in accordance with the
40
41 Declaration of Helsinki.
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47 Patient reported and physical assessment data will be collected at baseline prior to
48
49 commencing treatment. Outcome will be collected at the end of the fourth session of
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51 craniomandibular manual therapy (at one month). This timeline has been selected based on
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53 previous studies investigating 1) the effects of manual therapy on pain¹⁸⁻¹⁹; and 2) work
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55 confirming the effectiveness of manual therapy for TMD patients²⁰ and is believed to be
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57 reasonable for the purposes of this study.
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Setting and Participants

Participant recruitment will be carried out at the TMJ Unit of the Italian Stomatological Institute (Dental Hospital) in Milan, Italy over a period of up to 12 months (planned start date July 2019). Consecutive eligible participants will be approached for recruitment until the sample size is reached.

Eligibility criteria

Inclusion criteria: (1) adults aged ≥ 18 years; (2) TMD diagnosis according to the Diagnostic Criteria for TMDs (DC/TMD)¹⁶; (3) no therapeutic interventions reported (for their TMD) in the past six months²¹; (4) capacity to use and understand written and verbal Italian language; (5) mental capacity to provide informed consent.

Exclusion criteria: (1) TMD pain related to rheumatoid/inflammatory arthritis (2) any physical (e.g. facial paralysis, neurological disorders, neuropathic pain) or mental condition (e.g. cognitive deficit, mental illness and/or disorders) that could potentially influence the study results. Additionally, patients will be excluded if (3) they commence another treatment for their TMD (pharmacology, oral appliance, others) throughout the duration of the study.

Recruitment

Based on feasibility data from the last 5 years of activity at the TMJ Unit of Italian Stomatologic Institute, it is estimated that at least 130 eligible participants will be available for recruitment over 13 months. According to previous observational studies on the prediction of outcomes in musculoskeletal disorders¹²⁻¹³, it is estimated that 75% of eligible participants will consent to participation [100 participants].

All patients attending the TMJ Unit will be screened for the presence of a TMD. One expert dentist with >10 years' experience in the management of patients with TMD, will confirm the TMD diagnosis according to the DC/TMD using the Italian translation of the

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2
3 protocol²². Subsequently, in accordance with the inclusion/exclusion criteria, he will explain
4 the study to the potential participant and provide the patient information sheet. Participants
5 will then give their written informed consent prior to inclusion in the study. Afterwards, the
6 participant will be referred to see a physiotherapist [independent assessor, >5 years'
7 experience in managing patients with TMD] for the baseline assessments (summarised in
8 Table 1) and then treatment will commence within the same week. After the last session (i.e.
9 one month from baseline), the participants will be assessed again by the assessing
10 physiotherapist to measure outcome. Participant flow through the study is outlined in Figure
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26 [FIGURE 1]
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30 31 **Treatment**

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33 Participants will receive four sessions of manual therapy applied to craniomandibular
34 structures over 4 weeks²³⁻²⁵. Two physiotherapists, each with >5 years' experience in manual
35 therapy / TMD will perform the treatments. They will not be involved in participant
36 recruitment, assessment or the collection of the outcome measure. Manual therapy techniques
37 will be based on the clinical examination, and will be selected at the discretion of the treating
38 physiotherapist according to their clinical reasoning of the individual case. Overall, the
39 application of manual therapy aims to decrease pain by treating masticatory muscle trigger
40 points, muscle tightness, and restricted temporomandibular joint movements. Several
41 techniques will be considered including: (i) ventral and caudal anterior glide
42 temporomandibular joint mobilization²⁶; (ii) soft tissue interventions for the management of
43 trigger points in masticatory muscles²⁷; (iii) myofascial induction therapy [functional
44 restoration of the fascial system] applied to craniomandibular structures²⁸.
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3 The structures targeted in the treatment sessions will be the temporomandibular joint,
4 temporal muscles, masseter muscles, medial and lateral pterygoid muscles and suprahyoid
5 muscles, applied at the discretion of the physiotherapist based on the patient's individual
6 presentation. During the treatment sessions, the treating physiotherapists will provide
7 explanations about the patient's condition and answer any participant questions by promoting
8 general advice. The treatment sessions will last from 20 to 30 minutes duration. No other
9 treatment (e.g. oral appliance) will be performed for the management of their TMD. If during
10 the course of the four-week intervention, a patient seeks treatment for an acute episode of
11 pain at another site (e.g. neck pain, low back pain, shoulder pain) they will be withdrawn
12 from the study.
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28 **Outcome**

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30 The outcome being predicted by the prediction model is pain intensity since patients
31 with TMD typically report pain to be their primary problem⁵, manual therapy is largely
32 known to be effective principally for pain modulation²⁹ and change in pain intensity has most
33 commonly been the primary outcome of choice in several other studies of patients with
34 TMD³⁰⁻³³.
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42 Pain intensity will be calculated by averaging the ratings of current pain, average pain
43 in the past week, and worst pain in the past week using the Visual Analogue Scale (VAS),
44 consisting of a horizontal line measuring 10 cm (without marks), with "no pain" written at the
45 left extremity, and "worst pain imaginable" at the right extremity³⁴. The VAS is a reliable and
46 valid scale to assess pain intensity as an outcome measure in intervention studies³⁵. Based on
47 the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)
48 recommendations about TMD reviewed by Haythornthwaite³⁶, a reduction of at least 30% of
49 the VAS score for pain intensity is considered clinically significant. Consequently, a
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reduction in the total VAS score [$\geq 30\%$] will be defined as a good outcome. The outcome measure will be evaluated by the same independent assessor to minimise detection bias³⁷.

To capture a potential change in function which may occur with a change in pain intensity, patients will also complete the patient specific functional scale [PSFS]³⁸ pre and post treatment. The PSFS is a self-reported outcome measure assessing functional change in patients with musculoskeletal disorders³⁹⁻⁴⁰. It is responsive to clinically significant change over time⁴¹. Patients will be invited to rate, on an 11-point scale, their level of difficulty performing at least three different daily activities. Following the treatment, patients will be required to score again the activities previously rated. The PSFS is a valid, reliable, and responsive outcome measure with a high test-retest reliability in different musculoskeletal disorders such as low back and neck pain⁴²⁻⁴⁴.

Candidate predictors

The candidate predictors that have been chosen are reliable and valid measures which have a relationship with pain. The selection is based on previous research on prognostic factors for TMD and altered pain modulation in musculoskeletal disorders⁴⁵⁻⁴⁶. Candidate predictors are summarised in Table 1, with further detail in Supplementary file S1. All data collection will be standardised through protocols and clinical report forms.

Table 1: Summary of candidate predictors.

| Domain / Candidate predictor | Measure / data item |
|-------------------------------------|--|
| Demographical variables | |
| Age | Years |
| Gender | Female / male |
| Education | Basic education, intermediate education and university-level education |

| General health variables | |
|---|--|
| Health-related quality of life | EuroQol EQ-5D-5L ⁴⁷ |
| Sleep quality | 11-point [0-10] Numerical Rating Scales, relating to current pain, from 'best possible sleep' to 'worst possible sleep' ⁴⁸ |
| Psychosocial features | |
| Coping strategies applied during a painful experience | Coping Strategies Questionnaire 27 [CSQ-27] ⁴⁹ |
| Anxiety and depression | Hospital Anxiety and Depression Scales [HADS] ⁵⁰ |
| Treatment expectation | Positive / negative expectation ⁵¹ |
| TMD characteristics | |
| Pain duration | Days |
| Pain intensity | VAS: averaging ratings of current pain, average pain, and worst pain in the past week ⁵² |
| Pain location | Pain drawing as described in the protocol of Diagnostic Criteria for TMD (DC/TMD) ¹⁶ |
| Central sensitization | Central Sensitization Inventory (CS) ⁵³ |
| Classification of TMD | In according to DC/TMD Taxonomy ⁵⁴ |
| Oral Behaviours | Oral Behaviours Checklist [OBC] ⁵⁵ |
| Characteristic pain intensity and disability | Graded Chronic Pain Scale (GCPS) version 2.0 [Italian version - www.rdc-tmdinternational.org] |
| TMJ and masticatory muscles clinical test | |
| TMJ range of motion | Maximal Mouth Opening (MMO) without pain measured in mm through a ruler as described in the DC/TMD protocol ¹⁶ |
| TMJ palpation pain | Dynamic TMJ lateral pole palpation [1 kg of palpation pressure] in according to DC/TMD protocol ¹⁶ Score range: 0-1 [no pain =0; pain = 1] |
| Muscle palpation pain | Palpation in the following 6 bilateral points: lateral pterygoid area [0.5 kg intraoral palpation], temporalis tendon [0.5 kg intraoral palpation], masseter muscle [1 kg extraoral palpation] as described in the DC/TMD protocol ¹⁶ . Score range: 0–1 [< 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain = 1] |
| JAw-test | Immediate effects of brief intraoral MT techniques on pain [VRS] and TMJ range of motion [MMO]. A standardised procedure is fully described in Supplementary file S1. Score range 0-2: [0 = no change; 1 = pain improvement or MMO improvement; 2 = improvement of both] |

Data handling

Candidate predictors will be collected by independent physiotherapist assessor. All data will be confidentially secured by storing it on a password-protected computer attainable only by the principal investigators (GA). All individual details will be replaced with ID codes. At the end of the data collection, all data stored on the principal investigator's computer will be transferred securely to a server at the Centre of Precision Rehabilitation for Spinal Pain at Birmingham University where the data will be analysed. All data will be stored on a secure server at the University of Birmingham for a period of 10-years in line with Research Governance procedures. Data will be analysed using IBM SPSS Statistics (Version 25, IBM).

Sample Size

Exploratory factor analysis will be utilised to reduce the number of predictors⁵⁶. This method will guarantee an adequate sample size (at least 10 cases per candidate predictor) to power the final regression analysis⁵⁷⁻⁵⁸. Data will be collected for a sample size of 100 participants so that, considering 10% of potential drops out, final data are available for 90 participants.

Statistical analysis methods

A flow diagram will report eligible participants, examined for eligibility, confirmed eligible, recruited into the study, completed follow-up and analysed. Reasons for non-participation, exclusion, drop-outs and withdrawal will be fully documented and all missing data of participants will be reported. Participant characteristics (candidate predictors - Table 1) will be summarised with a descriptive method.

A primary phase of the exploratory data analysis will summarise data to implement the predictive model⁵⁹. Multicollinearity between candidate predictors will be assessed at baseline. Outcome [VAS pain intensity] will be split into good versus poor as described previously [good outcome: reduction in VAS score $\geq 30\%$]³⁶. Exploratory factor analysis will be applied to

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2
3 analyse factor loading of candidate predictors (summary scores) on good outcome at one
4 month. This process will reduce candidate predictors (supported by the cohort sample of 90) to
5 enter into the final model.
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10 The statistical model has been designed a priori. To investigate the impact of each
11 predictive factor on good outcome, a logistic multivariable regression model will be performed.
12 For each candidate predictor, the mean differences or the odds ratio with their 95% confidence
13 intervals will be calculated. A multiple imputation analysis⁶⁰ will be applied to manage possible
14 missing data. The multivariable analysis will initially consider all candidate predictors. In the
15 case of a high correlation between candidate predictors, a reduced multivariate analysis will be
16 considered.
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28 **DISCUSSION**

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30 There is a need to identify predictors for pain reduction in patients with TMD following
31 specific treatments in order to inform clinical decision-making. Several therapies are described
32 for patients with TMD such as the use of oral appliances, different types of physical therapy
33 modalities, pharmacology or temporomandibular joint arthrocentesis yet the amount of pain
34 relief that different people receive from each intervention is variable^{7,10}. As shown by Forssell
35 et al.¹⁴ and Kapos et al.¹⁵, many patients continue to experience pain following such
36 interventions. Investigating factors associated with pain relief to such treatments can facilitate
37 clinical assessment and treatment selection.
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49 Physical therapy is one of the most common conservative interventions to treat TMD⁷.
50 Among different physical therapy modalities, manual therapy can provide symptom and
51 functional improvements¹⁰ including pain relief^{11,31}. Knowledge of predictive factors
52 associated with good outcome to a specific intervention such as manual therapy applied to
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3 craniomandibular structures will facilitate clinical decision making. Ultimately, such
4
5 knowledge will lead to improved clinical and cost effectiveness of rehabilitation approaches.
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8 **Quality assurance**

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10 Only participants that have not received therapeutic intervention for their TMD in the
11
12 past six months will be included in the current study. It is possible that such eligibility criteria
13
14 could generate selection bias. To address this potential bias, the number of eligible and included
15
16 subjects with the reason for non-participation will be documented.
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19 **Patient and Public Involvement**

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21 The research question in this study was developed following consultations and
22
23 discussion with patients. Patients will not be involved in the analysis and data collection but
24
25 will contribute to data interpretation and production of a lay summary of the findings.
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28 **Ethics and Dissemination**

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30 The research protocol has been submitted to the Ethics Committee of the “Fondazione
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32 IRCCS Ca’ Granda Ospedale Maggiore Policlinico” and subsequently will be submitted to the
33
34 University of Birmingham Ethics Committee for approval. Researchers will inform all
35
36 participants on the characteristics of the research and will obtain written consent. Participants
37
38 will be informed that they are free to withdraw from the study at any time, without needing to
39
40 provide reason. Any concerns for a participant by the study team will be fed back to the primary
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42 investigator (GA). Baseline characteristics of withdrawn participants will be compared to those
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44 of retained participants to assess for any differences. In the event of any unlikely adverse
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46 events, this will be immediately reported by the principal investigator to the ethics committee.
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51 The results of this study will submitted for publication in a peer review journal and
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53 presented at conferences.
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Limitations

The study could potentially generate a non-representative sample of patients with TMD due to a possible selection bias. Subjects reporting other treatments before [6 months] and during the study will be excluded to minimise confounding bias and preserve internal validity. This could potentially generate a non representative sample of TMDs because of exclusion of patients with high levels of pain which seek additional treatment. This potential event, associated with the fact that this observational study will be performed at a single site only, could reduce the external validity and the generalisability of the results.

Conclusion

This protocol paper describes what will be the first study to identify factors associated with pain reduction following manual therapy in patients with TMD. It is anticipated that the knowledge gained from the study described within this protocol, will facilitate clinical decision making for manual therapists managing patients with TMD.

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Author Contributions

GA, AEB and DF formulated the research question and study focus. GA drafted the initial version of the manuscript with DF. NH, AR, GB and ML provided guidance on topic, methodology and analyses. All authors reviewed and commented on each draft of the protocol. All authors have approved the final manuscript. DF is guarantor

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Competing Interests Statement

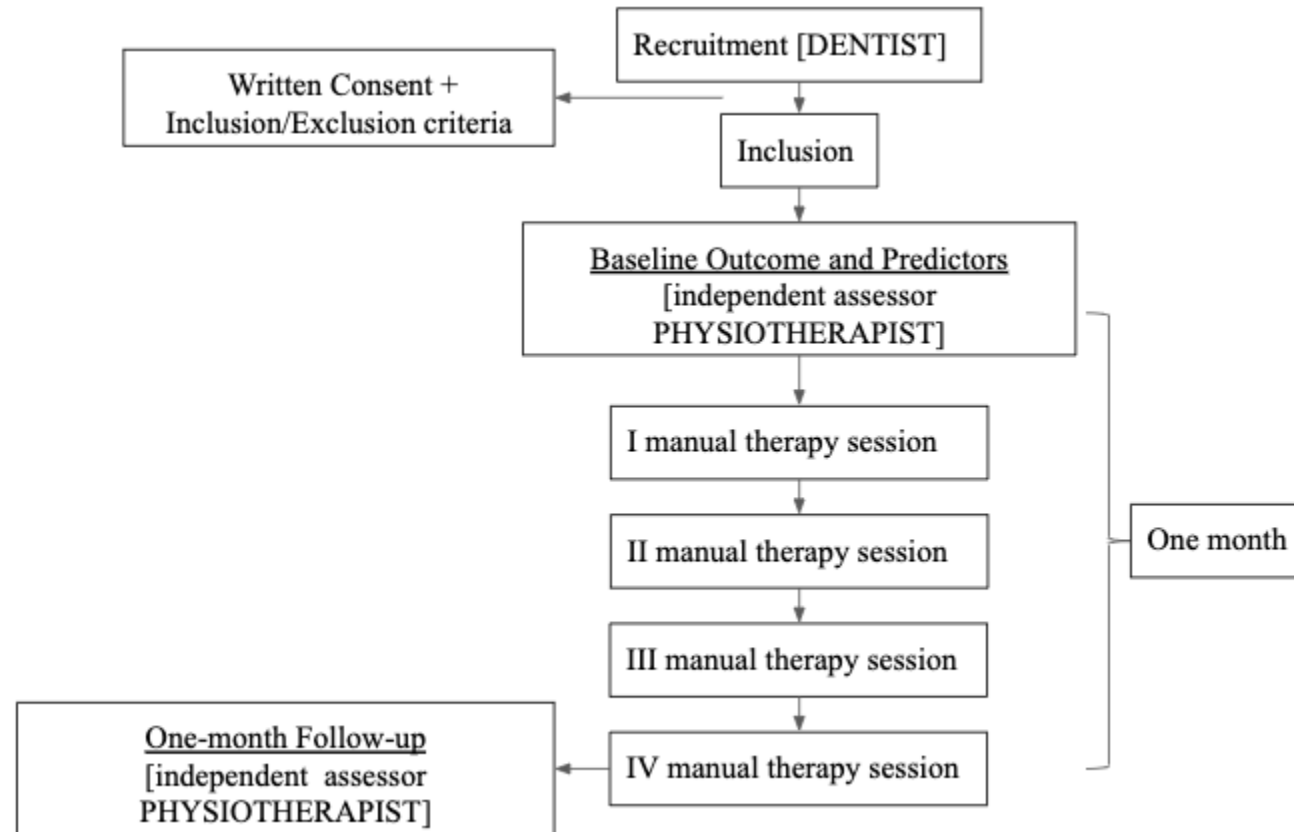
The authors have no competing interests to report.

Data sharing statement

No additional data are available.

FIGURE LEGEND

Figure 1: Participant flow through the study



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3 **PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN**
4 **PATIENTS WITH TEMPOROMANDIBULAR DISORDERS:**
5 **A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY**
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11 **Supplementary file 1 - Candidate predictors**
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18 ***Demographical variables***
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21 Participants' demographic variables [age, gender, education] will be collected at baseline
22 from open hospital records and patient interview.
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27 **Age**
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31 Age is a significant factor in TMD incidence and prevalence. Lipton et al. found different
32 age-specific prevalence for face/jaw pain: 6.5% in aged 18-34, 5.0% in 35-54 years old, 4.0% in
33 55-74 years old and 3.9% in people > 74 year old, showing a prevalence reduction across the
34 lifetime¹. By contrast, data from the OPPERA study² showed a 40% increased risk for TMD among
35 individuals aged 25-34 years and a 50% increased risk for TMD among individuals aged 35-50
36 years.
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46 **Gender**
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50 Women are 1.5-2 times more likely to develop TMD than men³⁻⁵. Currently, there is no
51 study examining the extent of recovery from TMD in men and women. Nevertheless, gender is a
52 significant factor to be considered.
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Education

The National Centre of Health and Statistic (NCHS)⁶ found that the differences in jaw pain prevalence among different educational groups are minimal. On the other hand, there is evidence that people with lower levels of education adopt maladaptive coping strategies, including a tendency to catastrophize about their pain⁷. As a result, the education levels will be collected as candidate predictor of outcome by classifying education into three categories: basic education, intermediate education and university-level education.

General health variable

EuroQol Five Dimension Scale, 5-level [EQ-5D-5L]

According to Kapos et al.⁸, health-related quality of life can be a significant factor influencing treatment outcome for TMD. The results showed that a higher health-related quality of life predicted lower TMD pain intensity at an 8 year follow-up. Health-related quality of life will be measured using the Italian version of the EQ-5D-5L [www.euroqol.org]. This instrument transforms different health states into a single value with range 0-1 where 1 is perfect health, and it measures the patient's own judgement about his/her health outcome through a visual analogue scale range 0–100, representing respectively 'worst' to 'best' imaginable health state⁹. The EQ-5D-5L, with 5 possible responses to each item, has increased inter-observer [ICC 2,1 0.57] and test-retest [ICC 2,1 0.69] reliability compared to the previous EQ-5D-3L¹⁰. Additionally, it has less ceiling effects [20.8% reduction] and adequate convergent validity when compared with the WHO-5 [Spearman rank 0.38-0.51]¹¹.

Sleep quality

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3 It is known that chronic pain patients may suffer from poor sleep quality, even if it is
4 difficult to draw a causal relation¹². Consequently, sleep quality will be assessed as a candidate
5 predictor because of its possible role among other factors in the transition from acute to chronic
6 pain. Sleep quality will be evaluated through an 11-point Numerical Rating Scale [NRS], where 0
7 is 'the best possible sleep' and 10 is 'the worst possible sleep'. This scale owns moderate
8 psychometric properties in fibromyalgia patients to assess current sleep quality [over the previous
9 24 hour period] with a symptom diary¹³. We will use the 0-10 NRS to assess average sleep quality,
10 related to the preceding 6-months at baseline¹⁴, although no psychometric properties have
11 previously been reported for this recall period.
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24 *Psychosocial features*

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29 Psychosocial factors are known to influence TMD onset and chronicity¹⁵. Psychological
30 distress is significantly linked to a greater severity and persistence of TMD pain¹⁶. Moreover,
31 depression and high levels of stress are significantly more common in people with chronic TMD¹⁷⁻
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18. In addition, there is agreement about the predictive strength of psychosocial factors in primary
care among different musculoskeletal pain conditions¹⁹⁻²⁰.

41 The Hospital Anxiety and Depression Scales [HADS]

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The Italian version of the HAD²¹ will be utilised to investigate depression, anxiety and
manifestations of somatic symptoms²². This scale consists of two subscales [anxiety: HADS-A;
depression: HADS-D] with 7 items and a total score from 0 to 21, with a higher score indicating
elevated levels of anxiety and depression²³.

56 HADS has been studied in different groups confirming adequate to excellent internal

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3 consistency of HADS-A [0.68-0.93] and HADS-D [0.67-0.90]²³. In a coronary heart disease
4 sample, the standard measurement of error was 1.37 for anxiety and 1.44 for depression; the
5 minimal detectable change was 3.80 for anxiety and 3.99 for depression²⁴. The HADS has
6 excellent concurrent validity in comparison to other depression/anxiety scales²³.
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13 Coping Strategies Questionnaire 27 [CSQ-27]

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17 Forssell et al.²⁵ found that a low perceived ability to control pain increases the risk for poor
18 prognosis of TMD pain at one year regardless of the type of treatment. The Italian version of the
19 CSQ-27²⁶ will be used to provide an indication of coping strategies used by participants when they
20 are in pain. This 27-item questionnaire contains six domains to assess the strategies for coping
21 with pain: *Distraction*, *Catastrophizing*, *Ignoring pain sensations*, *Distancing from pain*, *Coping*
22 *self-statements*, and *Praying*. Patients rate the specific strategies for coping with pain using a
23 seven-point Likert scale [for each domain] ranging from 0 “Never do that” to 6 “Always do that”,
24 with higher scores indicating greater use²⁷. A recent study in a low back pain cohort²⁸, in which
25 individual items from multiple questionnaires were factorised, suggested that diversion,
26 reinterpreting and cognitive coping clustered together as a single factor, representing coping
27 cognitions; by contrast, catastrophizing clustered with pain-related distress items. The original
28 form was examined in English-speaking subjects and revealed acceptable internal consistency
29 [Cronbach’s alpha estimates ranging from 0.72 to 0.86] and satisfying construct validity²⁷.
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48 Treatment expectation

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52 A positive treatment expectation is considered as a treatment moderator because of its
53 influence on treatment outcome²⁹. A positive treatment expectation is predictive of good outcome
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3 because the expectation of benefit (placebo) has a robust effect on pain³⁰. In the current study we
4 will investigate treatment expectation following the same protocol used by Puentedura et al³¹.
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6 Participants will be asked whether they “Completely disagree”, “Somewhat disagree”, “Neutral”,
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8 “Somewhat agree”, “Completely agree” with the following statement: “I believe that *manual*
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10 *techniques applied to my jaw* will significantly help to improve my pain”. If the participant chooses
11
12 “completely disagree,” “somewhat disagree,” or “neutral,” there is not a positive expectation that
13
14 manual therapy applied to craniomandibular structures will significantly help their
15
16 temporomandibular disorder. If the participant chooses “somewhat agree” or “completely agree,”
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18 there is a positive expectation that manual therapy applied to craniomandibular structures will
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20 significantly help their temporomandibular disorder.
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27 ***TMD characteristics***

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31 Based on previous studies on predictive factors of outcome in TMD patients^{8,25,32}, pain
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33 characteristics [e.g. pain duration, pain intensity, pain location] are good predictors for pain change
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35 in the long-term. In addition, across a variety of different conditions, pain features were reported
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37 to hold predictive value for pain modulation^{19,33-35}.
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41 **Pain Duration**

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45 According to Grossman et al.³², pain duration could be a significant factor influencing the
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47 treatment outcome for TMD. Their results underline the fact that a longer pain duration is
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49 associated with a more refractory therapeutic approach. Consequently, the pain duration [measured
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51 in “days”] will be collected as candidate predictor of outcome from open hospital records and
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53 patient interview.
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Pain intensity

As shown in a previous study³², high levels of pain intensity at baseline in people with TMD, can be associated with no-clinically significant results at a midterm [3-4 months] follow up. Pain intensity will be calculated by averaging ratings of current pain, average pain, and worst pain in the past week using the visual analogue scale (VAS), consisting of a horizontal line measuring 10 cm (without marks), with “no pain” written at the left extremity, and “unbearable pain” written at the right extremity³⁶. Patients will be educated to trace a perpendicular line on the horizontal line to intend the pain intensity. The distance from the 0 points will be after measured in millimetres. The VAS is a reliable and valid scale to assess pain intensity³⁷.

Pain location and extent

Forssell et al.²⁵ found that a high number of pain conditions increases the risk for poor prognosis of TMD pain at one year regardless of the type of treatment. Comorbid painful areas are common in patients with TMD pain³⁸. Therefore, the pain location and the pain extent will be collected as a candidate predictor of outcome. This will be recorded as described in the DC/TMD protocol^{16,39-44}. Patients will be asked to complete a pain drawing symbolising the spatial distribution of the pain, over one chart with a frontal view of the body, one with a dorsal view and one with a dental setting (more specific for the jaw and teeth pain). Pain reported in different body areas (e.g., headache, back pain, pelvic pain, neck pain) can be summarised as a count variable. The extent of pain will be calculated as % of the body area by using an image scanning software (ImageJ: Image Processing and Analysis in Java, <http://imagej.nih.gov/ij/>; Klong Image Measurement: <http://www.imagemasurement.com/experience-image-measurement/pain-assessment-image-measurement>)

Central Sensitization Inventory (CSI)⁴⁵

Central sensitization can be present in different pain disorders including low back pain⁴⁶, neck pain⁴⁷, fibromyalgia⁴⁸, and TMD⁴⁹. The Italian version of the Central Sensitization Inventory (CSI)⁵⁰ will be used. Part A consists of a 0-100 score for 25 items on current health symptoms with five options ranging from ‘never’ (0) to ‘always’ (4). Part B examines previous physician diagnoses among seven different conditions⁴⁵. The CSI has significant test-retest reliability and internal consistency in subjects with and without pain⁴⁵. The Italian version of the CSI showed a satisfactory Cronbach’s alpha [0.87]⁵⁰.

Classification of TMD

Manual therapy could potentially be beneficial for both myogenous and arthrogeous TMD⁵¹. The TMD type will therefore be collected as a candidate predictor of outcome. As stated in the inclusion criteria, every patient included in the study will be diagnosed according to the Axis I of the Diagnostic Criteria for TMD DC/TMD³⁹. Based on these criteria, Peck et al.⁵² reported different types of TMD. This Taxonomic Classification of TMD includes four main domains: TMJ Disorders, Masticatory Muscle Disorders, Headache and Associated Disorders. An additional domain, called Mixed TMD (simultaneous presence of TMJ Disorders and Masticatory Muscle Disorders) will be included. For every patient the type of TMD (total of 5 domains) will be collected as candidate predictors from the patient medical records.

Characteristic pain intensity and disability

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3 A greater number of disability days increases the risk of having clinically significant pain
4 one year after an initial assessment²⁵. In this study we will use the Italian version of Graded
5 Chronic Pain Scale [GCPS] version 2.0 [www.rdc-tmdinternational.org]⁵³ following the DC/TMD
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10 protocol recommendations^{39,42,44}. This scale has good internal consistency in temporomandibular
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13 pain [Cronbach's alpha of 0.84]⁵⁴. The GCPS measures the facial pain severity over the preceding
14
15 6-months by unifying pain intensity and pain-related disability. The characteristic pain intensity
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17 score [range: 0-100] is the mean of three pain intensity measurements: 'at the present time' and
18
19 'worst pain' and the 'average' pain over the preceding 6 months. The disability status is measured
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21 with a 0-6 point score derived from a combination of the number of disability days and the
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23 disability level [range: 0-100; limitation given by pain in performing activities of daily living].
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25 Based on these scores, the participant's chronic pain and disability status can be classified into one
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27 of the five ordinal categories of chronic pain severity⁵⁵.
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31 Oral Behaviour

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35 People with abnormal oral behaviours with scores above 25 in the Oral Behaviours
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37 Checklist [OBC] are 75% more likely to develop TMD than individuals with a score below
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39 17^{42,44,56}. Parafunctional habits could play a significant role in the development and the persistence
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41 of TMD pain⁵⁸. In this study we will use the Italian version of the RDC/TMD questionnaire Axis
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43 II Oral Behaviours Checklist [www.rdc-tmdinternational.org]^{42,56} following the DC/TMD protocol
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45 recommendations^{39,56}. The OBC measures the self-reported frequency over the preceding month
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47 of each of 21 activities involving the jaw such as clenching the teeth or bracing the jaw (five ordinal
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49 response options, ranging from "none of the time," coded 0, to "all of the time," coded 4).
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51 Psychometric properties of this instrument suggest that it is valid, with patient behaviours
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53 matching those measured^{56,57,59}. Scoring is computed as the sum of the number of items with non-
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3 zero response or as a weighted sum [e.g. the sum of the endorsed frequencies of the respective
4 items]⁵⁶.
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8 9 10 **Clinical tests of the TMJ and masticatory muscles**

11 TMJ range of motion

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15 Mobility testing of the TMJ denotes an essential sign of TMD, it is one of the most reliable
16 clinical measures³⁹. Grossman et al.⁸ examined the preoperative variables of TMD patients with
17 articular disc displacement without reduction that may alter the effects of arthrocentesis on joint
18 effusion. They observed that small maximum interincisal distance influences treatment outcome.
19
20 As a result, we will use the Maximal Mouth Opening (MMO) without pain as measure of TMJ
21 range of motion. The measurements will be in millimeters and will be taken with a ruler in a
22 neutral craniocervical position [e.g. sitting or supine]. The distance between the incisal edges of
23 the maxillary and mandibular reference teeth, as described in the DC/TMD protocol⁴⁴, will be
24 measured. Participants will be asked to open the mouth as wide as they can without feeling any
25 pain, or without increasing any present pain. The tip of the ruler will be located against the incisal
26 edge of the mandibular reference incisor, and the distance to the mesial-distal center of the edge
27 of the maxillary central incisor will be read. The test will be repeated twice if the pain-free opening
28 if less than 30mm⁴⁴. Assessment of mandibular ROM in a neutral craniocervical position obtained
29 good inter- and intra-rater reliability for MMO⁶⁰.
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48 TMJ palpation pain:

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51 Pain induced in joints via palpation is a useful clinical test that allows to understand if the
52 provoked pain duplicates or replicates the patient's pain complaint by identifying potential joint
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3 origin⁴⁴. For this palpation, finger pressure is calibrated [1.0 kg], as described in the DC/TMD
4 protocol⁴⁴, using a simple hand-held algometer prior to palpation examination. While the
5 participant mandible is in a comfortable position or in a slightly protruded position, the examiner's
6 index finger will be placed just anterior to the tragus of the ear and dorsal to the TMJ with the
7 participant in neutral craniocervical position e.g. sitting or supine. The index finger will press while
8 orbiting around the lateral pole in a circular fashion over the superior aspect of the condyle and
9 then anteriorly [from the 9:00 to the 3:00 position, and then continuing fully around the condyle].
10 Palpation will last 5 seconds for each pressed point⁴⁴. If a participant complains of familiar pain in
11 at least one pressed point the point score of this test will be 1; if there is no pain at any points the
12 point score of this test will be 0 [range 0-1: no pain =0; pain = 1]. Palpation will be performed in
13 the left and right side. The interexaminer reliability values of TMJ palpation in TMD patients is
14 0.59 and the specificity values is acceptable [above 0.90]⁶¹.

31 Muscle palpation pain

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34 For this assessment, finger pressure is calibrated to 1.0 kg for masseter muscles and 0.5 kg
35 for lateral pterygoid area and temporalis tendons as described in the DC/TMD protocol⁴⁴, using a
36 simple hand-held algometer prior to palpation examination. Pain induced in muscles via palpation
37 is a useful clinical test that allows to understand whether the provoked pain duplicates or replicates
38 the patient's pain complaint by identifying potential muscular origin⁴⁴. Palpation will be performed
39 with the participant in a neutral craniocervical position (e.g. sitting or supine), on the left and right
40 side and will last 5 seconds for each testing point⁴⁴. The inter-examiner reliability values of
41 palpation in TMD patients is 0.59 and the specificity values are acceptable [above 0.90]⁶¹. The
42 feasibility of the lateral pterygoid muscle palpation is controversial. Some authors defined it as a
43 feasible palpation technique⁶², and others considered this muscle inaccessible⁶³. Therefore, in this
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3 study, this parameter [pain at lateral pterygoid site] will not be considered alone but in combination
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5 with pain at other muscular sites.
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11 *Lateral pterygoid area:* palpation will be performed with a finger pressure calibrated at 0.5
12 kg (DC/TMD protocol⁴⁴). The palpation will take place as described in FIG.1. If a participant
13 complains of familiar pain during palpation the lateral pterygoid area will be considered as a
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15 painful site.
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27 **FIG. 1 Lateral pterygoid area:** Finger is placed as
28 shown. Palpate the vestibule in posterior-superior-
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30 medial direction while the mandible is omolaterally
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32 deviated.
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41 *Masseter muscle:* masseter palpation consists of a sequence of three palpation sites with
42 finger pressure calibrated to 1.0 kg (DC/TMD protocol⁴⁴): origin zone [inferior to the bony margin
43 of the zygomatic process], body zone [in front of ear lobe] and insertion zone [superior to the
44 mandibular angle]. In each zone, the palpation continues until the anterior boundary of the muscle
45 is reached⁴⁴. If a participant complains of familiar pain in at least one pressed point, the masseter
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47 muscle will be considered as a painful site.
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54 *Temporalis tendon area:* the palpation will be performed with a finger pressure calibrated
55 to 0.5 kg (DC/TMD protocol⁴⁴). The palpation will take place as described in FIG.2. If a participant
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3 complains of familiar pain during the palpation the temporalis tendon area will be considered as a
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5 painful site.
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11 **FIG. 2 Temporalis tendon area:** Finger is located against the ascending mandibular ramus
12 while the mouth is slightly open. The palpation direction is
13 superior as far as possible by following the bone surface.
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22 *Total score:* if a participant complains of familiar pain
23 in at least three of the six examined sites the score will be 1,
24 otherwise it will be 0 [score range 0–1: < 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain
25 = 1]⁶⁴.
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36 JAw-test

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39 The JAw-test is a clinical test that aims to investigate the immediate effects of four brief
40 intraoral manual therapy techniques on pain and on TMJ range of motion. The participant will be
41 positioned in supine position. Before starting the test, the TMJ range of motion without pain will
42 be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD
43 protocol⁴⁴. Then the participant will be asked to rate his/her pain through the Verbal Rating Scale
44 (VRS) “at rest”, “during clenching” and “during the maximal opening of the mouth”; an average
45 of the three pain scores will be registered. For this test, finger pressure is calibrated [1.0 kg], in the
46 same way described in the DC/TMD protocol⁴⁴, using a simple hand-held algometer prior to
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3 palpation examination.
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5 Participants will be informed with the following words: “*I am going to perform four manual*
6 *techniques on some muscles and joints in your jaw region. You may feel a little pain, if the pain*
7 *increases and becomes too intense, let me know, I will reduce the pressure until the pain returns*
8 *to acceptable levels*”.
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14 *First technique: Lateral pterygoid area*

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17 This techniques will be performed on the most painful side. While one hand stabilizes the
18 participant’s head on the least painful side, the other hand will be used to apply pressure over the
19 lateral pterygoid area as described above and in accordance with the DC/TMD protocol⁴⁴. In this
20 position, compression [1.0 kg] is applied for 30-60 seconds.
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26 *Second technique: Temporalis tendon area*

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28 This techniques will be performed on the most painful side. While one hand stabilizes the
29 participant’s head on the least painful side, the other hand (index finger) will be used to apply
30 pressure over the Temporalis tendon area as described above and in accordance with the DC/TMD
31 protocol⁴⁴. In this position, compression [1.0 kg] is applied for 30-60 seconds.
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38 *Third technique: Mylohyoid area*

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40 The participant will be instructed to open the mouth to let the examiner’s finger reach the
41 mylohyoid area in a central position on the mylohyoid raphe. The other hand of the examiner will
42 reach the same area using a finger through an extraoral approach. In this position a combined
43 compression (1.0 kg) will be applied for 30-60 seconds.
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49 *Fourth technique: TMJ mobilization*

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51 An intraoral ventral and caudal anterior glide [mobilisation grades I and II] of both the
52 TMJs will be performed for 30 seconds as described by Cleland et al.⁶⁵
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3 *Final scores:*
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5 After the tests, the TMJ range of motion without pain will be measured [MMO -
6 millimeters] with a ruler, as described above, according to DC/TMD protocol⁴⁴. Then the
7 participant will be asked to rate his/her pain using the Verbal Rating Scale (VRS) “at rest”, “during
8 clenching” and “during the maximal opening of the mouth”; an average of these three pain scores
9 will be registered. If a participant shows only an improvement in pain [average score VRS pre-test
10 > average score VRS post-test] the score will be 1; if a participant shows only an improvement of
11 TMJ mobility [MMO pre-test < MMO post-test at least 2 millimeters] the score will be 1; if a
12 participant shows improvements in both pain and TMJ mobility, the score will be 2; if a participant
13 shows no improvements the score will be 0 [Score range 0-2: 0 = no change; 1 = VRS improvement
14 or MMO improvement; 2 = improvement of both].
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|-----------------------------------|---------|--|
| Administrative information | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – Page 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry – N/A |
| | 2b | All items from the World Health Organization Trial Registration Data Set – N/A |
| Protocol version | 3 | Date and version identifier – Page 1 |
| Funding | 4 | Sources and types of financial, material, and other support – Page 22 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors – Pages 1 and 22 |
| | 5b | Name and contact information for the trial sponsor – N/A |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities – N/A |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – N/A |
| Introduction | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – Pages 4-6 |
| | 6b | Explanation for choice of comparators – Supplementary file |
| Objectives | 7 | Specific objectives or hypotheses - Page 5-6 |

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| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) – N/A |
|--------------|---|---|

Methods: Participants, interventions, and outcomes

| | | |
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| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained – Page 6 |
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| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) – Pages 7 |
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| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – Pages 8-9 |
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| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) – Page 9 |
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| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – N/A |
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| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial – Pages 7 and 9 |
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| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended – Page 9 and 10 (primary outcome), Supplementary file (candidate predictors) |
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| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) – Pages 7-8 |
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| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations – Page 12 |
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| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size – Pages 7 |
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Methods: Assignment of interventions (for controlled trials)

Allocation:

| | | | |
|----|----------------|-----|---|
| 1 | | | |
| 2 | Sequence | 16a | Method of generating the allocation sequence (eg, computer- |
| 3 | generation | | generated random numbers), and list of any factors for stratification. |
| 4 | | | To reduce predictability of a random sequence, details of any planned |
| 5 | | | restriction (eg, blocking) should be provided in a separate document |
| 6 | | | that is unavailable to those who enrol participants or assign |
| 7 | | | interventions – N/A |
| 8 | | | |
| 9 | | | |
| 10 | Allocation | 16b | Mechanism of implementing the allocation sequence (eg, central |
| 11 | concealment | | telephone; sequentially numbered, opaque, sealed envelopes), |
| 12 | mechanism | | describing any steps to conceal the sequence until interventions are |
| 13 | | | assigned – N/A |
| 14 | | | |
| 15 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, |
| 16 | | | and who will assign participants to interventions – N/A |
| 17 | | | |
| 18 | | | |
| 19 | Blinding | 17a | Who will be blinded after assignment to interventions (eg, trial |
| 20 | (masking) | | participants, care providers, outcome assessors, data analysts), and |
| 21 | | | how N/A |
| 22 | | | |
| 23 | | 17b | If blinded, circumstances under which unblinding is permissible, and |
| 24 | | | procedure for revealing a participant's allocated intervention during |
| 25 | | | the trial – N/A |
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Methods: Data collection, management, and analysis

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| 28 | | | |
| 29 | | | |
| 30 | Data collection | 18a | Plans for assessment and collection of outcome, baseline, and other |
| 31 | methods | | trial data, including any related processes to promote data quality (eg, |
| 32 | | | duplicate measurements, training of assessors) and a description of |
| 33 | | | study instruments (eg, questionnaires, laboratory tests) along with |
| 34 | | | their reliability and validity, if known. Reference to where data |
| 35 | | | collection forms can be found, if not in the protocol – Pages 9-11, |
| 36 | | | Supplementary file |
| 37 | | | |
| 38 | | | |
| 39 | | 18b | Plans to promote participant retention and complete follow-up, |
| 40 | | | including list of any outcome data to be collected for participants who |
| 41 | | | discontinue or deviate from intervention protocols – Page 12-13 |
| 42 | | | (withdrawals) |
| 43 | | | |
| 44 | | | |
| 45 | Data | 19 | Plans for data entry, coding, security, and storage, including any |
| 46 | management | | related processes to promote data quality (eg, double data entry; |
| 47 | | | range checks for data values). Reference to where details of data |
| 48 | | | management procedures can be found, if not in the protocol – Page |
| 49 | | | 12 |
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| 51 | | | |
| 52 | Statistical | 20a | Statistical methods for analysing primary and secondary outcomes. |
| 53 | methods | | Reference to where other details of the statistical analysis plan can be |
| 54 | | | found, if not in the protocol – Page 12-13 |
| 55 | | | |
| 56 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted |
| 57 | | | analyses) – n/A |
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- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – Page 12

Methods: Monitoring

- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed – N/A
- 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – N/A
- Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – Page 14
- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – N/A

Ethics and dissemination

- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – Pages 6 and 14
- Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – N/A
- Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – Page 7
- 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – N/A
- Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – Page 12
- Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site – Page 22
- Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – Not present
- Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – N/A

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| 1 | | | |
| 2 | Dissemination | 31a | Plans for investigators and sponsor to communicate trial results to |
| 3 | policy | | participants, healthcare professionals, the public, and other relevant |
| 4 | | | groups (eg, via publication, reporting in results databases, or other |
| 5 | | | data sharing arrangements), including any publication restrictions – |
| 6 | | | N/A |
| 7 | | | |
| 8 | | 31b | Authorship eligibility guidelines and any intended use of professional |
| 9 | | | writers – N/A |
| 10 | | | |
| 11 | | 31c | Plans, if any, for granting public access to the full protocol, participant- |
| 12 | | | level dataset, and statistical code – N/A |
| 13 | | | |
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Appendices

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| 15 | | | |
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| 17 | Informed consent | 32 | Model consent form and other related documentation given to |
| 18 | materials | | participants and authorised surrogates – N/A |
| 19 | | | |
| 20 | Biological | 33 | Plans for collection, laboratory evaluation, and storage of biological |
| 21 | specimens | | specimens for genetic or molecular analysis in the current trial and for |
| 22 | | | future use in ancillary studies, if applicable – N/A |
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.