BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032113
Article Type:	Protocol
Date Submitted by the Author:	03-Jun-2019
Complete List of Authors:	Asquini, Giacomo; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Edoardo Bianchi , Andrea ; Italian Stomatologic Institute Heneghan, Nicola; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rushton, Alison; niversity of Birmingham, School of Health and Population Sciences, College of Medical and Dental Sciences Borromeo, Giulia; Italian Stomatologic Institute Locatelli , Matteo; IRCCS San Raffaele Scientific Institute Falla, Deborah; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences
Keywords:	Temporomandibular Disorders, Temporomandibular Joint Dysfunction Syndrome, Pain, Prediction, Manual Therapy

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

Asquini G[1,2], Bianchi AE[2], Heneghan NR[1], Rushton A[1], Borromeo G[2], Locatelli M[3], Falla D[1]

Affiliations

[1] Centre of Precision Rehabilitation for Spinal Pain (CPR Spine)
School of Sport, Exercise and Rehabilitation Sciences
College of Life and Environmental Sciences
University of Birmingham
Birmingham B15 2TT
United Kingdom

[2] Italian Stomatologic Institute
Craniomandibular Physiotherapy Service
Via Pace 21, 20122 Milan
Italy

[3] IRCCS San Raffaele Scientific Institute
Via Olgettina Milano 60,
20132 Milano,
Italy

Corresponding author:

Deborah Falla
Centre of Precision Rehabilitation for Spinal Pain (CPR Spine)
School of Sport, Exercise and Rehabilitation Sciences
College of Life and Environmental Sciences
University of Birmingham
Birmingham, UK
E-mail: d.falla@bham.ac.uk

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. In this study we will use a unique combination of patient-reported outcome measures and clinical tests to identify predictors associated with pain reduction in patients with TMD following manual therapy. 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 (≥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: 3322 [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 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 at 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

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. (2016) conducted a prospective cohort study with 263 primary care patients with TMD pain. They analysed several potential predictors of persistent pain at one-year follow-up including demographic, pain-related and psychosocial variables. It was concluded that patients with TMD who have had numerous previous healthcare visits, complained of high-intensity pain at other body sites and had a greater number of disability days, were at greater risk of having pain one year after the initial assessment. Nevertheless, this study did not examine predictors of pain reduction related to a therapeutic intervention which could be useful to inform clinical practice. Kapos et al. (2018) investigated the association of long-term pain intensity with baseline health-related quality of life and jaw functional limitation in patients with TMD. Findings suggested that baseline health-related quality of life is inversely proportional with pain intensity at an eight-year follow-up regardless of the type of treatment that they received (e.g. surgery, drugs, physical therapy or unconventional therapy). After adjusting for the type of treatments received, by clustering the participants into three groups (medical/conventional management, alternative medicine, and surgical intervention), each predictor analysed (demographic, pain-related and health-related quality of life) maintained similar statistical significance. Notwithstanding, the group classified as "medical/ conventional management" included participants receiving diverse treatments ranging from physical therapy, pharmacology (Acetaminophen, Antidepressants, Anti-inflammatories) to the application of a mouth appliance. This previous work can facilitate clinicians to identify patients who are more challenging to treat by identifying clinical features associated with persistent pain in the long term regardless of the type of

interventions applied. However, currently no study has examined predictive factors associated with pain reduction following manual therapy interventions in patients with TMD.

In this study we will use a combination of: (1) demographical variables, (2) general health variables, (3) psychosocial features, (4) TMD characteristics, and (5) clinical tests of the temporomandibular joint and masticatory muscles to identify predictors associated with pain reduction in patients with TMD following manual therapy applied to craniomandibular structures. The knowledge gained from this study will facilitate clinical decision-making for manual therapists managing patients with TMD by providing clinicians with key factors to evaluate, to determine whether or not the patient is likely to have a clinically relevant reduction in their pain immediately following four weekly applications of manual therapy.

METHODS AND ANALYSIS

Source of data

A prospective observational study will recruit a cohort of patients referred to the Italian Stomatologic Institute with a TMD diagnosis according to the Axis I of the Diagnostic Criteria for TMDs (DC/TMD) (Shiffman et al., 2014). This protocol is written according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement (Collins at al., 2015) in which recommendations are provided about prediction model development and validation. Ethical clearance will be obtained from the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and the University of Birmingham Ethics Committee, and the study will be conducted in accordance with the Declaration of Helsinki.

Patient reported and physical assessment data will be collected at baseline prior to commencing treatment. Outcome will be collected at the end of the fourth session of

craniomandibular manual therapy (at one month). This timeline has been selected based on previous studies investigating 1) the effects of manual therapy on pain (Bishop et al., 2015; Vigotsky et al., 2015); and 2) work confirming the effectiveness of manual therapy for TMD patients (Calixtre et al., 2015) and is believed to be reasonable for the purposes of this study.

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 Axis I of the Diagnostic Criteria for TMDs (DC/TMD) (Shiffman et al., 2014); (3) no therapeutic interventions reported (for their TMD) in the past six months (Wahlund et al., 2015); (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 or mental condition that could potentially influence the study. 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 disorders, it is estimated that 75% of eligible participants will consent to participation [100 participants] (Flynn et al., 2002; Cleland et al., 2007).

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

[FIGURE 1]

Treatment

Participants will receive four sessions of manual therapy applied to craniomandibular structures over 4 weeks (Crockett et al., 1986; Guarda-Nardini et al., 2012; Nascimento et al., 2013). Two physiotherapists, each with >5 years' experience in manual therapy / TMD will perform the treatments. They will not be involved in participant recruitment, assessment or the collection of the outcome measure. Manual therapy techniques will be based on the clinical examination, and will be selected at the discretion of the treating physiotherapist

according to their clinical reasoning of the individual case. Overall, the application of manual therapy aims to decrease pain by treating masticatory muscle trigger points, muscle tightness, and restricted temporomandibular joint movements. Several techniques will be considered including: (i) ventral and caudal anterior glide temporomandibular joint mobilization (Cleland et al. 2004); (ii) soft tissue interventions for the management of trigger points in masticatory muscles (Miernik et al. 2012); (iii) myofascial induction therapy [functional restoration of the fascial system] applied to craniomandibular structures (Fernàndez-de-la-Peñas et al. 2018).

The structures targeted in the treatment sessions will be the temporomandibular joint, temporal muscles, masseter muscles, medial and lateral pterygoid muscles and suprahyoid muscles, applied at the discretion of the physiotherapist based on the patient's individual presentation. During the treatment sessions, the treating physiotherapists will provide explanations about the patient's condition and answer any participant questions by promoting general advice. The treatment sessions will last from 20 to 30 minutes duration. No other treatment (e.g. oral appliance) will be performed for the management of their TMD. If during the course of the four-week intervention, a patient seeks treatment for an acute episode of pain at another site (e.g. neck pain, low back pain, shoulder pain) they will be withdrawn from the study.

Outcome

The outcome being predicted by the prediction model is pain intensity since patients with TMD typically report pain to be their primary problem (de Leeuw & Klasser, 2013), manual therapy is largely known to be effective principally for pain modulation (Bialosky et al., 2009) and change in pain intensity has most commonly been the primary outcome of

choice in several other studies of patients with TMD (Kalamir et al., 2010; Gomes et al., 2014; Tuncer et al., 2013; Von Piekartz et al., 2013).

Pain intensity will be calculated by averaging the ratings of current pain, average pain in the past week, 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 "worst pain imaginable" at the right extremity (Haefeli et al., 2005). The VAS is a reliable and valid scale to assess pain intensity as an outcome measure in intervention studies (Dworkin et al. 2005). Based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations about TMD reviewed by Haythornthwaite (2010), a reduction of at least 30% of the VAS score for pain intensity is considered clinically significant. Consequently, a reduction in the total VAS score [≥ 30%] will be defined as a good outcome. The outcome measure will be evaluated by the same independent assessor to minimise detection bias (Higgins et al., 2011).

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] (Stratford et al. 1995) pre and post treatment. The PSFS is a self-reported outcome measure assessing functional change in patients with musculoskeletal disorders (Horn et al., 2012; Abbott et al., 2014). It is responsive to clinically significant change over time (Maughan et al., 2010). 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 pain (Hefford et al., 2012; Westaway et al., 1998; Chatman et al., 1997).

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 disorders (Bair et al., 2016; Clark et al., 2017). 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 (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)

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]

277

278

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 predictors (Fabrigar et al., 1999). This method will guarantee an adequate sample size (at least 10 cases per candidate predictor) to power the final regression analysis (Peduzzi et al., 1996; Vittinghoff et al., 2007). 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 model (Shmueli, 2010). 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 ≥30%] (Haythornthwaite, 2010). Exploratory factor analysis will be applied to analyse factor loading of candidate predictors (summary scores) on good outcome at one month. This process will reduce candidate predictors (supported by the cohort sample of 90) to enter into the final model.

The statistical model has been designed a priori. To investigate the impact of each predictive factor on good outcome, a logistic multivariable regression model will be performed. For each candidate predictor, the mean differences or the odds ratio with their 95% confidence intervals will be calculated. A multiple imputation analysis (Sterne et al., 2009) will be applied to manage possible missing data. The multivariable analysis will initially consider all candidate predictors. In the case of a high correlation between candidate predictors, a reduced multivariate analysis will be considered.

DISCUSSION

There is a need to identify predictors for pain reduction in patients with TMD following specific treatments in order to inform clinical decision-making. Several therapies are described for patients with TMD such as the use of oral appliances, different types of physical therapy modalities, pharmacology or temporomandibular joint arthrocentesis yet the amount of pain relief that different people receive from each intervention is variable (Armijo-Olivo et al., 2016; Calixtre et al., 2016). As shown by Forssell et al. (2016) and Kapos et al. (2018), many patients continue to experience pain following such interventions. Investigating factors associated with pain relief to such treatments can facilitate clinical assessment and treatment selection.

Physical therapy is one of the most common conservative interventions to treat TMD (Calixtre et al., 2016). Among different physical therapy modalities, manual therapy can provide symptom and functional improvements (Armijo-Olivo et al., 2016) including pain relief (Kalamir et al., 2013; Gomes et al., 2014). Knowledge of predictive factors associated with good outcome to a specific intervention such as manual therapy applied to craniomandibular structures will facilitate clinical decision making. Ultimately, such knowledge will lead to improved clinical and cost effectiveness of rehabilitation approaches.

Quality assurance

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

Patient and Public Involvement

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

Ethics and Dissemination

The research protocol has been submitted to the Ethics Committee of the "Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico" and subsequently will be submitted to the University of Birmingham Ethics Committee for approval. Researchers will inform all participants on the characteristics of the research and will obtain written consent. Participants will be informed that they are free to withdraw from the study at any time, without needing to provide reason. Any concerns for a participant by the study team will be fed back to the primary investigator (GA). Baseline characteristics of withdrawn participants will be compared to those

of retained participants to assess for any differences. In the event of any unlikely adverse events, this will be immediately reported by the principal investigator to the ethics committee.

The results of this study will submitted for publication in a peer review journal and presented at conferences.

Limitations

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

Conclusion

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

REFERENCES

Abramowitz, M., & Stegun, I. A., eds. (1965). 'Handbook of Mathematical Functions'. New York, NY: *Dover*

Abbott, J., H., & Schmitt, J., (2014). 'Minimum important differences for the patient-specific functional scale, 4 region-specific outcome measures, and the numeric pain rating scale'. *Journal of Orthopaedic & Sports Physical Therapy*, 44(8):560-4.

Antonarakis, G. S., Kalberer, N., Courvoisier, D. S., & Scolozzi, P., (2017). 'Clinical predictive factors for temporomandibular disorders following combined orthodontic and orthognathic surgical treatment in patients with Class III malocclusion'. *CRANIO*, 35(6), 397–404

Armijo-Olivo, S., Pitance, L., Singh, V., Neto, F., Thie, N., & Michelotti, A., (2016) 'Effectiveness of Manual Therapy and Therapeutic Exercise for Temporomandibular Disorders: Systematic Review and Meta-Analysis'. *Physical Therapy*, *96*(1): 9–25

Bair, E., Gaynor, S., Slade. G. D., Ohrbach, R., Fillingim, R. B., Greenspan, J. D., Dubner, R., Smith, S. B., Diatchenko, L., & Maixner, W., (2016). 'Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study'. *Pain*, 157(6):1266-78

Bialosky, J. E., Bishop, M. D., Price, D. D., Robinson, M. E., & George, S. Z., (2009). 'The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model'. *Man Ther*, 14:531–538.

Bishop, M. D., Torres-Cueco, R., Gay, C. W., Lluch-Girbés, E., Beneciuk, J. M., & Bialosky, J. E., (2015). 'What effect can manual therapy have on a patient's pain experience?'. *Pain management*, 5(6), 455-64.

Brooks, R., (1996). 'EuroQol: the current state of play'. *Health Policy,* 37(1):53-72.

Bryman, A., (2004). 'Social Research Methods'. 2nd ed. Oxford: *Oxford University Press*

Calixtre, L. B., Moreira, R. F. C., Franchini, G. H., Alburquerque-Sendín, F., & Oliveira, A. B. (2015). 'Manual therapy for the management of pain and limited range of motion in subjects with signs and symptoms of temporomandibular disorder: A systematic review of randomised controlled trials'. *Journal of Oral Rehabilitation, 42(11), 847–861.*

Calixtre, L. B., Grüninger, B. L. da S., Haik, M. N., Alburquerque-Sendín, F., & Oliveira, A. B. (2016) 'Effects of cervical mobilization and exercise on pain, movement and function in subjects with temporomandibular disorders: a single group pre-post test'. *Journal of Applied Oral Science*, 24(3): 188–197

Cappelleri, J. C., McDermott, A. M., Sadosky, A. B., Petrie, C. D., & Martin, S. (2009). 'Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia'. *Health Qual Life Outcomes*, 17(7):54.

Chatman, A. B., Hyams, S. P., Neel, J. M., Binkley, J. M., Stratford, P. W., Schomberg, A., & Stabler M. (1997). 'The Patient-Specific Functional Scale: measurement properties in patients with knee dysfunction'. *Physical therapy*; 77(8):820-9.

Clark, J., Nijs, J., Yeowell, G., & Goodwin, P. C., (2017). 'What Are the Predictors of Altered Central Pain Modulation in Chronic Musculoskeletal Pain Populations? A Systematic Review'. *Pain Physician*. 20(6):487-500

Cleland, J., & Palmer, J. (2004). 'Effectiveness of Manual Physical Therapy, Therapeutic Exercise, and Patient Education on Bilateral Disc Displacement Without Reduction of the

Temporomandibular Joint: A Single-Case Design'. J*ournal of Orthopaedic & Sports Physical Therapy*, 34(9), 535–548

Cleland, J. A., Childs, J. D., Fritz, J. M., Whitman, J. M., & Eberhart, S. L., (2007). 'Development of a Clinical Prediction Rule for Guiding Treatment of a Subgroup of Patients With Neck Pain: Use of Thoracic Spine Manipulation, Exercise, and Patient Education'. *Physical Therapy,* 87 (1): 9–23

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2003) 'Applied multiple regression/correlation analysis for the behavioral sciences (3rd ed.). Mahwah, NJ: *Lawrence Erlbaum Associates*.

Cohen, J. (1988). 'Statistical Power Analysis for the Behavioral Sciences' (2nd Edition). Hillsdale, NJ: *Lawrence Erlbaum Associates*

Collins, G. S., Reitsma, J. B., Altman, D. G. & Moons, K.G., (2015). 'Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement'. *BMC Medicine*, 13(1)

Cook, R. D., & Weisberg, S. (1982). 'Residuals and influence in regression'. New York, NY: *Chapman & Hall*.

Coskun Benlidayi, I., Salimov, F., Kurkcu, M., & Guzel, R. (2016). 'Kinesio-Taping for temporomandibular Disorders: Single-blind, ramdomized, controlled trial of effectiveness'. *J Back Musculoskelet Rehabil*, 29:373-380

Crockett, D. J., Foreman, M. E., Alden, L., & Blasberg, B. (1986). 'A comparison of treatment modes in the management of myofascial pain dysfunction syndrome'. *Biofeedback and self-regulation*, 11(4):279-291.

Davis, C. E., Stockstill, J. W., Stanley, W. D., & Wu, Q. (2014). 'Pain-related worry in patients with chronic orofacial pain'. *J Am Dent Assoc*. 145(7):722-30

De Leeuw, R., & Klasser, G. D. (2013) 'Orofacial pain guidelines for assessment, diagnosis, and management'. 5th ed. Hanover park, II: *Quintessence publishing*

Demirkol, N., Usumez, A., Demirkol, M., Sari, F., & Akcaboy, C. (2017). 'Efficacy of Low-Level Laser Therapy in Subjective Tinnitus Patients with Temporomandibular Disorders'. *Photomed Laser Surg* , 35(8): 427-431.

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., & Witter, J. (2005). 'Core outcome measures for chronic pain clinical trials : IMMPACT recommendations'. *Pain*, 113:9–19.

Fabrigar, L. R., Wegener, D. T., MacCallum, R. C., & Strahan, E. J. (1999). 'Evaluating the use of exploratory factor analysis in psychological research'. *Psychological Methods*, 4, 272–299.

Fernandez-de-las-Pena, C. & Mesa-Jimenez, J. (2018) 'Temporomandibular Disorders: manual Therapy, exercise and needling'. United Kingdom: *Handspring Publishing*

Flynn, T., Fritz, J., Whitman, J., Wainner, R., Magel, J., Rendeiro, D., Butler, B., Garber, M., & Allison, S., (2002). 'A clinical prediction rule for classifying patients with low back pain who demonstrate short-term improvement with spinal manipulation'. *Spine*. 27(24):2835-2843

Forssell, H., Kauko, T., Kotiranta, U., & Suvinen, T. (2017). 'Predictors for future clinically significant pain in patients with temporomandibular disorder: A prospective cohort study'. *European Journal of Pain*, 21(1), 188–197.

Fricton, J., (1988). Physical evaluation: the need for a standardized examination. In: Fricton J.R., ed. Temporomandibular joint and craniofacial pain: diagnosis and management. St Louis: *Ishiyaku Euroamerica*, pp 46–47.

Gomes, C. A., Politti, F., Andrade, D. V., de Sousa, D. F., Herpich, C. M., Dibai-Filho, A. V., Gonzalez, Tde O., & Biasotto-Gonzalez, D. A. (2014). 'Effects of Massage Therapy and Occlusal Splint Therapy on Mandibular Range of Motion in Individuals With Temporomandibular Disorder: A Randomized Clinical Trial'. *Journal of Manipulative and Physiological Therapeutics*, 37(3), 164–169.

Grossmann, E., Poluha, R. L., Iwaki, L. C. V., Santana, R. G., & Filho, L. I. (2018). 'Predictors of arthrocentesis outcome on joint effusion in patients with disk displacement without reduction'. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 125(4), 382–388.

Guarda-Nardini, L., Stecco, A., Stecco, C., Masiero, S., & Manfredini, D. (2012). 'Myofascial Pain of the Jaw Muscles: Comparison of Short-Term Effectiveness of Botulinum Toxin Injections and Fascial Manipulation Technique'. *CRANIO*, 30(2), 95–102

Guba, E. G., Lincoln, Y. S. (1981) 'Effective evaluation: Improving the usefulness of evaluation results through responsive and naturalistic approaches'. San Francisco: *Jossey-Bass*

Haefeli, M., & Elfering, A. (2005). 'Pain assessment: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society'. *European spine journal,* 15 Suppl 1(Suppl 1), S17–S24

Haythornthwaite, J. A. (2010). IMMPACT recommendations for clinical trials: Opportunities for the RDC/TMD. *Journal of Oral Rehabilitation*, 37(10), 799–806.

Harland, N.J., & Georgieff K. 'Development of the coping strategies questionnaire 24, a clinically utilitarian version of the coping strategies questionnaire'. *Rehabilitation Psychology* 2003;48(4):296–300.

Hefford, C., Abbott, J. H., Arnold, R., & Baxter G. D. (2012). 'The patient-specific functional scale: validity, reliability, and responsiveness in patients with upper extremity musculoskeletal problems'. *Journal of orthopaedic & sports physical therapy*; 42(2):56-65.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L., & Sterne, J. A. (2011). 'The Cochrane Collaboration's tool for assessing risk of bias in randomised trials'. *BMJ*, 18;343:d5928

Horn, K. K., Jennings, S., Richardson, G., Van Vliet, D., Hefford, C., & Abbott, J. H. (2012). 'The patient-specific functional scale: psychometrics, clinimetrics, and application as a clinical outcome measure'. *Journal of orthopaedic & sports physical therapy*; 42(1):30-D17.

Kalamir, A., Pollard, H., Vitiello, A., & Bonello, R. (2010). 'Intra-oral myofascial therapy for chronic myogenous temporomandibular disorders: a randomized, controlled pilot study'. *Journal of Manual & Manipulative Therapy*, 18(3), 139–146.

Kalamir, A., Graham, P. L., Vitiello, A. L., Bonello, R., & Pollard, H. (2013). 'Intra-oral myofascial therapy versus education and self-care in the treatment of chronic, myogenous temporomandibular disorder: A randomised, clinical trial'. *Chiropractic and Manual Therapies*, 21(1)

Kapos, F. P., Look, J. O., Zhang, L., Hodges, J. S., & Schiffman, E. L. (2018). 'Predictors of Long-Term Temporomandibular Disorder Pain Intensity: An 8-Year Cohort Study'. *Journal of Oral & Facial Pain and Headache*, 32(2), 113–122.

Lipton, J. A., Ship, J. A., & Larach-Robinson, D. (1993) 'Estimated prevalence and distribution of reported orofacial pain in United States'. *J Am Dent Assoc*, 124: 115-112.

Linton, S. J., & Boersma, K. (2003). 'Early identification of patients at risk of developing a persistent back problem: The predictive validity of the Orebro Musculoskeletal Pain Questionnaire'. *Clin J Pain* 19, 80–86.

Mayer, T. G., Neblett, R., Cohen, H., Howard, K. J., Choi, Y. H., Williams, M. J., & Gatchel, R. J. (2012). 'The Development and Psychometric Validation of the Central Sensitization Inventory'. *Pain Practise,* 12(4), 276–285.

Miernik, M., Wieckiewicz, M., & Paradowska, A. (2012) 'Massage therapy in myofascial TMD pain management'. *Adv Clin Exp Med*, 21(5):681-5

Maughan, E. F., & Lewis, J. S. (2010). 'Outcome measures in chronic low back pain'. *European Spine Journal*, 1;19(9):1484-94.

Nascimento, M., Vasconcelos, B. C., Porto, G. G., Ferdinanda, G., Nogueira, C. M., & Raimundo, R. D., (2013). 'Physical therapy and anesthetic blockage for treating temporomandibular disorders: a clinical trial'. *Med Oral Patol Oral Cir Bucal*, 1;18(1):81-5.

NIDCR. Facial Pain (2014). *National Institute of Health* [Online]. http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain/ [Accessed Dec 28 2018]

Peduzzi, P., Concato, J., Kemper, E., Holford, T. R., & Feinstein, A. R., (1996). 'A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49(12):1373-9.

Plesh, O., Adams, S.H., & Gansky, S.A. (2011). 'Temporomandibular joint and muscle disorders-type pain and comorbid pains in a national US sample'. *J Orofacial Pain*, 25: 190-198.

Rai, S., Ranjan, V., Misra, D., & Panjwani, S. (2016). 'Management of myofascial pain by therapeutic ultrasound and transcutaneous electrical nerve stimulation: A comparative study'. *Eur J Dent,* 10(1): 46-53.

Rocabado, M. (1987). 'The importance of soft tissue mechanism in stability and instability of the cervical spine: a functional diagnosis for treatment planning'. *Cranio*, 5: 130-138.

Rushton. A. B., Evans, D.W., Middlebrook, N., Heneghan, N. R., Small, C., Lord, J., Patel, J. M., & Falla, D. (2018). 'Development of a screening tool to predict the risk of chronic pain and disability following musculoskeletal trauma: protocol for a prospective observational study in the United Kingdom'. *BMJ Open*, 28;8(4):e017876

Sainani, K. L., (2013). 'Multivariate Regression: The Pitfalls of Automated Variable Selection'. *Physical Medicine and Rehabilitation*, 5:791-94.

Saks, M. & Allsop, J. (2013) 'Researching Health: Qualitative, Quantitative and Mixed Methods'. 2nd ed. London: *Sage*

Sperandei, S. (2014). 'Understanding logistic regression analysis'. *Biochemia medica*, 24(1), 12-8

Schiffman, E., Ohrbach, R., Truelove, E., Look, J., Anderson, G., Goulet, J.-P., … & Dworkin, S. F. (2014). 'Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: Recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group'. J*ournal of Oral & Facial Pain and Headache*, 28(1)

Shmueli, G. (2010). 'To explain or to predict?'. *Statistical Science*, 25(3):289-310.

Schulz, K., Altman, D., & Moher, D. (2010) 'CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials'. *British Medical Journal*, 340:698-702

Slade, G. D., Bair, E., Greenspan, J. D., Dubner, R., Fillingim, R. B., Diatchenko, L., Maixner, W., Knott, C., & Ohrbach, R., (2013). 'Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: the OPPERA prospective cohort study'. *J Pain*, 14: T20-T32.

Stelzenmueller, W., Umstadt, H., Weber, D., Goenner-oezkan, V., Kopp, S., & Lisson, J. (2015). 'Evidence - The intraoral palpability of the lateral pterygoid muscle - A prospective study'. *Annals of Anatomy*, 206:89-95.

Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., Wood, A. M., & Carpenter, J. R., (2009). 'Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls'. *BMJ* , 338:b2393.

Stratford, P., Gill, C., Westaway, M., & Binkley, J. (1995). 'Assessing disability and change on individual patients: a report of a patient specific measure'. *Physiotherapy Canada*, 47, 258-263

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). 'The pain catastrophizing scale: Development and validation'. *Psychol Assess* 7, 524–532.

Tuncer, A. B., Ergun, N., Tuncer, A. H., & Karahan, S. (2013). 'Effectiveness of manual therapy and home physical therapy in patients with temporomandibular disorders: A randomized controlled trial'. *Journal of Bodywork and Movement Therapies,* 17(3), 302–308.

Van Oort, L., Van den Berg, T,, Koes, B. W., de Vet, R. H., Anema, H. J., Heymans, M. W., Verhagen, A. P., (2012). 'Preliminary state of development of prediction models for primary care physical therapy: a systematic review'. *J Clin Epidemiol,* 65(12):1257-66.

Vigotsky, A. D., & Bruhns, R. P. (2015). 'The Role of Descending Modulation in Manual Therapy and Its Analgesic Implications: A Narrative Review'. *Pain research and treatment*, 2015, 292805.

Vittinghoff, E., & McCulloch, C. E., (2007). 'Relaxing the rule of ten events per variable in logistic and Cox regression'. *Am J Epidemiol*, 165(6):710-8.

Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P, (2008). 'The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies'. *J Clin Epidemiol*, 61(4):344-9

von Piekartz, H., & Hall, T. (2013). 'Orofacial manual therapy improves cervical movement impairment associated with headache and features of temporomandibular dysfunction: A randomized controlled trial'. *Manual Therapy, 18(4):345-50*

Weisberg, S. (2014). 'Applied linear regression' (4th ed.). New York, NY: *Wiley*

Westaway, M. D., Stratford, P. W., & Binkley, J. M. (1998). 'The patient-specific functional scale: validation of its use in persons with neck dysfunction'. *Journal of Orthopaedic & Sports Physical Therapy*; 27(5):331-8.

Wahlund, K., Nilsson, I. M., & Larsson, B. (2015) 'Treating temporomandibular disorders in adolescents: a randomized, controlled, sequential comparison of relaxation training and occlusal appliance therapy'. *J Oral Facial Pain Headache*, 29(1):41-50

Woby, S. R., Roach, N. K., Urmston, M., Watson, P. J., (2005). 'Psychometric properties of the TSK-11: a shortened version of the Tampa Scale for Kinesiophobia' . *Pain*, 117(1-2):137-44.

Zigmond, A. S., Snaith, R. P., (1983). 'The hospital anxiety and depression scale'. *Acta Psychiatr Scand*, 67(6):361-70

Author Contributions

GA, AEB and DF formulated the research question and study focus. GA drafted the initial version of the manuscript with DF. All authors 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

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests Statement

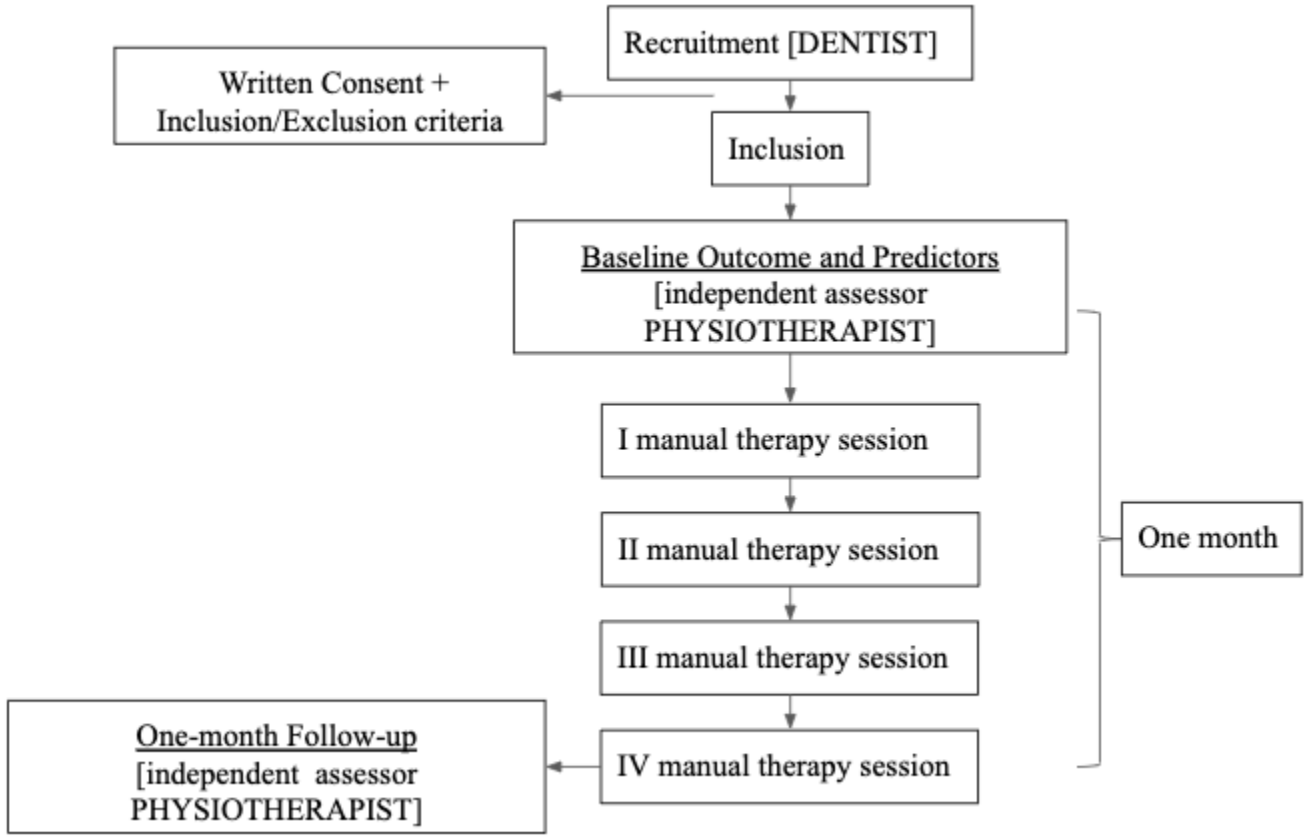
The authors have no competing interests to report.

Data sharing statement

No additional data are available.

FIGURE LEGEND

Figure 1: Participant flow through the study


Recruitment [DENTIST]
Written Consent +
Inclusion/Exclusion criteria
Inclusion
Baseline Outcome and Predictors
[independent assessor
PHYSIOTHERAPIST]
I manual therapy session
II manual therapy session
III manual therapy session
IV manual therapy session
One month
One-month Follow-up
[independent assessor
PHYSIOTHERAPIST]

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

Supplementary file 1 - Candidate predictors

Demographical variables

Participants' demographic variables [age, gender, education] will be collected at baseline from open hospital records and patient interview.

Age

Age is a significant factor in TMD incidence and prevalence. Lipton et al. (1993) found different age-specific prevalence for face/jaw pain: 6.5% in aged 18-34, 5.0% in 35-54 years old, 4.0% in 55-74 years old and 3.9% in people > 74 year old, showing a prevalence reduction across the lifetime. By contrast, data from the OPPERA study (Fillingim et al., 2011) showed a 40% increased risk for TMD among individuals aged 25-34 years and a 50% increased risk for TMD among individuals aged 35-50 years.

Gender

Women are 1.5-2 times more likely to develop TMD than men (Helkimo, 1974; Von Korff et al., 1988; Plesh et al., 2011). Currently, there is no study examining the extent of recovery from TMD in men and women. Nevertheless, gender is a significant factor to be considered.

Education

The National Centre of Health and Statistic (NCHS) 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 pain (Roth et al., 2002). 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. (2018), 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 state (Brooks, 1996). 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-3L (Janssen et al., 2008). 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] (Janssen et al., 2013).

Sleep quality

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

Psychosocial features

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

The Hospital Anxiety and Depression Scales [HADS]

The Italian version of the HADS (Iani et al., 2104) will be utilised to investigate depression, anxiety and manifestations of somatic symptoms (Zigmond et al. 1983). 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 depression (Bjelland et al., 2002).

HADS has been studied in different groups confirming adequate to excellent internal consistency of HADS-A [0.68-0.93] and HADS-D [0.67-0.90] (Bjelland et al., 2002). In a coronary heart disease sample, the standard measurement of error was 1.37 for anxiety and 1.44 for depression; the minimal detectable change was 3.80 for anxiety and 3.99 for depression (Wang et al., 2009). The HADS has excellent concurrent validity in comparison to other depression/anxiety scales (Bjelland et al., 2002).

Coping Strategies Questionnaire 27 [CSQ-27]

Forssell et al. (2016) found that a low perceived ability to control pain increases the risk for poor prognosis of TMD pain at one year regardless of the type of treatment. The Italian version of the CSQ-27 (Monticone et al., 2014) will be used to provide an indication of coping strategies used by participants when they are in pain. This 27-item questionnaire contains six domains to assess the strategies for coping with pain: *Distraction, Catastrophizing, Ignoring pain sensations, Distancing from pain, Coping self-statements,* and *Praying*. Patients rate the specific strategies for coping with pain using a seven-point Likert scale [for each domain] ranging from 0 "Never do that" to 6 "Always do that", with higher scores indicating greater use (Robinson et al., 1997). A recent study in a low back pain cohort (Campbell et al., 2013), in which individual items from multiple questionnaires were factorised, suggested that diversion, reinterpreting and cognitive coping clustered together as a single factor, representing coping cognitions; by contrast, catastrophizing clustered with pain-related distress items. The original form was examined in English-speaking subjects and revealed acceptable internal consistency [Cronbach's alpha estimates ranging from 0.72 to 0.86] and satisfying construct validity (Robinson et al., 1997).

Treatment expectation

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

TMD characteristics

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

Pain Duration

According to Grossman et al. (2017), pain duration could be a significant factor influencing the treatment outcome for TMD. Their results underline the fact that a longer pain duration is associated with a more refractory therapeutic approach. Consequently, the pain duration [measured in "days"] will be collected as candidate predictor of outcome from open hospital records and patient interview.

Pain intensity

As shown in a previous study (Grossman et al., 2017), 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 extremity (Wewers et al., 1990). 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 intensity (Dworkin et al. 2005).

Pain location and extent

Forssell et al. (2016) 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 pain (Velly et al., 2013). Therefore, the pain location and the pain extent will be collected as a candidate predictor of outcome. This will be recorded as described by Shiffman et al., (2014) in the DC/TMD protocol (Dworkin et al., 1990; Macfarlane et al., 1996; Margolis et al., 1988; Ohrbach et al., 2011; Sanders et al., 2013; Ohrbach et al., 2013).

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.imagemeasurement.com/experience-image-measurement/pain-assessment-image-measurement)

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

Central sensitization can be present in different pain disorders including low back pain (Roussel et al. , 2013), neck pain (Van Oosterwijck et al. , 2013), fibromyalgia (Desmeules et al. , 2014), and TMD (Fernández-de Las-Peñas et al. , 2009). The Italian version of the Central Sensitization Inventory (CSI) (Chiarotto et al., 2018) 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 conditions (Mayer et al., 2012). The CSI has significant test-retest reliability and internal consistency in subjects with and without pain (Mayer et al., 2012). The Italian version of the CSI showed a satisfactory Cronbach’s alpha [0.87] (Chiarotto et al., 2018).

Classification of TMD

Manual therapy could potentially be beneficial for both myogenous and arthrogenous TMD (Armijo-Olivo et al., 2016). 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/TMD (Shiffman et al., 2014). Based on these criteria, Shiffman et al., (2014) 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

A greater number of disability days increases the risk of having clinically significant pain one year after an initial assessment (Forssell et al., 2016). In this study we will use the Italian version of the RDC/TMD questionnaire Axis II Graded Chronic Pain Scale [GCPS] version-2 [www.rdc-tmdinternational.org] (Von Korff et al., 1992; Von Korff et al., 2011) following the DC/TMD protocol recommendations (Ohrbach et al., 2010; Shiffman et al. 2014; Ohrbach et al., 2013). This scale has good internal consistency in temporomandibular pain [Cronbach's alpha of 0.84] (Von Korff et al. 1992). The GCPS measures the facial pain severity over the preceding 6-months by unifying pain intensity and pain-related disability. The characteristic pain intensity score [range: 0-100] is the mean of three pain intensity measurements: 'at the present time' and 'worst pain' and the 'average' pain over the preceding 6 months. The disability status is measured with a 0-6 point score derived from a combination of the number of disability days and the disability level [range: 0-100; limitation given by pain in performing activities of daily living].

Based on these scores, the participant's chronic pain and disability status can be classified into one of the five ordinal categories of chronic pain severity (Von Korff et al. 1992).

Parafunction

People with parafunctional behaviours with scores above 25 in the Oral Behaviours Checklist [OBC] are 75% more likely to develop TMD than individuals with a score below 17 (Ohrbach et al., 2008; Ohrbach et al., 2012; Ohrbach et al., 2013). Parafunctional habits could play a significant role in the development and the persistence of TMD pain (Glaros et al. 2016). In this study we will use the Italian version of the RDC/TMD questionnaire Axis II Oral Behaviours Checklist [www.rdc-tmdinternational.org] (Ohrbach et al., 2008; Ohrbach et al., 2012;) following the DC/TMD protocol recommendations (Ohrbach et al., 2010; Shiffman et al. 2014). The OBC measures the self-reported frequency over the preceding month of each of 21 activities involving the jaw such as clenching the teeth or bracing the jaw (five ordinal response options, ranging from ''none of the time,'' coded 0, to ''all of the time,'' coded 4). Psychometric properties of this instrument suggest that it is valid, with patient behaviours matching those measured (Ohrbach et al., 2008; Ohrbach et al., 2010; Markiewicz et al., 2006). Scoring is computed as the sum of the number of items with non-zero response or as a weighted sum [e.g. the sum of the endorsed frequencies of the respective items] (Ohrbach et al., 2008).

Clinical tests of the TMJ and masticatory muscles

TMJ range of motion

Mobility testing of the TMJ denotes an essential sign of TMD, it is one of the most reliable clinical measures (Shiffman et al., 2014). Grossman et al. (2017) examined the preoperative

variables of TMD patients with articular disc displacement without reduction that may alter the effects of arthrocentesis on joint effusion. They observed that small maximum interincisal distance influences treatment outcome. As a result, we will use the Maximal Mouth Opening (MMO) without pain as measure of TMJ range of motion. The measurements will be in millimeters and will be taken with a ruler in a neutral craniocervical position [e.g. sitting or supine]. The distance between the incisal edges of the maxillary and mandibular reference teeth, as described in the DC/TMD protocol (Ohrbach et al., 2013), will be measured. Participants will be asked to open the mouth as wide as they can without feeling any pain, or without increasing any present pain. The tip of the ruler will be located against the incisal edge of the mandibular reference incisor, and the distance to the mesial-distal center of the edge of the maxillary central incisor will be read. The test will be repeated twice if the pain-free opening if less than 30mm (Ohrbach et al., 2013). Assessment of mandibular ROM in a neutral craniocervical position obtained good inter- and intra-rater reliability for MMO (Beltran-Alacreu et al. 2014).

TMJ palpation pain:

Pain induced in joints via palpation is a useful clinical test that allows to understand if the provoked pain duplicates or replicates the patient's pain complaint by identifying potential joint origin (Ohrbach et al., 2013). For this palpation, finger pressure is calibrated [1.0 kg], as described in the DC/TMD protocol (Ohrbach et al., 2013), using a simple hand-held algometer prior to palpation examination. While the participant mandible is in a comfortable position or in a slightly protruded position, the examiner's index finger will be placed just anterior to the tragus of the ear and dorsal to the TMJ with the participant in neutral craniocervical position e.g. sitting or supine. The index finger will press while orbiting around the lateral pole in a circular fashion over the superior aspect of the condyle and then anteriorly [from the 9:00 to the 3:00 position, and then

continuing fully around the condyle]. Palpation will last 5 seconds for each pressed point (Ohrbach et al., 2013). If a participant complains of familiar pain in at least one pressed point the point score of this test will be 1; if there is no pain at any points the point score of this test will be 0 [range 0-1: no pain =0; pain = 1]. Palpation will be performed in the left and right side. The interexaminer reliability values of TMJ palpation in TMD patients is 0.59 and the specificity values is acceptable [above 0.90] (Gomes et al. 2008).

Muscle palpation pain

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

Lateral pterygoid area: palpation will be performed with a finger pressure calibrated at 0.5 kg (DC/TMD protocol - Ohrbach et al., 2013). The palpation will take place as described in FIG.1. If a participant complains of familiar pain during palpation, then the lateral pterygoid area will be considered as a painful site.

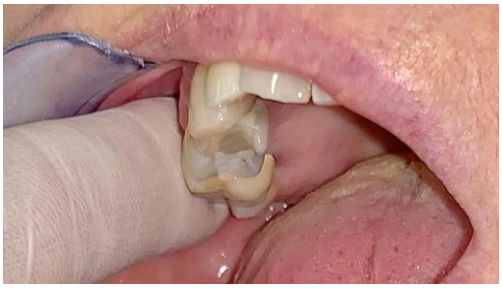


FIG. 1 Lateral pterygoid area: Palpation of the vestibule in a posterior-superior-medial direction while the mandible is omolaterally deviated.

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

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

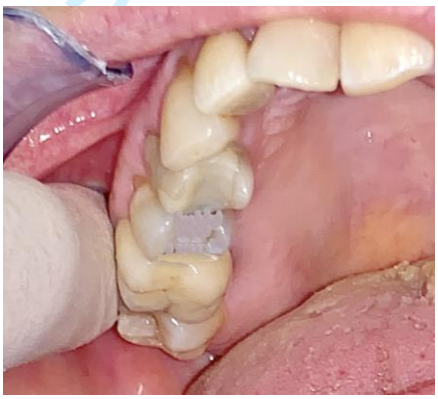


FIG. 2 Temporalis tendon area: Palpation against the ascending mandibular ramus while the mouth is slightly open. The palpation direction is superior as far as possible by following the bone surface.

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

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

JAw-test

The JAw-test is a clinical test that aims to investigate the immediate effects of four brief intraoral manual therapy techniques on pain and on TMJ range of motion. The participant will be positioned in supine. Before starting the test, the pain-free range of motion of the TMJ will be measured [MMO - millimeters] with a ruler, as described above, according to the DC/TMD protocol (Ohrbach et al., 2013). Then the participant will be asked to rate his/her pain through the Verbal Rating Scale (VRS) "at rest", "during clenching" and "during the maximal opening of the mouth"; and the average of the three pain scores will be registered. For this test, finger pressure is calibrated [1.0 kg], in the same way described in the DC/TMD protocol (Ohrbach et al., 2013), using a simple hand-held algometer prior to palpation examination.

Participants will be informed with the following words: "*I am going to perform four manual techniques on some muscles and joints in your jaw region. You may feel a little pain, if the pain increases and becomes too intense, let me know, I will reduce the pressure until the pain returns to acceptable levels".*

First technique: Lateral pterygoid area

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

Second technique: Temporalis tendon area

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

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

Third technique: Mylohyoid area

The participant will be instructed to open the mouth to let the examiner's finger reach the mylohyoid area in a central position on the mylohyoid raphe. The other hand of the examiner will reach the same area using a finger through an extraoral approach. In this position a combined compression (1.0 kg) will be applied for 30-60 seconds.

Fourth technique: TMJ mobilization

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

Final scores:

After the tests, the pain-free range of motion of the TMJ will be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD protocol (Ohrbach et al., 2013). Then the participant will be asked to rate his/her pain using the Verbal Rating Scale (VRS) "at rest", "during clenching" and "during the maximal opening of the mouth"; an average oh this three pain scores will be registered. If a participant shows only an improvement in pain [average score VRS pre-test > average score VRS post-test] the score will be 1; if a participant shows only an improvement of TMJ mobility [MMO pre-test < MMO post-test at least 2 millimeters] the score will be 1; if a participant shows improvements in both pain and TMJ mobility, the score will be 2; if a participant shows no improvements the score will be 0 [Score range 0-2: 0 = no change; 1 = VRS improvement or MMO improvement; 2 = improvement of both].

REFERENCES

Armijo-Olivo, S., Pitance, L., Singh, V., Neto, F., Thie, N., & Michelotti, A. (2016) 'Effectiveness of Manual Therapy and Therapeutic Exercise for Temporomandibular Disorders: Systematic Review and Meta-Analysis'. *Physical Therapy* , *96*(1): 9–25

Artus M, Campbell P, Mallen CD, et al. Generic prognostic factors for musculoskeletal pain in primary care: a systematic review. *BMJ Open* 2017;7(1):e012901.

Beltran-Alacreu, H., López-de-Uralde-Villanueva, I., Paris-Alemany, A., Angulo-Díaz-Parreño, S., & La Touche, R. (2014). Intra-rater and Inter-rater Reliability of Mandibular Range of Motion Measures Considering a Neutral Craniocervical Position. *Journal of physical therapy science*, 26(6), 915-20.

Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An
updated literature review. J Psychosom Res 2002;52(2):69-77.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37(1):53-72.

Campbell P, Foster NF, Thomas E, Dunn KM. Prognostic Indicators of Low Back Pain in Primary
Care: Five-Year Prospective Study. J Pain 2013;14(8):873–83.

Cappelleri JC BA, McDermott AM, Sadosky AB, Petrie CD, Martin S.(2009) 'Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. Health Qual Life Outcomes' ;17(7):54.

Chiarotto A, Viti C, Sulli A, Cutolo M, Testa M, Piscitelli D. (2018). 'Cross-cultural adaptation and validity of the Italian version of the Central Sensitization Inventory'. *Musculoskelet Sci Pract*.37:20-28.

Chiu C JJ, Fujikawa M, Strand D, Cheing G, Lee G, Chan F Measurement Structure of the Coping Strategies Questionnaire-24 in a Sample of Individuals with Musculoskeletal Pain: A Confirmatory Factor Analysis. . Rehabilitation Research, Policy, and Education 2014;28(2):80-90.

Clay FJ, Watson WL, Newstead SV, et al. A systematic review of early prognostic factors for persisting pain following acute orthopedic trauma. Pain Res Manag 2012;17(1):35-44.

Clay FJ, Newstead SV, Watson WL, et al. Bio-psychosocial determinants of persistent pain 6 months after non-life-threatening acute orthopaedic trauma. J Pain 2010;11(5):420-30. doi: 10.1016/j.jpain.2009.12.002

Cleland, J., & Palmer, J. (2004). 'Effectiveness of Manual Physical Therapy, Therapeutic Exercise, and Patient Education on Bilateral Disc Displacement Without Reduction of the Temporomandibular Joint: A Single-Case Design'. J*ournal of Orthopaedic & Sports Physical Therapy*, 34(9), 535–548

Desmeules J, Chabert J, Rebsamen M, Rapiti E, Piguet V, Besson M, et al. (2014). 'Central pain sensitization, COMT Val158Met polymorphism, and emotional factors in fibromyalgia'. *The Journal of Pain*, 15:129-35.

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., … Witter, J. (2005). Core outcome measures for chronic pain clinical trials : IMMPACT recommendations. *Pain*, 113:9–19.

Dworkin SF, Von Korff MR, LeResche L. Multiple pains and psychiatric disturbance: An epidemiologic investigation. Archives of General Psychiatry 1990;47:239-44.

Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, et al. (2016). 'Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations'. *Pain*, 157:1851-71.

Fernández-de-Las-Peñas C, Galán-del-Río F, Fernández-Carnero J, Pesquera J, Arendt Nielsen L, Svensson P. (2009). 'Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing'. *The Journal of Pain*, 10:1170-8.

Fillingim RB, Ohrbach R, et al., (2011). 'Potentiam psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study'. *J Pain*, 2: T46-T60

Forssell, H., Kauko, T., Kotiranta, U., & Suvinen, T. (2017). Predictors for future clinically significant pain in patients with temporomandibular disorder: A prospective cohort study. *European Journal of Pain*, 21(1), 188–197.

Fricton J. Physical evaluation: the need for a standardized examination. In: Fricton JR, ed. Temporomandibular joint and craniofacial pain: diagnosis and management. St Louis: Ishiyaku Euroamerica; 1988:46–47.

Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. (2007).'The biopsychosocial approach to chronic pain: scientific advances and future directions'. *Psychol Bull*, 133(4):581-624.

Glaros, A. G., Marszalek, J. M., & Williams, K. B. (2016). Longitudinal Multilevel Modeling of Facial Pain, Muscle Tension, and Stress. Journal of dental research, 95(4), 416-22.

Gomes MB, Guimarães JP, Guimarães FC, Neves AC. (2008). 'Palpation and pressure pain threshold: reliability and validity in patients with temporomandibular disorders'. *Cranio*, 26(3):202-10.

Grossmann, E., Poluha, R. L., Iwaki, L. C. V., Santana, R. G., & Filho, L. I. (2018). 'Predictors of arthrocentesis outcome on joint effusion in patients with disk displacement without reduction'. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 125(4), 382–388.

Harland NJ Georgieff K. Development of the coping strategies questionnaire 24, a clinically utilitarian version of the coping strategies questionnaire. Rehabilitation Psychology 2003;48(4):296–300.

Haythornthwaite, J. A. (2010). IMMPACT recommendations for clinical trials: Opportunities for the RDC/TMD. *Journal of Oral Rehabilitation*, 37(10), 799–806.

Helkimo M. (1974). 'Studies on function and dysfunction of the masticatory system. IV. Age and sex distribution of symptoms of dysfunction of the masticatory system in Lapps in the north of Finland'. *Acta Odontol Scand*, 32(4):255-67.

Iani, L., Lauriola, M., & Costantini, M. (2014). 'A confirmatory bifactor analysis of the Hospital Anxiety and Depression Scale in an Italian community sample'. *Health and quality of life outcomes*, 12, 84.

Janssen MF, Birnie E, Haagsma JA, et al. Comparing the standard EQ-5D three-level system with a five-level version. Value Health 2008;11(2):275-84.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22(7):1717-27.

Kamaleri Y, Natvig B, Ihlebaek CM, et al. Change in the number of musculoskeletal pain sites: A 14-year prospective study. Pain 2009;141(1-2):25-30. doi: 10.1016/j.pain.2008.09.013

Kapos, F. P., Look, J. O., Zhang, L., Hodges, J. S., & Schiffman, E. L. (2018). 'Predictors of Long-Term Temporomandibular Disorder Pain Intensity: An 8-Year Cohort Study'. *Journal of Oral & Facial Pain and Headache*, 32(2), 113–122.

Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM.(2004). 'Psychological aspects of persistent pain: current state of the science'. *J Pain*, 5(4):195-211.

Keilani, M., Crevenna, R., & Dorner, T. E. (2017). Sleep quality in subjects suffering from chronic pain. Wiener klinische Wochenschrift, 130(1-2), 31-36.

Kight M, Gatchel RJ, Wesley L. (1999). 'Temporomandibular disorders: evidence for significant overlap with psychopathology'. *Health Psychol*. 18(2):177-82.

Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in United States. J Am Dent Assoc 1993; 124: 115-112.

Macfarlane, G. J., et al. (1996). Widespread pain: is an improved classification possible? Journal of
Rheumatology 23(9): 1628-1632.

Mallen CD, Peat G, Thomas E, et al. Prognostic factors for musculoskeletal pain in primary care: a
systematic review. Br J Gen Pract 2007;57(541):655-61.

Margolis, R. B., et al. (1988). Test-retest reliability of the pain drawing instrument. Pain 33: 49-51.

Markiewicz MR, Ohrbach R, McCall WD Jr. (2006). 'Oral behaviors checklist: Reliability of performance in targeted waking-state behaviors'. *J Orofacial Pain* 20:306-316

Monticone, M., Ferrante, S., Giorgi, I., Galandra, C., Rocca, B., & Foti, C. (2014). The 27-item coping strategies questionnaire-revised: confirmatory factor analysis, reliability and validity in Italian-speaking subjects with chronic pain. *Pain research & management*, 19(3), 153-8.

NCHS. Summary Health Statistics Tables for the U.S. Population: National Health Interview Survey, 2014 (12/2015) [Online]. CDC/National Centre of Health and Statistics. Available: http://www.cdc.gov/nchs/nhis/SHS/tables.htm [March 10, 2019]

Nicholas MK, Linton SJ, Watson PJ, Main CJ. (2011). 'Early identification and management of psychological risk factors ("yellow flags") in patients with low back pain: a reappraisal'. *Phys Ther*, 91:737-753.

Ohrbach R, Gonzalez Y, List T, Michelotti A, Schiffman E. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Clinical Examination Protocol: Version 02June2013. www.rdc-tmdinternational.org Accessed on <March 10, 2019>.

Ohrbach R, Fillingim RB, Mulkey F, et al. Clinical findings and pain symptoms as potential risk factors for
chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control
study. Journal of Pain 2011;12 (11, Supplement 3):T27-T45.

Ohrbach R, List T, Goulet J-P, Svensson P. Recommendations from the International Consensus Workshop:
Convergence on an Orofacial Pain Taxonomy. *Journal of Oral Rehabilitation* 2010;37:807-12.

Ohrbach, R., et al. (2008). "Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography." European Journal of Oral Sciences 116: 438-444.

Ohrbach, R., et al. (2011). "Clinical findings and pain symptoms as potential risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control study." Journal of Pain 12(11, Supplement 3): T27-T45.

Ohrbach, R., et al. (2013). "Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study." Journal of Pain 14 (Supplement 2)(12): T33-T50.

Plesh, O., Adams, S.H., Gansky, S.A. (2011). 'Temporomandibular joint and muscle disorders-type pain and comorbid pains in a national US sample'. *J Orofacial Pain*, 25: 190-198.

Puentedura EJ, Cleland JA, Landers MR, Mintken PE, Louw A, Fernández-de-Las-Peñas C. (2012). 'Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine'. *J Orthop Sports Phys Ther*, 42(7):577-92.

Robinson ME, Riley JL 3rd, Myers CD, Sadler IJ, Kvaal SA, Geisser ME, Keefe FJ. (1997). 'The Coping Strategies Questionnaire: a large sample, item level factor analysis'. *Clin J Pain*, 13(1):43-9

Rosenstiel AK KF. The use of coping strategies in chronic low back pain patients: Relationship to
patient characteristics and current adjustment. . Pain 1983;17: 33–44.

Roth RS, Geisser ME. (2002). 'Educational achievement and chronic pain disability: mediating role of pain-related cognitions'. *Clin J Pain*, 18(5):286-96

Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. (2013). 'Central sensitization and altered central pain processing in chronic low back pain: fact or myth?'. *The Clinical journal 216 of pain*, 29:625-38.

Rushton AB, Evans DW, Middlebrook N, Heneghan NR, Small C, Lord J, Patel JM, Falla D. (2018). 'Development of a screening tool to predict the risk of chronic pain and disability following musculoskeletal trauma: protocol for a prospective observational study in the United Kingdom'. *BMJ Open*, 28;8(4):e017876

Sanders AE, Slade GD, Bair E, et al. General health status and incidence of first-onset temporomandibular disorder: OPPERA prospective cohort study. Journal of Pain 2013.

Sayar K, Arikan M, Yontem T.(2002). 'Sleep quality in chronic pain patients'. *Can J Psychiatry*, 47(9):844-8.

Schiffman, E., Ohrbach, R., Truelove, E., Look, J., Anderson, G., Goulet, J.-P., … Dworkin, S. F. (2014). 'Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and

Research Applications: Recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†'. J*ournal of Oral & Facial Pain and Headache*, 28(1)

Smith SM, Dworkin RH, Turk DC, Baron R, Polydefkis M, Tracey I, et al. (2017). 'The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations'. *The Journal of Pain*,

Smith BH, Penny KI, Purves AM, et al. The Chronic Pain Grade questionnaire: validation and reliability in postal research. Pain 1997;71(2):141-7.

Van Oosterwijck J, Nijs J, Meeus M, Paul L. (2013). 'Evidence for central sensitization in chronic whiplash: a systematic literature review'. *European Journal of Pain*, 17:299-312.

Vase L, Petersen GL, Riley JL, 3rd, Price DD. (2009). 'Factors contributing to large analgesic effects in
placebo mechanism studies conducted between 2002 and 2007'. *Pain*, 145:36-44

Velly, A., Schweinhardt, P., Fricton, J. (2013). Comorbid conditions: How they affect orofacial pain. In Treatment of TMDs: Bridging the Gap Between Advances in Research and Clinical Patient Management, Greene, C.S., Laskin, D.M., eds. (Chicago: Quintessence) pp. 91–98

Von Korff M, Dworkin SF, Le Resche L, Kruger A. (1988). 'An epidemiologic comparison of pain complaints'. *Pain*, 32(2):173-83.

Von Korff, M. (2011). Assessment of chronic pain in epidemiological and health services research: Empirical bases and new directions. *Handbook of Pain Assessment*. D. C. Turk and R. Melzack. New York, Guilford Press: 455- 473.

Von Korff, M., et al. (1992). Grading the severity of chronic pain. *Pain* 50: 133-149.

Von Korff, M. R., et al. (1992). Research diagnostic criteria. Axis II: Pain-related disability and psychological status. In: S.F. Dworkin & L. LeResche (Eds.), Research Diagnostic Criteria for Temporomandibular Disorders. *Journal of Craniomandibular Disorders, Facial and Oral Pain* 6: 330-334.

Wang W, Chair, S.Y., Thompson, D.R., Twinn, S.F. A Psychometric Evaluation of the Chinese Version of the Hospital Anxiety and Depression Scale in Patients with Coronary Heart Disease Journal of Clinical Nursing 2009;18:1908-15.

Wewers, M.E., Lowe, N.K. (1990) 'A critical review of visual analogue scales in the measurement of clinical phenomena'. *Res Nurs Health*, 13:227–236

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-70.

580
581

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

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		
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
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – Pages 8-9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – Pages 7 and 9
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)
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – Pages 7
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – Pages 9-11, Supplementary file
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – Page 12-13 (withdrawals)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – Page 12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – n/A

	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

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
	31b	Authorship eligibility guidelines and any intended use of professional writers – N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – N/A
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" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032113.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Oct-2019
Complete List of Authors:	Asquini, Giacomo; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Edoardo Bianchi , Andrea ; Italian Stomatologic Institute Heneghan, Nicola; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rushton, Alison; niversity of Birmingham, School of Health and Population Sciences, College of Medical and Dental Sciences Borromeo, Giulia; Italian Stomatologic Institute Locatelli , Matteo; IRCCS San Raffaele Scientific Institute Falla, Deborah; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Dentistry and oral medicine
Keywords:	Temporomandibular Disorders, Temporomandibular Joint Dysfunction Syndrome, Pain, Prediction, Manual Therapy

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

Asquini G[1,2], Edoardo Bianchi A[2], Heneghan N[1], Rushton A[1], Borromeo G[2], Locatelli M[3], Falla D[1]

Affiliations

[1] Centre of Precision Rehabilitation for Spinal Pain (CPR Spine)
School of Sport, Exercise and Rehabilitation Sciences
College of Life and Environmental Sciences
University of Birmingham
Birmingham B15 2TT
United Kingdom

[2] Italian Stomatologic Institute
Craniomandibular Physiotherapy Service
Via Pace 21, 20122 Milan
Italy

[3] IRCCS San Raffaele Scientific Institute
Via Olgettina Milano 60,
20132 Milano,
Italy

Corresponding author:

Deborah Falla

Centre of Precision Rehabilitation for Spinal Pain (CPR Spine)

School of Sport, Exercise and Rehabilitation Sciences

College of Life and Environmental Sciences

University of Birmingham

Birmingham, UK

E-mail: d.falla@bham.ac.uk

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 (≥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 management[1-2]. 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 period[3]. 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 opening[5] but many patients also complain of neck and back pain or pain at other sites[6].

Physical therapy is one of the most common conservative interventions for the management of TMD[7] and given that the aetiology may be unclear[8], several therapeutic approaches have been described[9]. One approach is manual therapy applied to the craniomandibular structures with evidence suggesting a significant reduction in pain with manual therapy treatment[10], although responses are highly variable[11]. 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[12-13]. 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

patients with TMD pain[14]. They analysed several potential predictors of persistent pain at one-year follow-up including demographic, pain-related and psychosocial variables. It was concluded that patients with TMD who have had numerous previous healthcare visits, complained of high-intensity pain at other body sites and had a greater number of disability days, were at greater risk of having pain one year after the initial assessment. Nevertheless, this study did not examine predictors of pain reduction related to a therapeutic intervention which could be useful to inform clinical practice. Kapos et al. investigated the association of long-term pain intensity with baseline health-related quality of life and jaw functional limitation in patients with TMD[15]. Findings suggested that baseline health-related quality of life is inversely proportional with pain intensity at an eight-year follow-up regardless of the type of treatment that they received (e.g. surgery, drugs, physical therapy or unconventional therapy). After adjusting for the type of treatments received, by clustering the participants into three groups (medical/conventional management, alternative medicine, and surgical intervention), each predictor analysed (demographic, pain-related and health-related quality of life) maintained similar statistical significance. Notwithstanding, the group classified as "medical/ conventional management" included participants receiving diverse treatments ranging from physical therapy, pharmacology (Acetaminophen, Antidepressants, Anti-inflammatories) to the application of a mouth appliance (e.g. Michigan splint). This previous work can facilitate clinicians to identify patients who are more challenging to treat by identifying clinical features associated with persistent pain in the long term regardless of the type of interventions applied. However, currently no study has examined predictive factors associated with pain reduction following manual therapy interventions in patients with TMD.

The aim of this study is to identify predictors associated with pain reduction in patients with TMD following manual therapy applied to craniomandibular structures by analysing a combination of: (1) demographical variables, (2) general health variables, (3)

psychosocial features, (4) TMD characteristics, and (5) clinical tests of the temporomandibular joint and masticatory muscles. The knowledge gained from this study will facilitate clinical decision-making for manual therapists managing patients with TMD by providing clinicians with key factors to evaluate, to determine whether or not the patient is likely to have a clinically relevant reduction in their pain immediately following four weekly applications of manual therapy.

METHODS AND ANALYSIS

Source of data

A prospective observational study will recruit a cohort of patients referred to the Italian Stomatologic Institute with a TMD diagnosis according to the Axis I of the Diagnostic Criteria for TMDs (DC/TMD)[16]. This protocol is written according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement[17] in which recommendations are provided about prediction model development and validation. Ethical clearance will be obtained from the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and the University of Birmingham Ethics Committee, and the study will be conducted in accordance with the Declaration of Helsinki.

Patient reported and physical assessment data will be collected at baseline prior to commencing treatment. Outcome will be collected at the end of the fourth session of craniomandibular manual therapy (at one month). This timeline has been selected based on previous studies investigating 1) the effects of manual therapy on pain[18-19]; and 2) work confirming the effectiveness of manual therapy for TMD patients[20] and is believed to be reasonable for the purposes of this study.

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 months[21]; (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 disorders[12-13], 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

protocol[22]. Subsequently, in accordance with the inclusion/exclusion criteria, he will explain the study to the potential participant and provide the patient information sheet. Participants will then give their written informed consent prior to inclusion in the study. Afterwards, the participant will be referred to see a physiotherapist [independent assessor, >5 years' experience in managing patients with TMD] for the baseline assessments (summarised in Table 1) and then treatment will commence within the same week. After the last session (i.e. one month from baseline), the participants will be assessed again by the assessing physiotherapist to measure outcome. Participant flow through the study is outlined in Figure 1.

[FIGURE 1]

Treatment

Participants will receive four sessions of manual therapy applied to craniomandibular structures over 4 weeks[23-25]. Two physiotherapists, each with >5 years' experience in manual therapy / TMD will perform the treatments. They will not be involved in participant recruitment, assessment or the collection of the outcome measure. Manual therapy techniques will be based on the clinical examination, and will be selected at the discretion of the treating physiotherapist according to their clinical reasoning of the individual case. Overall, the application of manual therapy aims to decrease pain by treating masticatory muscle trigger points, muscle tightness, and restricted temporomandibular joint movements. Several techniques will be considered including: (i) ventral and caudal anterior glide temporomandibular joint mobilization[26]; (ii) soft tissue interventions for the management of trigger points in masticatory muscles[27]; (iii) myofascial induction therapy [functional restoration of the fascial system] applied to craniomandibular structures[28].

The structures targeted in the treatment sessions will be the temporomandibular joint, temporal muscles, masseter muscles, medial and lateral pterygoid muscles and suprahyoid muscles, applied at the discretion of the physiotherapist based on the patient's individual presentation. During the treatment sessions, the treating physiotherapists will provide explanations about the patient's condition and answer any participant questions by promoting general advice. The treatment sessions will last from 20 to 30 minutes duration. No other treatment (e.g. oral appliance) will be performed for the management of their TMD. If during the course of the four-week intervention, a patient seeks treatment for an acute episode of pain at another site (e.g. neck pain, low back pain, shoulder pain) they will be withdrawn from the study.

Outcome

The outcome being predicted by the prediction model is pain intensity since patients with TMD typically report pain to be their primary problem[5], manual therapy is largely known to be effective principally for pain modulation[29] and change in pain intensity has most commonly been the primary outcome of choice in several other studies of patients with TMD[30-33].

Pain intensity will be calculated by averaging the ratings of current pain, average pain in the past week, 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 "worst pain imaginable" at the right extremity[34]. The VAS is a reliable and valid scale to assess pain intensity as an outcome measure in intervention studies[35]. Based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations about TMD reviewed by Haythornthwaite[36], a reduction of at least 30% of the VAS score for pain intensity is considered clinically significant. Consequently, a

reduction in the total VAS score [≥ 30%] will be defined as a good outcome. The outcome measure will be evaluated by the same independent assessor to minimise detection bias[37].

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 disorders[39-40]. It is responsive to clinically significant change over time[41]. 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 pain[42-44].

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 disorders[45-46]. 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 predictors[56]. This method will guarantee an adequate sample size (at least 10 cases per candidate predictor) to power the final regression analysis[57-58]. 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 model[59]. 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 ≥30%][36]. Exploratory factor analysis will be applied to

analyse factor loading of candidate predictors (summary scores) on good outcome at one month. This process will reduce candidate predictors (supported by the cohort sample of 90) to enter into the final model.

The statistical model has been designed a priori. To investigate the impact of each predictive factor on good outcome, a logistic multivariable regression model will be performed. For each candidate predictor, the mean differences or the odds ratio with their 95% confidence intervals will be calculated. A multiple imputation analysis[60] will be applied to manage possible missing data. The multivariable analysis will initially consider all candidate predictors. In the case of a high correlation between candidate predictors, a reduced multivariate analysis will be considered.

DISCUSSION

There is a need to identify predictors for pain reduction in patients with TMD following specific treatments in order to inform clinical decision-making. Several therapies are described for patients with TMD such as the use of oral appliances, different types of physical therapy modalities, pharmacology or temporomandibular joint arthrocentesis yet the amount of pain relief that different people receive from each intervention is variable[7,10]. As shown by Forssell et al.[14] and Kapos et al.[15], many patients continue to experience pain following such interventions. Investigating factors associated with pain relief to such treatments can facilitate clinical assessment and treatment selection.

Physical therapy is one of the most common conservative interventions to treat TMD[7]. Among different physical therapy modalities, manual therapy can provide symptom and functional improvements[10] including pain relief[11,31]. Knowledge of predictive factors associated with good outcome to a specific intervention such as manual therapy applied to

craniomandibular structures will facilitate clinical decision making. Ultimately, such knowledge will lead to improved clinical and cost effectiveness of rehabilitation approaches.

Quality assurance

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

Patient and Public Involvement

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

Ethics and Dissemination

The research protocol has been submitted to the Ethics Committee of the "Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico" and subsequently will be submitted to the University of Birmingham Ethics Committee for approval. Researchers will inform all participants on the characteristics of the research and will obtain written consent. Participants will be informed that they are free to withdraw from the study at any time, without needing to provide reason. Any concerns for a participant by the study team will be fed back to the primary investigator (GA). Baseline characteristics of withdrawn participants will be compared to those of retained participants to assess for any differences. In the event of any unlikely adverse events, this will be immediately reported by the principal investigator to the ethics committee.

The results of this study will submitted for publication in a peer review journal and presented at conferences.

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

REFERENCES

1. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in United States. *J Am Dent Assoc*. 1993;124:115-112.

2. NIDCR. Facial Pain (2014). *National Institute of Health* [Online]. http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain/ [Accessed Dec 28 2018]

3. Adèrn B, Minston A, Nohlert E, Tegelberg Å. Self-reportance of temporomandibular disorders in adult patients attending general dental practice in Sweden from 2011 to 2013. *Acta Odontol Scand*. 2018;76(7):530-534.

4. Montero J, Llodra JC, Bravo M. Prevalence of the Signs and Symptoms of Temporomandibular Disorders Among Spanish Adults and Seniors According to Five National Surveys Performed Between 1993 and 2015. *J Oral Facial Pain Headache.* 2018;32(4):349-357.

5. De Leeuw R, Klasser GD. *Orofacial pain guidelines for assessment, diagnosis, and management*. 5th ed. Hanover park, II: Quintessence publishing; 2013.

6. Plesh O, Adams SH, Gansky SA. Temporomandibular joint and muscle disorders-type pain and comorbid pains in a national US sample. *J Orofacial Pain*. 2011;25: 190-198.

7. Calixtre LB, Grüninger BL, Haik MN, Alburquerque-Sendín F, Oliveira AB. Effects of cervical mobilization and exercise on pain, movement and function in subjects with temporomandibular disorders: a single group pre-post test. *Journal of Applied Oral Science*. 2016;24(3):188–197.

8. Slade GD, Bair E, Greenspan JD, Dubner R, Fillingim RB, Diatchenko L, Maixner W, Knott C, Ohrbach R. Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: the OPPERA prospective cohort study. *J Pain*. 2013;14:T20-T32

9. Coskun Benlidayi I, Salimov F, Kurkcu M, Guzel R. Kinesio-Taping for temporomandibular Disorders: Single-blind, ramdomized, controlled trial of effectiveness. *J Back Musculoskelet Rehabil*. 2016; 29:373-380.

10. Armijo-Olivo S, Pitance L, Singh V, Neto F, Thie N, Michelotti A. Effectiveness of Manual Therapy and Therapeutic Exercise for Temporomandibular Disorders: Systematic Review and Meta-Analysis. *Physical Therapy*. 2016; 96(1): 9–25.

11. Kalamir A, Graham PL, Vitiello AL, Bonello R, Pollard H. Intra-oral myofascial therapy versus education and self-care in the treatment of chronic, myogenous temporomandibular disorder: A randomised, clinical trial. *Chiropractic and Manual Therapies*. 2013; 21(1):17.

12. Cleland JA, Childs JD, Fritz JM, Whitman JM, Eberhart SL. Development of a Clinical Prediction Rule for Guiding Treatment of a Subgroup of Patients With Neck Pain: Use of Thoracic Spine Manipulation, Exercise, and Patient Education. *Physical Therapy*. 2007; 87(1): 9–23.

13. Flynn T, Fritz J, Whitman J, Wainner R, Magel J, Rendeiro D, Butler B, Garber M, Allison S. A clinical prediction rule for classifying patients with low back pain who demonstrate short-term improvement with spinal manipulation. *Spine*; 2002; 27(24):2835-2843.

14. Forssell H, Kauko T, Kotiranta U, Suvinen T. Predictors for future clinically significant pain in patients with temporomandibular disorder: A prospective cohort study. *European Journal of Pain*. 2017; 21(1):188–197.

15. Kapos FP, Look JO, Zhang L, Hodges JS, Schiffman EL. Predictors of Long-Term Temporomandibular Disorder Pain Intensity: An 8-Year Cohort Study. *Journal of Oral & Facial Pain and Headache*. 2018; 32(2):113–122.

16. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF; International RDC/TMD Consortium Network, International association for Dental Research; Orofacial Pain Special Interest Group, International Association for the Study of Pain. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. *J Oral Facial Pain Headache*. 2014; 28(1):6-27.

17. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement'. *BMC Medicine*. 2015; 350:g7594

18. Bishop MD, Torres-Cueco R, Gay CW, Lluch-Girbés E, Beneciuk JM, Bialosky JE. What effect can manual therapy have on a patient's pain experience?. *Pain management*. 2015; 5(6):455-64.

19. Vigotsky AD, Bruhns RP. Corrigendum to "The Role of Descending Modulation in Manual Therapy and Its Analgesic Implications: A Narrative Review". *Pain Res Treat*. 2017; 1535473.

20. Calixtre LB, Moreira RFC, Franchini GH, Alburquerque-Sendín F, Oliveira A.B. Manual therapy for the management of pain and limited range of motion in subjects with signs and symptoms of temporomandibular disorder: A systematic review of randomised controlled trials. *Journal of Oral Rehabilitation*. 2015; 42(11):847–861.

21. Wahlund K, Nilsson IM, Larsson B. Treating temporomandibular disorders in adolescents: a randomized, controlled, sequential comparison of relaxation training and occlusal appliance therapy. *J Oral Facial Pain Headache*. 2015; 29(1):41-50.

22. Ohrbach R, editor. Diagnostic Criteria for Temporomandibular Disorders: Assessment Instruments. Version 15May2016. [Criteri diagnostici per i disordini temporomandibolari: Strumenti valutativi (DC/TMD) Version 17Jan2017] Michelotti A., Segù M., Wrenn C., Rongo R. Trans. www.rdc-tmdinternational.org Accessed on <31 Mar 2019>.

23. Crockett DJ, Foreman ME, Alden L, Blasberg B. A comparison of treatment modes in the management of myofascial pain dysfunction syndrome. *Biofeedback and self-regulation*. 1986; 11(4):279-291.

24. Guarda-Nardini L, Stecco A, Stecco C, Masiero S, Manfredini D. Myofascial Pain of the Jaw Muscles: Comparison of Short-Term Effectiveness of Botulinum Toxin Injections and Fascial Manipulation Technique. *CRANIO*. 2012; 30(2):95–102.

25. Nascimento M, Vasconcelos BC, Porto GG, Ferdinanda G, Nogueira CM, Raimundo RD. Physical therapy and anesthetic blockage for treating temporomandibular disorders: a clinical trial. *Med Oral Patol Oral Cir Bucal*. 2013; 18(1):81-5.

26. Cleland J, Palmer J. Effectiveness of Manual Physical Therapy, Therapeutic Exercise, and Patient Education on Bilateral Disc Displacement Without Reduction of the Temporomandibular Joint: A Single-Case Design. *Journal of Orthopaedic & Sports Physical Therapy*. 2004; 34(9):535–548.

27. Miernik M, Wieckiewicz M, Paradowska A. Massage therapy in myofascial TMD pain management. *Adv Clin Exp Med*. 2012; 21(5):681-5.

28. Fernandez-de-las-Pena C, Mesa-Jimenez J. *Temporomandibular Disorders: manual Therapy, exercise and needling*. United Kingdom: Handspring Publishing; 2018

29. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther*. 2009; 14:531–538.

30. Kalamir A, Pollard H, Vitiello A, Bonello R. Intra-oral myofascial therapy for chronic myogenous temporomandibular disorders: a randomized, controlled pilot study. *Journal of Manual & Manipulative Therapy*, 2010; 18(3),:39–146.

31. Gomes CA, Politti F, Andrade DV, de Sousa DF, Herpich CM, Dibai-Filho AV, Gonzalez TO, Biasotto-Gonzalez DA. Effects of Massage Therapy and Occlusal Splint Therapy on Mandibular Range of Motion in Individuals With Temporomandibular Disorder: A Randomized Clinical Trial. *Journal of Manipulative and Physiological Therapeutics*. 2014; 37(3):164–169.

32. Tuncer AB, Ergun N, Tuncer AH, Karahan S. Effectiveness of manual therapy and home physical therapy in patients with temporomandibular disorders: A randomized controlled trial. *Journal of Bodywork and Movement Therapies*. 2013; 17(3):302–308.

33. von Piekartz H, Hall T. Orofacial manual therapy improves cervical movement impairment associated with headache and features of temporomandibular dysfunction: A randomized controlled trial. *Manual Therapy*. 2013; 18(4):345-50.

34. Haefeli M, Elfering A. 'Pain assessment: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. *European spine journal*. 2005; 15:S17–S24.

35. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Witter J. Core outcome measures for chronic pain clinical trials : IMMPACT recommendations. *Pain*. 2005; 113:9–19.

36. Haythornthwaite JA.IMMPACT recommendations for clinical trials: Opportunities for the RDC/TMD. *Journal of Oral Rehabilitation*. 2010; 37(10):799–806.

37. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011 Oct 18;343:d5928.

38. Stratford P, Gill C, Westaway M, Binkley J. Assessing disability and change on individual patients: a report of a patient specific measure. *Physiotherapy Canada*. 1995; 47:258-263.

39. Horn KK, Jennings S, Richardson G, Van Vliet D, Hefford C, Abbott JH. The patient-specific functional scale: psychometrics, clinimetrics, and application as a clinical outcome measure. *Journal of orthopaedic & sports physical therapy*. 2012; 42(1):30-D17.

40. Abbott JH, Schmitt J. Minimum important differences for the patient-specific functional scale, 4 region-specific outcome measures, and the numeric pain rating scale. *Journal of Orthopaedic & Sports Physical Therapy*. 2014; 44(8):560-4.

41. Maughan EF, Lewis JS. Outcome measures in chronic low back pain. *European Spine Journal*. 2010; 19(9):1484-94.

42. Hefford C, Abbott JH, Arnold R, Baxter GD. The patient-specific functional scale: validity, reliability, and responsiveness in patients with upper extremity musculoskeletal problems. *Journal of orthopaedic & sports physical therapy*. 2012; 42(2):56-65.

43. Westawa MD, Stratford PW, Binkley JM. The patient-specific functional scale: validation of its use in persons with neck dysfunction. *Journal of Orthopaedic & Sports Physical Therapy*. 1998; 27(5):331-8.

44. Chatman AB, Hyams SP, Neel JM, Binkley JM, Stratford PW, Schomberg A, Stabler M. The Patient-Specific Functional Scale: measurement properties in patients with knee dysfunction. *Physical therapy*. 1997; 77(8):820-9.

45. Bair E, Gaynor S, Slade GD, Ohrbach R, Fillingim RB, Greenspan JD, Dubner R, Smith SB, Diatchenko L, Maixner W. Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study. *Pain*. 2016; 157(6):1266-78.

46. Clark J, Nijs J, Yeowell G, Goodwin PC. What Are the Predictors of Altered Central Pain Modulation in Chronic Musculoskeletal Pain Populations? A Systematic Review. *Pain Physician*. 2017; 20(6):487-500.

47. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996; 37(1):53-72.

48. Cappelleri JC, McDermott AM, Sadosky AB, Petrie C.D, Martin S. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. *Health Qual Life Outcomes*. 2009; 17(7):54.

49. Monticone M, Ferrante S, Giorgi I, Galandra C, Rocca B, Foti C. The 27-item coping strategies questionnaire-revised: confirmatory factor analysis, reliability and validity in Italian-speaking subjects with chronic pain. *Pain Res Manag*. 2014; 19(3):153-8.

50. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983; 67(6):361-70.

51. Puentedura EJ, Cleland JA, Landers MR, Mintken PE, Louw A, Fernández-de-Las-Peñas C. Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine. *J Orthop Sports Phys Ther*. 2012; 42(7):577-92.

52. Davis CE, Stockstill JW, Stanley WD, Wu Q. Pain-related worry in patients with chronic orofacial pain. *J Am Dent Assoc*.2014; 145(7):722-30.

53. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Gatchel RJ. The Development and Psychometric Validation of the Central Sensitization Inventory. *Pain Practise*. 2012; 12(4):276–285.

54. Peck CC, Goulet JP, Lobbezoo F, Schiffman EL, Alstergren P, Anderson GC, de Leeuw R, Jensen R, Michelotti A, Ohrbach R, Petersson A, List T. Expanding the taxonomy of the diagnostic criteria for temporomandibular disorders. *J Oral Rehabil*. 201; 41(1):2-23.

55. Ohrbach R, Michael RM, Willard DM. Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography. *European Journal of Oral Sciences*. 2008; 116:438-444.

56. Fabrigar LR, Wegener DT, MacCallum RC, Strahan EJ. Evaluating the use of exploratory factor analysis in psychological research. *Psychological Methods*. 199; 4:272–299.

57. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996; 49(12):1373-9.

58. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007; 165(6):710-8.

59. Shmueli G. To explain or to predict?. *Statistical Science*. 2010; 25(3):289-310.

60. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009; 338:b2393.

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

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests Statement

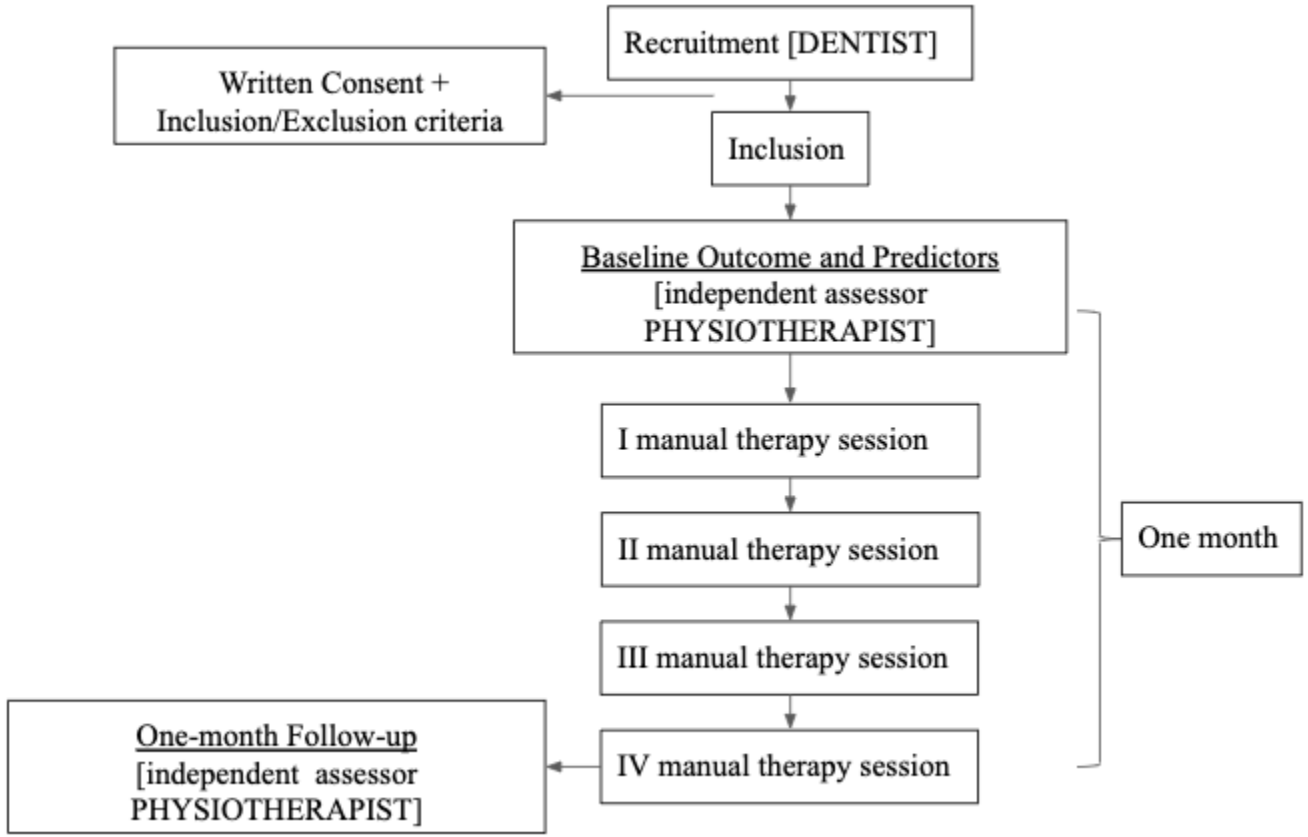
The authors have no competing interests to report.

Data sharing statement

No additional data are available.

FIGURE LEGEND

Figure 1: Participant flow through the study


Recruitment [DENTIST]
Written Consent +
Inclusion/Exclusion criteria
Inclusion
Baseline Outcome and Predictors
[independent assessor
PHYSIOTHERAPIST]
I manual therapy session
II manual therapy session
III manual therapy session
IV manual therapy session
One month
One-month Follow-up
[independent assessor
PHYSIOTHERAPIST]

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

Supplementary file 1 - Candidate predictors

Demographical variables

Participants' demographic variables [age, gender, education] will be collected at baseline from open hospital records and patient interview.

Age

Age is a significant factor in TMD incidence and prevalence. Lipton et al. found different age-specific prevalence for face/jaw pain: 6.5% in aged 18-34, 5.0% in 35-54 years old, 4.0% in 55-74 years old and 3.9% in people > 74 year old, showing a prevalence reduction across the lifetime[1]. By contrast, data from the OPPERA study[2] showed a 40% increased risk for TMD among individuals aged 25-34 years and a 50% increased risk for TMD among individuals aged 35-50 years.

Gender

Women are 1.5-2 times more likely to develop TMD than men[3-5]. Currently, there is no study examining the extent of recovery from TMD in men and women. Nevertheless, gender is a significant factor to be considered.

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 pain[7]. 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 state[9]. 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-3L[10]. 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

It is known that chronic pain patients may suffer from poor sleep quality, even if it is difficult to draw a causal relation[12]. Consequently, sleep quality will be assessed as a candidate predictor because of its possible role among other factors in the transition from acute to chronic pain. Sleep quality will be evaluated through an 11-point Numerical Rating Scale [NRS], where 0 is 'the best possible sleep' and 10 is 'the worst possible sleep'. This scale owns moderate psychometric properties in fibromyalgia patients to assess current sleep quality [over the previous 24 hour period] with a symptom diary[13]. We will use the 0-10 NRS to assess average sleep quality, related to the preceding 6-months at baseline[14], although no psychometric properties have previously been reported for this recall period.

Psychosocial features

Psychosocial factors are known to influence TMD onset and chronicity[15]. Psychological distress is significantly linked to a greater severity and persistence of TMD pain[16]. Moreover, depression and high levels of stress are significantly more common in people with chronic TMD[17-18]. In addition, there is agreement about the predictive strength of psychosocial factors in primary care among different musculoskeletal pain conditions[19-20].

<u>The Hospital Anxiety and Depression Scales [HADS]</u>

The Italian version of the HAD[21] will be utilised to investigate depression, anxiety and manifestations of somatic symptoms[22]. 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 depression[23].

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

consistency of HADS-A [0.68-0.93] and HADS-D [0.67-0.90][23]. In a coronary heart disease sample, the standard measurement of error was 1.37 for anxiety and 1.44 for depression; the minimal detectable change was 3.80 for anxiety and 3.99 for depression[24]. The HADS has excellent concurrent validity in comparison to other depression/anxiety scales[23].

Coping Strategies Questionnaire 27 [CSQ-27]

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

Treatment expectation

A positive treatment expectation is considered as a treatment moderator because of its influence on treatment outcome[29]. A positive treatment expectation is predictive of good outcome

because the expectation of benefit (placebo) has a robust effect on pain[30]. In the current study we will investigate treatment expectation following the same protocol used by Puentedura et al[31]. Participants will be asked whether they "Completely disagree", "Somewhat disagree", "Neutral", "Somewhat agree", "Completely agree" with the following statement: "I believe that *manual techniques applied to my jaw* will significantly help to improve my pain". If the participant chooses "completely disagree," "somewhat disagree," or "neutral," there is not a positive expectation that manual therapy applied to craniomandibular structures will significantly help their temporomandibular disorder. If the participant chooses "somewhat agree" or "completely agree," there is a positive expectation that manual therapy applied to craniomandibular structures will significantly help their temporomandibular disorder.

TMD characteristics

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

Pain Duration

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

Pain intensity

As shown in a previous study[32], 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 extremity[36]. 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 intensity[37].

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 pain[38]. 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.imagemeasurement.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 pain[46], neck pain[47], fibromyalgia[48], and TMD[49]. 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 conditions[45]. The CSI has significant test-retest reliability and internal consistency in subjects with and without pain[45]. 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 TMD[51]. 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/TMD[39]. 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

A greater number of disability days increases the risk of having clinically significant pain one year after an initial assessment[25]. In this study we will use the Italian version of Graded Chronic Pain Scale [GCPS] version 2.0 [www.rdc-tmdinternational.org][53] following the DC/TMD protocol recommendations[39,42,44]. This scale has good internal consistency in temporomandibular pain [Cronbach's alpha of 0.84][54]. The GCPS measures the facial pain severity over the preceding 6-months by unifying pain intensity and pain-related disability. The characteristic pain intensity score [range: 0-100] is the mean of three pain intensity measurements: 'at the present time' and 'worst pain' and the 'average' pain over the preceding 6 months. The disability status is measured with a 0-6 point score derived from a combination of the number of disability days and the disability level [range: 0-100; limitation given by pain in performing activities of daily living]. Based on these scores, the participant's chronic pain and disability status can be classified into one of the five ordinal categories of chronic pain severity[55].

Oral Behaviour

People with abnormal oral behaviours with scores above 25 in the Oral Behaviours Checklist [OBC] are 75% more likely to develop TMD than individuals with a score below 17[42,44,56]. Parafunctional habits could play a significant role in the development and the persistence of TMD pain[58]. In this study we will use the Italian version of the RDC/TMD questionnaire Axis II Oral Behaviours Checklist [www.rdc-tmdinternational.org][42,56] following the DC/TMD protocol recommendations[39,56]. The OBC measures the self-reported frequency over the preceding month of each of 21 activities involving the jaw such as clenching the teeth or bracing the jaw (five ordinal response options, ranging from ''none of the time,'' coded 0, to ''all of the time,'' coded 4). Psychometric properties of this instrument suggest that it is valid, with patient behaviours matching those measured[56,57,59]. Scoring is computed as the sum of the number of items with non-

zero response or as a weighted sum [e.g. the sum of the endorsed frequencies of the respective items][56].

Clinical tests of the TMJ and masticatory muscles

TMJ range of motion

Mobility testing of the TMJ denotes an essential sign of TMD, it is one of the most reliable clinical measures[39]. Grossman et al.[8] examined the preoperative variables of TMD patients with articular disc displacement without reduction that may alter the effects of arthrocentesis on joint effusion. They observed that small maximum interincisal distance influences treatment outcome. As a result, we will use the Maximal Mouth Opening (MMO) without pain as measure of TMJ range of motion. The measurements will be in millimeters and will be taken with a ruler in a neutral craniocervical position [e.g. sitting or supine]. The distance between the incisal edges of the maxillary and mandibular reference teeth, as described in the DC/TMD protocol[44], will be measured. Participants will be asked to open the mouth as wide as they can without feeling any pain, or without increasing any present pain. The tip of the ruler will be located against the incisal edge of the mandibular reference incisor, and the distance to the mesial-distal center of the edge of the maxillary central incisor will be read. The test will be repeated twice if the pain-free opening if less than 30mm[44]. Assessment of mandibular ROM in a neutral craniocervical position obtained good inter- and intra-rater reliability for MMO[60].

TMJ palpation pain:

Pain induced in joints via palpation is a useful clinical test that allows to understand if the provoked pain duplicates or replicates the patient's pain complaint by identifying potential joint

origin[44]. For this palpation, finger pressure is calibrated [1.0 kg], as described in the DC/TMD protocol[44], using a simple hand-held algometer prior to palpation examination. While the participant mandible is in a comfortable position or in a slightly protruded position, the examiner's index finger will be placed just anterior to the tragus of the ear and dorsal to the TMJ with the participant in neutral craniocervical position e.g. sitting or supine. The index finger will press while orbiting around the lateral pole in a circular fashion over the superior aspect of the condyle and then anteriorly [from the 9:00 to the 3:00 position, and then continuing fully around the condyle]. Palpation will last 5 seconds for each pressed point[44]. If a participant complains of familiar pain in at least one pressed point the point score of this test will be 1; if there is no pain at any points the point score of this test will be 0 [range 0-1: no pain =0; pain = 1]. Palpation will be performed in the left and right side. The interexaminer reliability values of TMJ palpation in TMD patients is 0.59 and the specificity values is acceptable [above 0.90][61].

Muscle palpation pain

For this assessment, finger pressure is calibrated to 1.0 kg for masseter muscles and 0.5 kg for lateral pterygoid area and temporalis tendons as described in the DC/TMD protocol[44], using a simple hand-held algometer prior to palpation examination. Pain induced in muscles via palpation is a useful clinical test that allows to understand whether the provoked pain duplicates or replicates the patient's pain complaint by identifying potential muscular origin[44]. Palpation will be performed with the participant in a neutral craniocervical position (e.g. sitting or supine), on the left and right side and will last 5 seconds for each testing point[44]. The inter-examiner reliability values of palpation in TMD patients is 0.59 and the specificity values are acceptable [above 0.90][61]. The feasibility of the lateral pterygoid muscle palpation is controversial. Some authors defined it as a feasible palpation technique[62], and others considered this muscle unaccessible[63]. Therefore, in this

study, this parameter [pain at lateral pterygoid site] will not be considered alone but in combination with pain at other muscular sites.

Lateral pterygoid area: palpation will be performed with a finger pressure calibrated at 0.5 kg (DC/TMD protocol[44]). The palpation will take place as described in FIG.1. If a participant complains of familiar pain during palpation the lateral pterygoid area will be considered as a painful site.

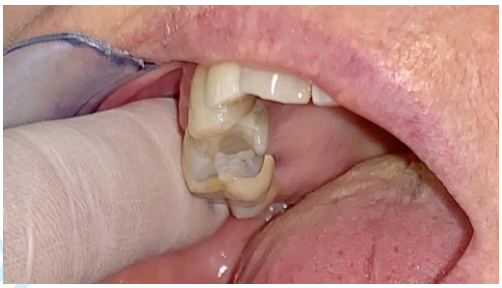


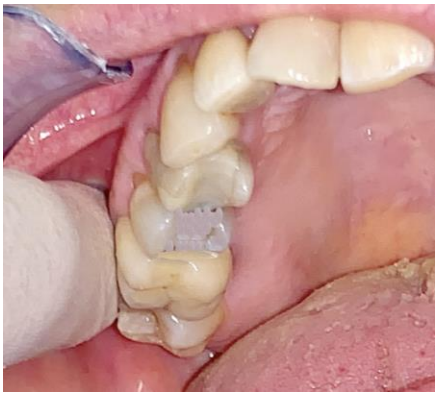
FIG. 1 Lateral pterygoid area: Finger is placed as shown. Palpate the vestibule in posterior-superior-medial direction while the mandible is omolaterally deviated.

Masseter muscle: masseter palpation consists of a sequence of three palpation sites with finger pressure calibrated to 1.0 kg (DC/TMD protocol[44]): origin zone [inferior to the bony margin of the zygomatic process], body zone [in front of ear lobe] and insertion zone [superior to the mandibular angle]. In each zone, the palpation continues until the anterior boundary of the muscle is reached[44]. If a participant complains of familiar pain in at least one pressed point, the masseter muscle will be considered as a painful site.

Temporalis tendon area: the palpation will be performed with a finger pressure calibrated to 0.5 kg (DC/TMD protocol[44]). The palpation will take place as described in FIG.2. If a participant

complains of familiar pain during the palpation the temporalis tendon area will be considered as a painful site.

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



Total score: if a participant complains of familiar pain in at least three of the six examined sites the score will be 1, otherwise it will be 0 [score range 0–1: < 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain = 1][64].

JAw-test

The JAw-test is a clinical test that aims to investigate the immediate effects of four brief intraoral manual therapy techniques on pain and on TMJ range of motion. The participant will be positioned in supine position. Before starting the test, the TMJ range of motion without pain will be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD protocol[44]. Then the participant will be asked to rate his/her pain through the Verbal Rating Scale (VRS) “at rest”, “during clenching” and “during the maximal opening of the mouth”; an average of the three pain scores will be registered. For this test, finger pressure is calibrated [1.0 kg], in the same way described in the DC/TMD protocol[44], using a simple hand-held algometer prior to

palpation examination.

Participants will be informed with the following words: "*I am going to perform four manual techniques on some muscles and joints in your jaw region. You may feel a little pain, if the pain increases and becomes too intense, let me know, I will reduce the pressure until the pain returns to acceptable levels".*

First technique: Lateral pterygoid area

This techniques will be performed on the most painful side. While one hand stabilizes the participant's head on the least painful side, the other hand will be used to apply pressure over the lateral pterygoid area as described above and in accordance with the DC/TMD protocol[44]. In this position, compression [1.0 kg] is applied for 30-60 seconds.

Second technique: Temporalis tendon area

This techniques will be performed on the most painful side. While one hand stabilizes the participant's head on the least painful side, the other hand (index finger) will be used to apply pressure over the Temporalis tendon area as described above and in accordance with the DC/TMD protocol[44]. In this position, compression [1.0 kg] is applied for 30-60 seconds.

Third technique: Mylohyoid area

The participant will be instructed to open the mouth to let the examiner's finger reach the mylohyoid area in a central position on the mylohyoid raphe. The other hand of the examiner will reach the same area using a finger through an extraoral approach. In this position a combined compression (1.0 kg) will be applied for 30-60 seconds.

Fourth technique: TMJ mobilization

An intraoral ventral and caudal anterior glide [mobilisation grades I and II] of both the TMJs will be performed for 30 seconds as described by Cleland et al.[65]

Final scores:

After the tests, the TMJ range of motion without pain will be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD protocol[44]. Then the participant will be asked to rate his/her pain using the Verbal Rating Scale (VRS) "at rest", "during clenching" and "during the maximal opening of the mouth"; an average oh this three pain scores will be registered. If a participant shows only an improvement in pain [average score VRS pre-test > average score VRS post-test] the score will be 1; if a participant shows only an improvement of TMJ mobility [MMO pre-test < MMO post-test at least 2 millimeters] the score will be 1; if a participant shows improvements in both pain and TMJ mobility, the score will be 2; if a participant shows no improvements the score will be 0 [Score range 0-2: 0 = no change; 1 = VRS improvement or MMO improvement; 2 = improvement of both].

REFERENCES

1. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in United States. *J Am Dent Assoc*. 1993;124:115-112.

2. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Dubner R, Bair E, Baraian C, Slade GD, Maixner W. Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 2011; 12(11 Suppl):T46-60.

3. Helkimo M. Studies on function and dysfunction of the masticatory system. IV. Age and sex distribution of symptoms of dysfunction of the masticatory system in Lapps in the north of Finland. *Acta Odontol Scand*. 194; 32(4):255-67.

4. Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints'. *Pain*. 1988; 32(2):173-83.

5. Plesh O, Adams SH, Gansky SA. Temporomandibular joint and muscle disorders-type pain and comorbid pains in a national US sample. *J Orofacial Pain*. 2011;25: 190-198.

6. NCHS. Summary Health Statistics Tables for the U.S. Population: National Health Interview Survey, 2014 (12/2015) [Online]. CDC/National Centre of Health and Statistics. Available: http://www.cdc.gov/nchs/nhis/SHS/tables.htm [March 10, 2019]

7. Roth RS, Geisser ME. Educational achievement and chronic pain disability: mediating role of pain-related cognitions. *Clin J Pain*. 2002; 18(5):286-96.

8. Kapos FP, Look JO, Zhang L, Hodges JS, Schiffman EL. Predictors of Long-Term Temporomandibular Disorder Pain Intensity: An 8-Year Cohort Study. *Journal of Oral & Facial Pain and Headache*. 2018; 32(2):113–122.

9. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996; 37(1):53-72.

10. Janssen MF, Birnie E, Haagsma JA. Comparing the standard EQ-5D three-level system with a five-level version. *Value Health*. 2008; 11(2):275-84.

11. Janssen MF, Pickard AS, Golicki D. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013; 22(7):1717-27.

12. Sayar K, Arikan M, Yontem T. Sleep quality in chronic pain patients. *Can J Psychiatry*. 2002; 47(9):844-8.

13. Cappelleri JC, McDermott AM, Sadosky AB, Petrie C.D, Martin S. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. *Health Qual Life Outcomes*. 2009; 17(7):54.

14. Rushton AB, Evans DW, Middlebrook N, Heneghan NR, Small C, Lord J, Patel JM, Falla D. Development of a screening tool to predict the risk of chronic pain and disability following musculoskeletal trauma: protocol for a prospective observational study in the United Kingdom. *BMJ Open*. 2018; 28;8(4):e017876.

15. Kight M, Gatchel RJ, Wesley L. Temporomandibular disorders: evidence for significant overlap with psychopathology. *Health Psychol*. 199; 18(2):177-82.

16. Dworkin SF, Von Korff MR, LeResche L. Multiple pains and psychiatric disturbance: An epidemiologic investigation. *Archives of General Psychiatry*. 1990; 47:239-44.

17. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science'. *J Pain*. 2004; 5(4):195-211.

18. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007; 133(4):581-624.

19. Mallen CD, Peat G, Thomas E. Prognostic factors for musculoskeletal pain in primary care: a systematic review. *Br J Gen Pract*. 2007; 57(541):655-61.

20. Artus M, Campbell P, Mallen CD. Generic prognostic factors for musculoskeletal pain in primary care: a systematic review. *BMJ Open*. 2017; 7(1):e012901.

21. Iani L, Lauriola M, Costantini M. A confirmatory bifactor analysis of the Hospital Anxiety and Depression Scale in an Italian community sample. *Health and quality of life outcomes*. 2014; 12:84.

22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983; 67(6):361-70.

23. Bjelland I, Dahl AA, Haug TT. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. 2002; 52(2):69-77.

24. Wang W, Chair SY, Thompson DR, Twinn SF. A Psychometric Evaluation of the Chinese Version of the Hospital Anxiety and Depression Scale in Patients with Coronary Heart Disease. *Journal of Clinical Nursing*. 2009; 18:1908-15.

25. Forssell H, Kauko T, Kotiranta U, Suvinen T. Predictors for future clinically significant pain in patients with temporomandibular disorder: A prospective cohort study. *European Journal of Pain*. 2017; 21(1):188–197.

26. Monticone M, Ferrante S, Giorgi I, Galandra C, Rocca B, Foti C. The 27-item coping strategies questionnaire-revised: confirmatory factor analysis, reliability and validity in Italian-speaking subjects with chronic pain. *Pain Res Manag*. 2014; 19(3):153-8.

27. Robinson ME, Riley JL, Myers CD, Sadler IJ, Kvaal SA, Geisser ME, Keefe FJ. The Coping Strategies Questionnaire: a large sample, item level factor analysis. *Clin J Pain*. 1997; 13(1):43-9.

28. Campbell P, Foster NF, Thomas E, Dunn KM. Prognostic Indicators of Low Back Pain in Primary Care: Five-Year Prospective Study. *J Pain*. 2013; 14(8):873–83.

29. Nicholas MK, Linton SJ, Watson PJ, Main CJ. Early identification and management of psychological risk factors ("yellow flags") in patients with low back pain: a reappraisal. *Phys Ther*. 2011; 91:737-753.

30. Vase L, Petersen GL, Riley JL, Price DD. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007'. *Pain*. 2009; 145:36-44.

31. Puentedura EJ, Cleland JA, Landers MR, Mintken PE, Louw A, Fernández-de-Las-Peñas C. Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine. *J Orthop Sports Phys Ther*. 2012; 42(7):577-92.

32. Grossman E, Poluha RL, Iwaki LCV, Santana RG, Filho LI. Predictors of arthrocentesis outcome on joint effusion in patients with disk displacement without reduction. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2018; 125(4), 382–388.

33. Clay FJ, Watson WL, Newstead SV. A systematic review of early prognostic factors for persisting pain following acute orthopedic trauma. *Pain Res Manag*. 2012; 17(1):35-44.

34. Clay FJ, Newstead SV, Watson WL. Bio-psychosocial determinants of persistent pain 6 months after non-life-threatening acute orthopaedic trauma. *J Pain*. 2010; 11(5):420-30.

35. Kamaleri Y, Natvig B, Ihlebaek CM. Change in the number of musculoskeletal pain sites: A 14-year prospective study. *Pain*. 2009; 141(1-2):25-30.

36. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health*. 1990; 13:227–236.

37. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Witter J. Core outcome measures for chronic pain clinical trials : IMMPACT recommendations. Pain. 2005; 113:9–19.

38. Velly A, Schweinhardt P, Fricton J. *Comorbid conditions: How they affect orofacial pain. In Treatment of TMDs: Bridging the Gap Between Advances in Research and Clinical Patient Management*. Greene, CS, Laskin DM, eds. (Chicago: Quintessence) pp. 91–98; 2013.

39. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF; International RDC/TMD Consortium Network,

International association for Dental Research; Orofacial Pain Special Interest Group, International Association for the Study of Pain. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. J Oral Facial Pain Headache. 2014; 28(1):6-27.

40. Macfarlane GJ. Widespread pain: is an improved classification possible?. *Journal of Rheumatology*. 1996, 23(9):1628-1632.

41. Margolis RB, et al. Test-retest reliability of the pain drawing instrument. *Pain*. 1988; 33: 49-51.

42. Ohrbach R, Fillingim RB, Mulkey F, et al. Clinical findings and pain symptoms as potential risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control study. *Journal of Pain*. 2011; 12 (11, Supplement 3):T27-T45.

43. Sanders AE, Slade GD, Bair E, Fillingim RB, Knott C, Dubner R, Greenspan JD, Maixner W, Ohrbach R. General health status and incidence of first-onset temporomandibular disorder: the OPPERA prospective cohort study. *J Pain*. 2013 Dec;14(12 Suppl):T51-62.

44. Ohrbach R, et al. Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study. Journal of Pain. 2013, 14(Supplement 2)(12):T33-T50.

45. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Gatchel RJ. The Development and Psychometric Validation of the Central Sensitization Inventory. Pain Practise. 2012; 12(4):276–285.

46. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth?. *The Clinical journal of pain*. 2013; 29:625-38.

47. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: a systematic literature review. *European Journal of Pain*. 2013; 17:299-312.

48. Desmeules J, Chabert J, Rebsamen M, Rapiti E, Piguet V, Besson M. Central pain sensitization, COMT Val158Met polymorphism, and emotional factors in fibromyalgia. *The Journal of Pain*. 2014; 15:129-35.

49. Fernández-de-Las-Peñas C, Galán-del-Río F, Fernández-Carnero J, Pesquera J, Arendt Nielsen L, Svensson P. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. *The Journal of Pain*. 2009; 10:1170-8.

50. Chiarotto A, Viti C, Sulli A, Cutolo M, Testa M, Piscitelli D. Cross-cultural adaptation and validity of the Italian version of the Central Sensitization Inventory. *Musculoskelet Sci Pract*. 2018; 37:20-28.

51. Armijo-Olivo S, Pitance L, Singh V, Neto F, Thie N, Michelotti A. Effectiveness of Manual Therapy and Therapeutic Exercise for Temporomandibular Disorders: Systematic Review and Meta-Analysis. *Physical Therapy*. 2016; 96(1): 9–25.

52. Peck CC, Goulet JP, Lobbezoo F, Schiffman EL, Alstergren P, Anderson GC, de Leeuw R, Jensen R, Michelotti A, Ohrbach R, Petersson A, List T. Expanding the taxonomy of the diagnostic criteria for temporomandibular disorders. *J Oral Rehabil*. 201; 41(1):2-23.

53. Von Korff, M. *Assessment of chronic pain in epidemiological and health services research: Empirical bases and new directions. Handbook of Pain Assessment*. D. C. Turk and R. Melzack. New York, Guilford Press: 455- 473. 2011.

54. Von Korff, M., et al. Grading the severity of chronic pain. *Pain*. 1992; 50:133-149.

55. Von Korff M, et al. *Research diagnostic criteria. Axis II: Pain-related disability and psychological status*. In: S.F. Dworkin & L. LeResche (Eds.), Research Diagnostic Criteria for Temporomandibular Disorders. Journal of Craniomandibular Disorders, Facial and Oral Pain 6: 330-334. 1992

56. Ohrbach, R., et al. Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography. *European Journal of Oral Sciences*. 2008; 116: 438-444.

57. Ohrbach R, List T, Goulet JP, Svensson P. Recommendations from the International Consensus Workshop: Convergence on an Orofacial Pain Taxonomy. Journal of Oral Rehabilitation. 2010;37:807-12.

58. Glaros AG, Marszalek JM, Williams KB. Longitudinal Multilevel Modeling of Facial Pain, Muscle Tension, and Stress. *Journal of dental research*. 2016; 95(4), 416-22.

59. Markiewicz MR, Ohrbach R, McCall WD Jr. Oral behaviors checklist: Reliability of performance in targeted waking-state behaviors. *J Orofacial Pain*. 2006; 20:306-316.

60. Beltran-Alacre H, López-de-Uralde-Villanueva I, Paris-Alemany A, Angulo-Díaz-Parreño S, La Touche R. Intra-rater and Inter-rater Reliability of Mandibular Range of Motion Measures Considering a Neutral Craniocervical Position. *Journal of physical therapy science*. 2014; 26(6), 915-20.

61. Gomes MB, Guimarães JP, Guimarães FC, Neves AC. Palpation and pressure pain threshold: reliability and validity in patients with temporomandibular disorders. *Cranio*. 2008; 26(3):202-10 .

62. Stelzenmueller W, Umstadt H, Weber D, Goenner-Oezkan V, Kopp S, Lisson J. Evidence - The intraoral palpability of the lateral pterygoid muscle - A prospective study. *Ann Anat*. 2016; 206:89-95.

63. Türp JC, Minagi S. Palpation of the lateral pterygoid region in TMD--where is the evidence?. *J Dent*. 2001; 29(7):475-83.

64. Fricton J. *Physical evaluation: the need for a standardized examination*. In: Fricton JR, ed. Temporomandibular joint and craniofacial pain: diagnosis and management. St Louis: Ishiyaku Euroamerica; 1988:46–47.

65. Cleland J, Palmer J. Effectiveness of Manual Physical Therapy, Therapeutic Exercise, and Patient Education on Bilateral Disc Displacement Without Reduction of the Temporomandibular Joint: A Single-Case Design. Journal of Orthopaedic & Sports Physical Therapy. 2004; 34(9):535–548.
.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

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
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – Pages 8-9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – Pages 7 and 9
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)
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – Pages 7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – Pages 9-11, Supplementary file
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – Page 12-13 (withdrawals)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – Page 12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – n/A

	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

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
	31b	Authorship eligibility guidelines and any intended use of professional writers – N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – N/A
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" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032113.R2
Article Type:	Protocol
Date Submitted by the Author:	11-Oct-2019
Complete List of Authors:	Asquini, Giacomo; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Edoardo Bianchi , Andrea ; Italian Stomatologic Institute Heneghan, Nicola; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rushton, Alison; niversity of Birmingham, School of Health and Population Sciences, College of Medical and Dental Sciences Borromeo, Giulia; Italian Stomatologic Institute Locatelli , Matteo; IRCCS San Raffaele Scientific Institute Falla, Deborah; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Dentistry and oral medicine
Keywords:	Temporomandibular Disorders, Temporomandibular Joint Dysfunction Syndrome, Pain, Prediction, Manual Therapy

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

Asquini G[1,2], Edoardo Bianchi A[2], Heneghan N[1], Rushton A[1], Borromeo G[2], Locatelli M[3], Falla D[1]

Affiliations

[1] Centre of Precision Rehabilitation for Spinal Pain (CPR Spine)
School of Sport, Exercise and Rehabilitation Sciences
College of Life and Environmental Sciences
University of Birmingham
Birmingham B15 2TT
United Kingdom

[2] Italian Stomatologic Institute
Craniomandibular Physiotherapy Service
Via Pace 21, 20122 Milan
Italy

[3] IRCCS San Raffaele Scientific Institute
Via Olgettina Milano 60,
20132 Milano,
Italy

Corresponding author:

Deborah Falla

Centre of Precision Rehabilitation for Spinal Pain (CPR Spine)

School of Sport, Exercise and Rehabilitation Sciences

College of Life and Environmental Sciences

University of Birmingham

Birmingham, UK

E-mail: d.falla@bham.ac.uk

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 (≥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 management[1-2]. 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 period[3]. 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 opening[5] but many patients also complain of neck and back pain or pain at other sites[6].

Physical therapy is one of the most common conservative interventions for the management of TMD[7] and given that the aetiology may be unclear[8], several therapeutic approaches have been described[9]. One approach is manual therapy applied to the craniomandibular structures with evidence suggesting a significant reduction in pain with manual therapy treatment[10], although responses are highly variable[11]. 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[12-13]. 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

patients with TMD pain[14]. They analysed several potential predictors of persistent pain at one-year follow-up including demographic, pain-related and psychosocial variables. It was concluded that patients with TMD who have had numerous previous healthcare visits, complained of high-intensity pain at other body sites and had a greater number of disability days, were at greater risk of having pain one year after the initial assessment. Nevertheless, this study did not examine predictors of pain reduction related to a therapeutic intervention which could be useful to inform clinical practice. Kapos et al. investigated the association of long-term pain intensity with baseline health-related quality of life and jaw functional limitation in patients with TMD[15]. Findings suggested that baseline health-related quality of life is inversely proportional with pain intensity at an eight-year follow-up regardless of the type of treatment that they received (e.g. surgery, drugs, physical therapy or unconventional therapy). After adjusting for the type of treatments received, by clustering the participants into three groups (medical/conventional management, alternative medicine, and surgical intervention), each predictor analysed (demographic, pain-related and health-related quality of life) maintained similar statistical significance. Notwithstanding, the group classified as "medical/ conventional management" included participants receiving diverse treatments ranging from physical therapy, pharmacology (Acetaminophen, Antidepressants, Anti-inflammatories) to the application of a mouth appliance (e.g. Michigan splint). This previous work can facilitate clinicians to identify patients who are more challenging to treat by identifying clinical features associated with persistent pain in the long term regardless of the type of interventions applied. However, currently no study has examined predictive factors associated with pain reduction following manual therapy interventions in patients with TMD.

The aim of this study is to identify predictors associated with pain reduction in patients with TMD following manual therapy applied to craniomandibular structures by analysing a combination of: (1) demographical variables, (2) general health variables, (3)

psychosocial features, (4) TMD characteristics, and (5) clinical tests of the temporomandibular joint and masticatory muscles. The knowledge gained from this study will facilitate clinical decision-making for manual therapists managing patients with TMD by providing clinicians with key factors to evaluate, to determine whether or not the patient is likely to have a clinically relevant reduction in their pain immediately following four weekly applications of manual therapy.

METHODS AND ANALYSIS

Source of data

A prospective observational study will recruit a cohort of patients referred to the Italian Stomatologic Institute with a TMD diagnosis according to the Axis I of the Diagnostic Criteria for TMDs (DC/TMD)[16]. This protocol is written according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement[17] in which recommendations are provided about prediction model development and validation. Ethical clearance will be obtained from the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and the University of Birmingham Ethics Committee, and the study will be conducted in accordance with the Declaration of Helsinki.

Patient reported and physical assessment data will be collected at baseline prior to commencing treatment. Outcome will be collected at the end of the fourth session of craniomandibular manual therapy (at one month). This timeline has been selected based on previous studies investigating 1) the effects of manual therapy on pain[18-19]; and 2) work confirming the effectiveness of manual therapy for TMD patients[20] and is believed to be reasonable for the purposes of this study.

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 months[21]; (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 disorders[12-13], 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

protocol[22]. Subsequently, in accordance with the inclusion/exclusion criteria, he will explain the study to the potential participant and provide the patient information sheet. Participants will then give their written informed consent prior to inclusion in the study. Afterwards, the participant will be referred to see a physiotherapist [independent assessor, >5 years' experience in managing patients with TMD] for the baseline assessments (summarised in Table 1) and then treatment will commence within the same week. After the last session (i.e. one month from baseline), the participants will be assessed again by the assessing physiotherapist to measure outcome. Participant flow through the study is outlined in Figure 1.

[FIGURE 1]

Treatment

Participants will receive four sessions of manual therapy applied to craniomandibular structures over 4 weeks[23-25]. Two physiotherapists, each with >5 years' experience in manual therapy / TMD will perform the treatments. They will not be involved in participant recruitment, assessment or the collection of the outcome measure. Manual therapy techniques will be based on the clinical examination, and will be selected at the discretion of the treating physiotherapist according to their clinical reasoning of the individual case. Overall, the application of manual therapy aims to decrease pain by treating masticatory muscle trigger points, muscle tightness, and restricted temporomandibular joint movements. Several techniques will be considered including: (i) ventral and caudal anterior glide temporomandibular joint mobilization[26]; (ii) soft tissue interventions for the management of trigger points in masticatory muscles[27]; (iii) myofascial induction therapy [functional restoration of the fascial system] applied to craniomandibular structures[28].

The structures targeted in the treatment sessions will be the temporomandibular joint, temporal muscles, masseter muscles, medial and lateral pterygoid muscles and suprahyoid muscles, applied at the discretion of the physiotherapist based on the patient's individual presentation. During the treatment sessions, the treating physiotherapists will provide explanations about the patient's condition and answer any participant questions by promoting general advice. The treatment sessions will last from 20 to 30 minutes duration. No other treatment (e.g. oral appliance) will be performed for the management of their TMD. If during the course of the four-week intervention, a patient seeks treatment for an acute episode of pain at another site (e.g. neck pain, low back pain, shoulder pain) they will be withdrawn from the study.

Outcome

The outcome being predicted by the prediction model is pain intensity since patients with TMD typically report pain to be their primary problem[5], manual therapy is largely known to be effective principally for pain modulation[29] and change in pain intensity has most commonly been the primary outcome of choice in several other studies of patients with TMD[30-33].

Pain intensity will be calculated by averaging the ratings of current pain, average pain in the past week, 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 "worst pain imaginable" at the right extremity[34]. The VAS is a reliable and valid scale to assess pain intensity as an outcome measure in intervention studies[35]. Based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations about TMD reviewed by Haythornthwaite[36], a reduction of at least 30% of the VAS score for pain intensity is considered clinically significant. Consequently, a

reduction in the total VAS score [≥ 30%] will be defined as a good outcome. The outcome measure will be evaluated by the same independent assessor to minimise detection bias[37].

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 disorders[39-40]. It is responsive to clinically significant change over time[41]. 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 pain[42-44].

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 disorders[45-46]. 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 predictors[56]. This method will guarantee an adequate sample size (at least 10 cases per candidate predictor) to power the final regression analysis[57-58]. 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 model[59]. 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 ≥30%][36]. Exploratory factor analysis will be applied to

analyse factor loading of candidate predictors (summary scores) on good outcome at one month. This process will reduce candidate predictors (supported by the cohort sample of 90) to enter into the final model.

The statistical model has been designed a priori. To investigate the impact of each predictive factor on good outcome, a logistic multivariable regression model will be performed. For each candidate predictor, the mean differences or the odds ratio with their 95% confidence intervals will be calculated. A multiple imputation analysis[60] will be applied to manage possible missing data. The multivariable analysis will initially consider all candidate predictors. In the case of a high correlation between candidate predictors, a reduced multivariate analysis will be considered.

DISCUSSION

There is a need to identify predictors for pain reduction in patients with TMD following specific treatments in order to inform clinical decision-making. Several therapies are described for patients with TMD such as the use of oral appliances, different types of physical therapy modalities, pharmacology or temporomandibular joint arthrocentesis yet the amount of pain relief that different people receive from each intervention is variable[7,10]. As shown by Forssell et al.[14] and Kapos et al.[15], many patients continue to experience pain following such interventions. Investigating factors associated with pain relief to such treatments can facilitate clinical assessment and treatment selection.

Physical therapy is one of the most common conservative interventions to treat TMD[7]. Among different physical therapy modalities, manual therapy can provide symptom and functional improvements[10] including pain relief[11,31]. Knowledge of predictive factors associated with good outcome to a specific intervention such as manual therapy applied to

craniomandibular structures will facilitate clinical decision making. Ultimately, such knowledge will lead to improved clinical and cost effectiveness of rehabilitation approaches.

Quality assurance

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

Patient and Public Involvement

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

Ethics and Dissemination

The research protocol has been submitted to the Ethics Committee of the "Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico" and subsequently will be submitted to the University of Birmingham Ethics Committee for approval. Researchers will inform all participants on the characteristics of the research and will obtain written consent. Participants will be informed that they are free to withdraw from the study at any time, without needing to provide reason. Any concerns for a participant by the study team will be fed back to the primary investigator (GA). Baseline characteristics of withdrawn participants will be compared to those of retained participants to assess for any differences. In the event of any unlikely adverse events, this will be immediately reported by the principal investigator to the ethics committee.

The results of this study will submitted for publication in a peer review journal and presented at conferences.

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.

REFERENCES

1. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in United States. *J Am Dent Assoc*. 1993;124:115-112.

2. NIDCR. Facial Pain (2014). *National Institute of Health* [Online]. http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain/ [Accessed Dec 28 2018]

3. Adèrn B, Minston A, Nohlert E, Tegelberg Å. Self-reportance of temporomandibular disorders in adult patients attending general dental practice in Sweden from 2011 to 2013. *Acta Odontol Scand*. 2018;76(7):530-534.

4. Montero J, Llodra JC, Bravo M. Prevalence of the Signs and Symptoms of Temporomandibular Disorders Among Spanish Adults and Seniors According to Five National Surveys Performed Between 1993 and 2015. *J Oral Facial Pain Headache.* 2018;32(4):349-357.

5. De Leeuw R, Klasser GD. *Orofacial pain guidelines for assessment, diagnosis, and management*. 5th ed. Hanover park, II: Quintessence publishing; 2013.

6. Plesh O, Adams SH, Gansky SA. Temporomandibular joint and muscle disorders-type pain and comorbid pains in a national US sample. *J Orofacial Pain*. 2011;25: 190-198.

7. Calixtre LB, Grüninger BL, Haik MN, Alburquerque-Sendín F, Oliveira AB. Effects of cervical mobilization and exercise on pain, movement and function in subjects with temporomandibular disorders: a single group pre-post test. *Journal of Applied Oral Science*. 2016;24(3):188–197.

8. Slade GD, Bair E, Greenspan JD, Dubner R, Fillingim RB, Diatchenko L, Maixner W, Knott C, Ohrbach R. Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: the OPPERA prospective cohort study. *J Pain*. 2013;14:T20-T32

9. Coskun Benlidayi I, Salimov F, Kurkcu M, Guzel R. Kinesio-Taping for temporomandibular Disorders: Single-blind, ramdomized, controlled trial of effectiveness. *J Back Musculoskelet Rehabil*. 2016; 29:373-380.

10. Armijo-Olivo S, Pitance L, Singh V, Neto F, Thie N, Michelotti A. Effectiveness of Manual Therapy and Therapeutic Exercise for Temporomandibular Disorders: Systematic Review and Meta-Analysis. *Physical Therapy*. 2016; 96(1): 9–25.

11. Kalamir A, Graham PL, Vitiello AL, Bonello R, Pollard H. Intra-oral myofascial therapy versus education and self-care in the treatment of chronic, myogenous temporomandibular disorder: A randomised, clinical trial. *Chiropractic and Manual Therapies*. 2013; 21(1):17.

12. Cleland JA, Childs JD, Fritz JM, Whitman JM, Eberhart SL. Development of a Clinical Prediction Rule for Guiding Treatment of a Subgroup of Patients With Neck Pain: Use of Thoracic Spine Manipulation, Exercise, and Patient Education. *Physical Therapy*. 2007; 87(1): 9–23.

13. Flynn T, Fritz J, Whitman J, Wainner R, Magel J, Rendeiro D, Butler B, Garber M, Allison S. A clinical prediction rule for classifying patients with low back pain who demonstrate short-term improvement with spinal manipulation. *Spine*; 2002; 27(24):2835-2843.

14. Forssell H, Kauko T, Kotiranta U, Suvinen T. Predictors for future clinically significant pain in patients with temporomandibular disorder: A prospective cohort study. *European Journal of Pain*. 2017; 21(1):188–197.

15. Kapos FP, Look JO, Zhang L, Hodges JS, Schiffman EL. Predictors of Long-Term Temporomandibular Disorder Pain Intensity: An 8-Year Cohort Study. *Journal of Oral & Facial Pain and Headache*. 2018; 32(2):113–122.

16. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF; International RDC/TMD Consortium Network, International association for Dental Research; Orofacial Pain Special Interest Group, International Association for the Study of Pain. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. *J Oral Facial Pain Headache*. 2014; 28(1):6-27.

17. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement'. *BMC Medicine*. 2015; 350:g7594

18. Bishop MD, Torres-Cueco R, Gay CW, Lluch-Girbés E, Beneciuk JM, Bialosky JE. What effect can manual therapy have on a patient's pain experience?. *Pain management*. 2015; 5(6):455-64.

19. Vigotsky AD, Bruhns RP. Corrigendum to "The Role of Descending Modulation in Manual Therapy and Its Analgesic Implications: A Narrative Review". *Pain Res Treat*. 2017; 1535473.

20. Calixtre LB, Moreira RFC, Franchini GH, Alburquerque-Sendín F, Oliveira A.B. Manual therapy for the management of pain and limited range of motion in subjects with signs and symptoms of temporomandibular disorder: A systematic review of randomised controlled trials. *Journal of Oral Rehabilitation*. 2015; 42(11):847–861.

21. Wahlund K, Nilsson IM, Larsson B. Treating temporomandibular disorders in adolescents: a randomized, controlled, sequential comparison of relaxation training and occlusal appliance therapy. *J Oral Facial Pain Headache*. 2015; 29(1):41-50.

22. Ohrbach R, editor. Diagnostic Criteria for Temporomandibular Disorders: Assessment Instruments. Version 15May2016. [Criteri diagnostici per i disordini temporomandibolari: Strumenti valutativi (DC/TMD) Version 17Jan2017] Michelotti A., Segù M., Wrenn C., Rongo R. Trans. www.rdc-tmdinternational.org Accessed on <31 Mar 2019>.

23. Crockett DJ, Foreman ME, Alden L, Blasberg B. A comparison of treatment modes in the management of myofascial pain dysfunction syndrome. *Biofeedback and self-regulation*. 1986; 11(4):279-291.

24. Guarda-Nardini L, Stecco A, Stecco C, Masiero S, Manfredini D. Myofascial Pain of the Jaw Muscles: Comparison of Short-Term Effectiveness of Botulinum Toxin Injections and Fascial Manipulation Technique. *CRANIO*. 2012; 30(2):95–102.

25. Nascimento M, Vasconcelos BC, Porto GG, Ferdinanda G, Nogueira CM, Raimundo RD. Physical therapy and anesthetic blockage for treating temporomandibular disorders: a clinical trial. *Med Oral Patol Oral Cir Bucal*. 2013; 18(1):81-5.

26. Cleland J, Palmer J. Effectiveness of Manual Physical Therapy, Therapeutic Exercise, and Patient Education on Bilateral Disc Displacement Without Reduction of the Temporomandibular Joint: A Single-Case Design. *Journal of Orthopaedic & Sports Physical Therapy*. 2004; 34(9):535–548.

27. Miernik M, Wieckiewicz M, Paradowska A. Massage therapy in myofascial TMD pain management. *Adv Clin Exp Med*. 2012; 21(5):681-5.

28. Fernandez-de-las-Pena C, Mesa-Jimenez J. *Temporomandibular Disorders: manual Therapy, exercise and needling*. United Kingdom: Handspring Publishing; 2018

29. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther*. 2009; 14:531–538.

30. Kalamir A, Pollard H, Vitiello A, Bonello R. Intra-oral myofascial therapy for chronic myogenous temporomandibular disorders: a randomized, controlled pilot study. *Journal of Manual & Manipulative Therapy*, 2010; 18(3),:39–146.

31. Gomes CA, Politti F, Andrade DV, de Sousa DF, Herpich CM, Dibai-Filho AV, Gonzalez TO, Biasotto-Gonzalez DA. Effects of Massage Therapy and Occlusal Splint Therapy on Mandibular Range of Motion in Individuals With Temporomandibular Disorder: A Randomized Clinical Trial. *Journal of Manipulative and Physiological Therapeutics*. 2014; 37(3):164–169.

32. Tuncer AB, Ergun N, Tuncer AH, Karahan S. Effectiveness of manual therapy and home physical therapy in patients with temporomandibular disorders: A randomized controlled trial. *Journal of Bodywork and Movement Therapies*. 2013; 17(3):302–308.

33. von Piekartz H, Hall T. Orofacial manual therapy improves cervical movement impairment associated with headache and features of temporomandibular dysfunction: A randomized controlled trial. *Manual Therapy*. 2013; 18(4):345-50.

34. Haefeli M, Elfering A. 'Pain assessment: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. *European spine journal*. 2005; 15:S17–S24.

35. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Witter J. Core outcome measures for chronic pain clinical trials : IMMPACT recommendations. *Pain*. 2005; 113:9–19.

36. Haythornthwaite JA.IMMPACT recommendations for clinical trials: Opportunities for the RDC/TMD. *Journal of Oral Rehabilitation*. 2010; 37(10):799–806.

37. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011 Oct 18;343:d5928.

38. Stratford P, Gill C, Westaway M, Binkley J. Assessing disability and change on individual patients: a report of a patient specific measure. *Physiotherapy Canada*. 1995; 47:258-263.

39. Horn KK, Jennings S, Richardson G, Van Vliet D, Hefford C, Abbott JH. The patient-specific functional scale: psychometrics, clinimetrics, and application as a clinical outcome measure. *Journal of orthopaedic & sports physical therapy*. 2012; 42(1):30-D17.

40. Abbott JH, Schmitt J. Minimum important differences for the patient-specific functional scale, 4 region-specific outcome measures, and the numeric pain rating scale. *Journal of Orthopaedic & Sports Physical Therapy*. 2014; 44(8):560-4.

41. Maughan EF, Lewis JS. Outcome measures in chronic low back pain. *European Spine Journal*. 2010; 19(9):1484-94.

42. Hefford C, Abbott JH, Arnold R, Baxter GD. The patient-specific functional scale: validity, reliability, and responsiveness in patients with upper extremity musculoskeletal problems. *Journal of orthopaedic & sports physical therapy*. 2012; 42(2):56-65.

43. Westawa MD, Stratford PW, Binkley JM. The patient-specific functional scale: validation of its use in persons with neck dysfunction. *Journal of Orthopaedic & Sports Physical Therapy*. 1998; 27(5):331-8.

44. Chatman AB, Hyams SP, Neel JM, Binkley JM, Stratford PW, Schomberg A, Stabler M. The Patient-Specific Functional Scale: measurement properties in patients with knee dysfunction. *Physical therapy*. 1997; 77(8):820-9.

45. Bair E, Gaynor S, Slade GD, Ohrbach R, Fillingim RB, Greenspan JD, Dubner R, Smith SB, Diatchenko L, Maixner W. Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study. *Pain*. 2016; 157(6):1266-78.

46. Clark J, Nijs J, Yeowell G, Goodwin PC. What Are the Predictors of Altered Central Pain Modulation in Chronic Musculoskeletal Pain Populations? A Systematic Review. *Pain Physician*. 2017; 20(6):487-500.

47. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996; 37(1):53-72.

48. Cappelleri JC, McDermott AM, Sadosky AB, Petrie C.D, Martin S. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. *Health Qual Life Outcomes*. 2009; 17(7):54.

49. Monticone M, Ferrante S, Giorgi I, Galandra C, Rocca B, Foti C. The 27-item coping strategies questionnaire-revised: confirmatory factor analysis, reliability and validity in Italian-speaking subjects with chronic pain. *Pain Res Manag*. 2014; 19(3):153-8.

50. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983; 67(6):361-70.

51. Puentedura EJ, Cleland JA, Landers MR, Mintken PE, Louw A, Fernández-de-Las-Peñas C. Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine. *J Orthop Sports Phys Ther*. 2012; 42(7):577-92.

52. Davis CE, Stockstill JW, Stanley WD, Wu Q. Pain-related worry in patients with chronic orofacial pain. *J Am Dent Assoc*.2014; 145(7):722-30.

53. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Gatchel RJ. The Development and Psychometric Validation of the Central Sensitization Inventory. *Pain Practise*. 2012; 12(4):276–285.

54. Peck CC, Goulet JP, Lobbezoo F, Schiffman EL, Alstergren P, Anderson GC, de Leeuw R, Jensen R, Michelotti A, Ohrbach R, Petersson A, List T. Expanding the taxonomy of the diagnostic criteria for temporomandibular disorders. *J Oral Rehabil*. 201; 41(1):2-23.

55. Ohrbach R, Michael RM, Willard DM. Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography. *European Journal of Oral Sciences*. 2008; 116:438-444.

56. Fabrigar LR, Wegener DT, MacCallum RC, Strahan EJ. Evaluating the use of exploratory factor analysis in psychological research. *Psychological Methods*. 199; 4:272–299.

57. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996; 49(12):1373-9.

58. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007; 165(6):710-8.

59. Shmueli G. To explain or to predict?. *Statistical Science*. 2010; 25(3):289-310.

60. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009; 338:b2393.

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

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests Statement

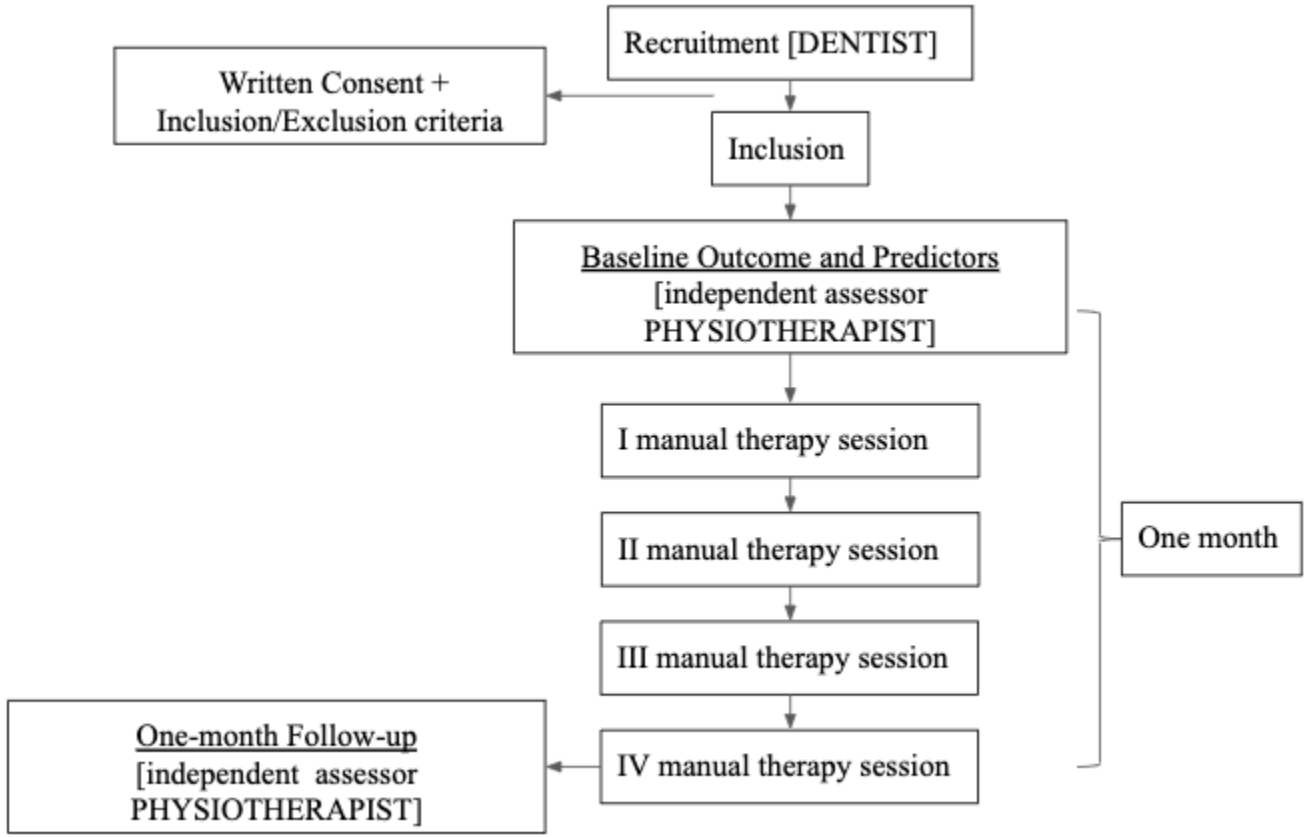
The authors have no competing interests to report.

Data sharing statement

No additional data are available.

FIGURE LEGEND

Figure 1: Participant flow through the study


Recruitment [DENTIST]
Written Consent +
Inclusion/Exclusion criteria
Inclusion
Baseline Outcome and Predictors
[independent assessor
PHYSIOTHERAPIST]
I manual therapy session
II manual therapy session
III manual therapy session
IV manual therapy session
One month
One-month Follow-up
[independent assessor
PHYSIOTHERAPIST]

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

Supplementary file 1 - Candidate predictors

Demographical variables

Participants' demographic variables [age, gender, education] will be collected at baseline from open hospital records and patient interview.

Age

Age is a significant factor in TMD incidence and prevalence. Lipton et al. found different age-specific prevalence for face/jaw pain: 6.5% in aged 18-34, 5.0% in 35-54 years old, 4.0% in 55-74 years old and 3.9% in people > 74 year old, showing a prevalence reduction across the lifetime[1]. By contrast, data from the OPPERA study[2] showed a 40% increased risk for TMD among individuals aged 25-34 years and a 50% increased risk for TMD among individuals aged 35-50 years.

Gender

Women are 1.5-2 times more likely to develop TMD than men[3-5]. Currently, there is no study examining the extent of recovery from TMD in men and women. Nevertheless, gender is a significant factor to be considered.

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 pain[7]. 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 state[9]. 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-3L[10]. 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

It is known that chronic pain patients may suffer from poor sleep quality, even if it is difficult to draw a causal relation[12]. Consequently, sleep quality will be assessed as a candidate predictor because of its possible role among other factors in the transition from acute to chronic pain. Sleep quality will be evaluated through an 11-point Numerical Rating Scale [NRS], where 0 is 'the best possible sleep' and 10 is 'the worst possible sleep'. This scale owns moderate psychometric properties in fibromyalgia patients to assess current sleep quality [over the previous 24 hour period] with a symptom diary[13]. We will use the 0-10 NRS to assess average sleep quality, related to the preceding 6-months at baseline[14], although no psychometric properties have previously been reported for this recall period.

Psychosocial features

Psychosocial factors are known to influence TMD onset and chronicity[15]. Psychological distress is significantly linked to a greater severity and persistence of TMD pain[16]. Moreover, depression and high levels of stress are significantly more common in people with chronic TMD[17-18]. In addition, there is agreement about the predictive strength of psychosocial factors in primary care among different musculoskeletal pain conditions[19-20].

<u>The Hospital Anxiety and Depression Scales [HADS]</u>

The Italian version of the HAD[21] will be utilised to investigate depression, anxiety and manifestations of somatic symptoms[22]. 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 depression[23].

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

consistency of HADS-A [0.68-0.93] and HADS-D [0.67-0.90][23]. In a coronary heart disease sample, the standard measurement of error was 1.37 for anxiety and 1.44 for depression; the minimal detectable change was 3.80 for anxiety and 3.99 for depression[24]. The HADS has excellent concurrent validity in comparison to other depression/anxiety scales[23].

Coping Strategies Questionnaire 27 [CSQ-27]

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

Treatment expectation

A positive treatment expectation is considered as a treatment moderator because of its influence on treatment outcome[29]. A positive treatment expectation is predictive of good outcome

because the expectation of benefit (placebo) has a robust effect on pain[30]. In the current study we will investigate treatment expectation following the same protocol used by Puentedura et al[31]. Participants will be asked whether they "Completely disagree", "Somewhat disagree", "Neutral", "Somewhat agree", "Completely agree" with the following statement: "I believe that *manual techniques applied to my jaw* will significantly help to improve my pain". If the participant chooses "completely disagree," "somewhat disagree," or "neutral," there is not a positive expectation that manual therapy applied to craniomandibular structures will significantly help their temporomandibular disorder. If the participant chooses "somewhat agree" or "completely agree," there is a positive expectation that manual therapy applied to craniomandibular structures will significantly help their temporomandibular disorder.

TMD characteristics

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

Pain Duration

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

Pain intensity

As shown in a previous study[32], 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 extremity[36]. 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 intensity[37].

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 pain[38]. 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.imagemeasurement.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 pain[46], neck pain[47], fibromyalgia[48], and TMD[49]. 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 conditions[45]. The CSI has significant test-retest reliability and internal consistency in subjects with and without pain[45]. 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 TMD[51]. 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/TMD[39]. 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

A greater number of disability days increases the risk of having clinically significant pain one year after an initial assessment[25]. In this study we will use the Italian version of Graded Chronic Pain Scale [GCPS] version 2.0 [www.rdc-tmdinternational.org][53] following the DC/TMD protocol recommendations[39,42,44]. This scale has good internal consistency in temporomandibular pain [Cronbach's alpha of 0.84][54]. The GCPS measures the facial pain severity over the preceding 6-months by unifying pain intensity and pain-related disability. The characteristic pain intensity score [range: 0-100] is the mean of three pain intensity measurements: 'at the present time' and 'worst pain' and the 'average' pain over the preceding 6 months. The disability status is measured with a 0-6 point score derived from a combination of the number of disability days and the disability level [range: 0-100; limitation given by pain in performing activities of daily living]. Based on these scores, the participant's chronic pain and disability status can be classified into one of the five ordinal categories of chronic pain severity[55].

Oral Behaviour

People with abnormal oral behaviours with scores above 25 in the Oral Behaviours Checklist [OBC] are 75% more likely to develop TMD than individuals with a score below 17[42,44,56]. Parafunctional habits could play a significant role in the development and the persistence of TMD pain[58]. In this study we will use the Italian version of the RDC/TMD questionnaire Axis II Oral Behaviours Checklist [www.rdc-tmdinternational.org][42,56] following the DC/TMD protocol recommendations[39,56]. The OBC measures the self-reported frequency over the preceding month of each of 21 activities involving the jaw such as clenching the teeth or bracing the jaw (five ordinal response options, ranging from ''none of the time,'' coded 0, to ''all of the time,'' coded 4). Psychometric properties of this instrument suggest that it is valid, with patient behaviours matching those measured[56,57,59]. Scoring is computed as the sum of the number of items with non-

zero response or as a weighted sum [e.g. the sum of the endorsed frequencies of the respective items][56].

Clinical tests of the TMJ and masticatory muscles

TMJ range of motion

Mobility testing of the TMJ denotes an essential sign of TMD, it is one of the most reliable clinical measures[39]. Grossman et al.[8] examined the preoperative variables of TMD patients with articular disc displacement without reduction that may alter the effects of arthrocentesis on joint effusion. They observed that small maximum interincisal distance influences treatment outcome. As a result, we will use the Maximal Mouth Opening (MMO) without pain as measure of TMJ range of motion. The measurements will be in millimeters and will be taken with a ruler in a neutral craniocervical position [e.g. sitting or supine]. The distance between the incisal edges of the maxillary and mandibular reference teeth, as described in the DC/TMD protocol[44], will be measured. Participants will be asked to open the mouth as wide as they can without feeling any pain, or without increasing any present pain. The tip of the ruler will be located against the incisal edge of the mandibular reference incisor, and the distance to the mesial-distal center of the edge of the maxillary central incisor will be read. The test will be repeated twice if the pain-free opening if less than 30mm[44]. Assessment of mandibular ROM in a neutral craniocervical position obtained good inter- and intra-rater reliability for MMO[60].

TMJ palpation pain:

Pain induced in joints via palpation is a useful clinical test that allows to understand if the provoked pain duplicates or replicates the patient's pain complaint by identifying potential joint

origin[44]. For this palpation, finger pressure is calibrated [1.0 kg], as described in the DC/TMD protocol[44], using a simple hand-held algometer prior to palpation examination. While the participant mandible is in a comfortable position or in a slightly protruded position, the examiner's index finger will be placed just anterior to the tragus of the ear and dorsal to the TMJ with the participant in neutral craniocervical position e.g. sitting or supine. The index finger will press while orbiting around the lateral pole in a circular fashion over the superior aspect of the condyle and then anteriorly [from the 9:00 to the 3:00 position, and then continuing fully around the condyle]. Palpation will last 5 seconds for each pressed point[44]. If a participant complains of familiar pain in at least one pressed point the point score of this test will be 1; if there is no pain at any points the point score of this test will be 0 [range 0-1: no pain =0; pain = 1]. Palpation will be performed in the left and right side. The interexaminer reliability values of TMJ palpation in TMD patients is 0.59 and the specificity values is acceptable [above 0.90][61].

Muscle palpation pain

For this assessment, finger pressure is calibrated to 1.0 kg for masseter muscles and 0.5 kg for lateral pterygoid area and temporalis tendons as described in the DC/TMD protocol[44], using a simple hand-held algometer prior to palpation examination. Pain induced in muscles via palpation is a useful clinical test that allows to understand whether the provoked pain duplicates or replicates the patient's pain complaint by identifying potential muscular origin[44]. Palpation will be performed with the participant in a neutral craniocervical position (e.g. sitting or supine), on the left and right side and will last 5 seconds for each testing point[44]. The inter-examiner reliability values of palpation in TMD patients is 0.59 and the specificity values are acceptable [above 0.90][61]. The feasibility of the lateral pterygoid muscle palpation is controversial. Some authors defined it as a feasible palpation technique[62], and others considered this muscle unaccessible[63]. Therefore, in this

study, this parameter [pain at lateral pterygoid site] will not be considered alone but in combination with pain at other muscular sites.

Lateral pterygoid area: palpation will be performed with a finger pressure calibrated at 0.5 kg (DC/TMD protocol[44]). The palpation will take place as described in FIG.1. If a participant complains of familiar pain during palpation the lateral pterygoid area will be considered as a painful site.

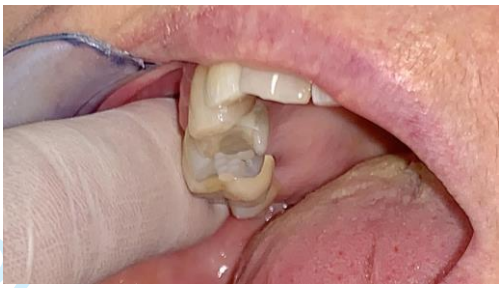


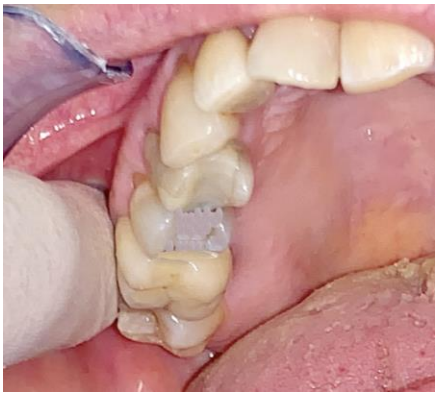
FIG. 1 Lateral pterygoid area: Finger is placed as shown. Palpate the vestibule in posterior-superior-medial direction while the mandible is omolaterally deviated.

Masseter muscle: masseter palpation consists of a sequence of three palpation sites with finger pressure calibrated to 1.0 kg (DC/TMD protocol[44]): origin zone [inferior to the bony margin of the zygomatic process], body zone [in front of ear lobe] and insertion zone [superior to the mandibular angle]. In each zone, the palpation continues until the anterior boundary of the muscle is reached[44]. If a participant complains of familiar pain in at least one pressed point, the masseter muscle will be considered as a painful site.

Temporalis tendon area: the palpation will be performed with a finger pressure calibrated to 0.5 kg (DC/TMD protocol[44]). The palpation will take place as described in FIG.2. If a participant

complains of familiar pain during the palpation the temporalis tendon area will be considered as a painful site.

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



Total score: if a participant complains of familiar pain in at least three of the six examined sites the score will be 1, otherwise it will be 0 [score range 0–1: < 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain = 1][64].

JAw-test

The JAw-test is a clinical test that aims to investigate the immediate effects of four brief intraoral manual therapy techniques on pain and on TMJ range of motion. The participant will be positioned in supine position. Before starting the test, the TMJ range of motion without pain will be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD protocol[44]. Then the participant will be asked to rate his/her pain through the Verbal Rating Scale (VRS) “at rest”, “during clenching” and “during the maximal opening of the mouth”; an average of the three pain scores will be registered. For this test, finger pressure is calibrated [1.0 kg], in the same way described in the DC/TMD protocol[44], using a simple hand-held algometer prior to

palpation examination.

Participants will be informed with the following words: "*I am going to perform four manual techniques on some muscles and joints in your jaw region. You may feel a little pain, if the pain increases and becomes too intense, let me know, I will reduce the pressure until the pain returns to acceptable levels".*

First technique: Lateral pterygoid area

This techniques will be performed on the most painful side. While one hand stabilizes the participant's head on the least painful side, the other hand will be used to apply pressure over the lateral pterygoid area as described above and in accordance with the DC/TMD protocol[44]. In this position, compression [1.0 kg] is applied for 30-60 seconds.

Second technique: Temporalis tendon area

This techniques will be performed on the most painful side. While one hand stabilizes the participant's head on the least painful side, the other hand (index finger) will be used to apply pressure over the Temporalis tendon area as described above and in accordance with the DC/TMD protocol[44]. In this position, compression [1.0 kg] is applied for 30-60 seconds.

Third technique: Mylohyoid area

The participant will be instructed to open the mouth to let the examiner's finger reach the mylohyoid area in a central position on the mylohyoid raphe. The other hand of the examiner will reach the same area using a finger through an extraoral approach. In this position a combined compression (1.0 kg) will be applied for 30-60 seconds.

Fourth technique: TMJ mobilization

An intraoral ventral and caudal anterior glide [mobilisation grades I and II] of both the TMJs will be performed for 30 seconds as described by Cleland et al.[65]

Final scores:

After the tests, the TMJ range of motion without pain will be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD protocol[44]. Then the participant will be asked to rate his/her pain using the Verbal Rating Scale (VRS) "at rest", "during clenching" and "during the maximal opening of the mouth"; an average oh this three pain scores will be registered. If a participant shows only an improvement in pain [average score VRS pre-test > average score VRS post-test] the score will be 1; if a participant shows only an improvement of TMJ mobility [MMO pre-test < MMO post-test at least 2 millimeters] the score will be 1; if a participant shows improvements in both pain and TMJ mobility, the score will be 2; if a participant shows no improvements the score will be 0 [Score range 0-2: 0 = no change; 1 = VRS improvement or MMO improvement; 2 = improvement of both].

REFERENCES

1. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in United States. *J Am Dent Assoc*. 1993;124:115-112.

2. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Dubner R, Bair E, Baraian C, Slade GD, Maixner W. Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 2011; 12(11 Suppl):T46-60.

3. Helkimo M. Studies on function and dysfunction of the masticatory system. IV. Age and sex distribution of symptoms of dysfunction of the masticatory system in Lapps in the north of Finland. *Acta Odontol Scand*. 194; 32(4):255-67.

4. Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints'. *Pain*. 1988; 32(2):173-83.

5. Plesh O, Adams SH, Gansky SA. Temporomandibular joint and muscle disorders-type pain and comorbid pains in a national US sample. *J Orofacial Pain*. 2011;25: 190-198.

6. NCHS. Summary Health Statistics Tables for the U.S. Population: National Health Interview Survey, 2014 (12/2015) [Online]. CDC/National Centre of Health and Statistics. Available: http://www.cdc.gov/nchs/nhis/SHS/tables.htm [March 10, 2019]

7. Roth RS, Geisser ME. Educational achievement and chronic pain disability: mediating role of pain-related cognitions. *Clin J Pain*. 2002; 18(5):286-96.

8. Kapos FP, Look JO, Zhang L, Hodges JS, Schiffman EL. Predictors of Long-Term Temporomandibular Disorder Pain Intensity: An 8-Year Cohort Study. *Journal of Oral & Facial Pain and Headache*. 2018; 32(2):113–122.

9. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996; 37(1):53-72.

10. Janssen MF, Birnie E, Haagsma JA. Comparing the standard EQ-5D three-level system with a five-level version. *Value Health*. 2008; 11(2):275-84.

11. Janssen MF, Pickard AS, Golicki D. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013; 22(7):1717-27.

12. Sayar K, Arikan M, Yontem T. Sleep quality in chronic pain patients. *Can J Psychiatry*. 2002; 47(9):844-8.

13. Cappelleri JC, McDermott AM, Sadosky AB, Petrie C.D, Martin S. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. *Health Qual Life Outcomes*. 2009; 17(7):54.

14. Rushton AB, Evans DW, Middlebrook N, Heneghan NR, Small C, Lord J, Patel JM, Falla D. Development of a screening tool to predict the risk of chronic pain and disability following musculoskeletal trauma: protocol for a prospective observational study in the United Kingdom. *BMJ Open*. 2018; 28;8(4):e017876.

15. Kight M, Gatchel RJ, Wesley L. Temporomandibular disorders: evidence for significant overlap with psychopathology. *Health Psychol*. 199; 18(2):177-82.

16. Dworkin SF, Von Korff MR, LeResche L. Multiple pains and psychiatric disturbance: An epidemiologic investigation. *Archives of General Psychiatry*. 1990; 47:239-44.

17. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science'. *J Pain*. 2004; 5(4):195-211.

18. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007; 133(4):581-624.

19. Mallen CD, Peat G, Thomas E. Prognostic factors for musculoskeletal pain in primary care: a systematic review. *Br J Gen Pract*. 2007; 57(541):655-61.

20. Artus M, Campbell P, Mallen CD. Generic prognostic factors for musculoskeletal pain in primary care: a systematic review. *BMJ Open*. 2017; 7(1):e012901.

21. Iani L, Lauriola M, Costantini M. A confirmatory bifactor analysis of the Hospital Anxiety and Depression Scale in an Italian community sample. *Health and quality of life outcomes*. 2014; 12:84.

22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983; 67(6):361-70.

23. Bjelland I, Dahl AA, Haug TT. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. 2002; 52(2):69-77.

24. Wang W, Chair SY, Thompson DR, Twinn SF. A Psychometric Evaluation of the Chinese Version of the Hospital Anxiety and Depression Scale in Patients with Coronary Heart Disease. *Journal of Clinical Nursing*. 2009; 18:1908-15.

25. Forssell H, Kauko T, Kotiranta U, Suvinen T. Predictors for future clinically significant pain in patients with temporomandibular disorder: A prospective cohort study. *European Journal of Pain*. 2017; 21(1):188–197.

26. Monticone M, Ferrante S, Giorgi I, Galandra C, Rocca B, Foti C. The 27-item coping strategies questionnaire-revised: confirmatory factor analysis, reliability and validity in Italian-speaking subjects with chronic pain. *Pain Res Manag*. 2014; 19(3):153-8.

27. Robinson ME, Riley JL, Myers CD, Sadler IJ, Kvaal SA, Geisser ME, Keefe FJ. The Coping Strategies Questionnaire: a large sample, item level factor analysis. *Clin J Pain*. 1997; 13(1):43-9.

28. Campbell P, Foster NF, Thomas E, Dunn KM. Prognostic Indicators of Low Back Pain in Primary Care: Five-Year Prospective Study. *J Pain*. 2013; 14(8):873–83.

29. Nicholas MK, Linton SJ, Watson PJ, Main CJ. Early identification and management of psychological risk factors ("yellow flags") in patients with low back pain: a reappraisal. *Phys Ther*. 2011; 91:737-753.

30. Vase L, Petersen GL, Riley JL, Price DD. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007'. *Pain*. 2009; 145:36-44.

31. Puentedura EJ, Cleland JA, Landers MR, Mintken PE, Louw A, Fernández-de-Las-Peñas C. Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine. *J Orthop Sports Phys Ther*. 2012; 42(7):577-92.

32. Grossman E, Poluha RL, Iwaki LCV, Santana RG, Filho LI. Predictors of arthrocentesis outcome on joint effusion in patients with disk displacement without reduction. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2018; 125(4), 382–388.

33. Clay FJ, Watson WL, Newstead SV. A systematic review of early prognostic factors for persisting pain following acute orthopedic trauma. *Pain Res Manag*. 2012; 17(1):35-44.

34. Clay FJ, Newstead SV, Watson WL. Bio-psychosocial determinants of persistent pain 6 months after non-life-threatening acute orthopaedic trauma. *J Pain*. 2010; 11(5):420-30.

35. Kamaleri Y, Natvig B, Ihlebaek CM. Change in the number of musculoskeletal pain sites: A 14-year prospective study. *Pain*. 2009; 141(1-2):25-30.

36. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health*. 1990; 13:227–236.

37. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Witter J. Core outcome measures for chronic pain clinical trials : IMMPACT recommendations. Pain. 2005; 113:9–19.

38. Velly A, Schweinhardt P, Fricton J. *Comorbid conditions: How they affect orofacial pain. In Treatment of TMDs: Bridging the Gap Between Advances in Research and Clinical Patient Management*. Greene, CS, Laskin DM, eds. (Chicago: Quintessence) pp. 91–98; 2013.

39. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF; International RDC/TMD Consortium Network,

International association for Dental Research; Orofacial Pain Special Interest Group, International Association for the Study of Pain. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. J Oral Facial Pain Headache. 2014; 28(1):6-27.

40. Macfarlane GJ. Widespread pain: is an improved classification possible?. *Journal of Rheumatology*. 1996, 23(9):1628-1632.

41. Margolis RB, et al. Test-retest reliability of the pain drawing instrument. *Pain*. 1988; 33: 49-51.

42. Ohrbach R, Fillingim RB, Mulkey F, et al. Clinical findings and pain symptoms as potential risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control study. *Journal of Pain*. 2011; 12 (11, Supplement 3):T27-T45.

43. Sanders AE, Slade GD, Bair E, Fillingim RB, Knott C, Dubner R, Greenspan JD, Maixner W, Ohrbach R. General health status and incidence of first-onset temporomandibular disorder: the OPPERA prospective cohort study. *J Pain*. 2013 Dec;14(12 Suppl):T51-62.

44. Ohrbach R, et al. Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study. Journal of Pain. 2013, 14(Supplement 2)(12):T33-T50.

45. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Gatchel RJ. The Development and Psychometric Validation of the Central Sensitization Inventory. Pain Practise. 2012; 12(4):276–285.

46. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth?. *The Clinical journal of pain*. 2013; 29:625-38.

47. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: a systematic literature review. *European Journal of Pain*. 2013; 17:299-312.

48. Desmeules J, Chabert J, Rebsamen M, Rapiti E, Piguet V, Besson M. Central pain sensitization, COMT Val158Met polymorphism, and emotional factors in fibromyalgia. *The Journal of Pain*. 2014; 15:129-35.

49. Fernández-de-Las-Peñas C, Galán-del-Río F, Fernández-Carnero J, Pesquera J, Arendt Nielsen L, Svensson P. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. *The Journal of Pain*. 2009; 10:1170-8.

50. Chiarotto A, Viti C, Sulli A, Cutolo M, Testa M, Piscitelli D. Cross-cultural adaptation and validity of the Italian version of the Central Sensitization Inventory. *Musculoskelet Sci Pract*. 2018; 37:20-28.

51. Armijo-Olivo S, Pitance L, Singh V, Neto F, Thie N, Michelotti A. Effectiveness of Manual Therapy and Therapeutic Exercise for Temporomandibular Disorders: Systematic Review and Meta-Analysis. *Physical Therapy*. 2016; 96(1): 9–25.

52. Peck CC, Goulet JP, Lobbezoo F, Schiffman EL, Alstergren P, Anderson GC, de Leeuw R, Jensen R, Michelotti A, Ohrbach R, Petersson A, List T. Expanding the taxonomy of the diagnostic criteria for temporomandibular disorders. *J Oral Rehabil*. 201; 41(1):2-23.

53. Von Korff, M. *Assessment of chronic pain in epidemiological and health services research: Empirical bases and new directions. Handbook of Pain Assessment*. D. C. Turk and R. Melzack. New York, Guilford Press: 455- 473. 2011.

54. Von Korff, M., et al. Grading the severity of chronic pain. *Pain*. 1992; 50:133-149.

55. Von Korff M, et al. *Research diagnostic criteria. Axis II: Pain-related disability and psychological status*. In: S.F. Dworkin & L. LeResche (Eds.), Research Diagnostic Criteria for Temporomandibular Disorders. Journal of Craniomandibular Disorders, Facial and Oral Pain 6: 330-334. 1992

56. Ohrbach, R., et al. Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography. *European Journal of Oral Sciences*. 2008; 116: 438-444.

57. Ohrbach R, List T, Goulet JP, Svensson P. Recommendations from the International Consensus Workshop: Convergence on an Orofacial Pain Taxonomy. Journal of Oral Rehabilitation. 2010;37:807-12.

58. Glaros AG, Marszalek JM, Williams KB. Longitudinal Multilevel Modeling of Facial Pain, Muscle Tension, and Stress. *Journal of dental research*. 2016; 95(4), 416-22.

59. Markiewicz MR, Ohrbach R, McCall WD Jr. Oral behaviors checklist: Reliability of performance in targeted waking-state behaviors. *J Orofacial Pain*. 2006; 20:306-316.

60. Beltran-Alacre H, López-de-Uralde-Villanueva I, Paris-Alemany A, Angulo-Díaz-Parreño S, La Touche R. Intra-rater and Inter-rater Reliability of Mandibular Range of Motion Measures Considering a Neutral Craniocervical Position. *Journal of physical therapy science*. 2014; 26(6), 915-20.

61. Gomes MB, Guimarães JP, Guimarães FC, Neves AC. Palpation and pressure pain threshold: reliability and validity in patients with temporomandibular disorders. *Cranio*. 2008; 26(3):202-10 .

62. Stelzenmueller W, Umstadt H, Weber D, Goenner-Oezkan V, Kopp S, Lisson J. Evidence - The intraoral palpability of the lateral pterygoid muscle - A prospective study. *Ann Anat*. 2016; 206:89-95.

63. Türp JC, Minagi S. Palpation of the lateral pterygoid region in TMD--where is the evidence?. *J Dent*. 2001; 29(7):475-83.

64. Fricton J. *Physical evaluation: the need for a standardized examination*. In: Fricton JR, ed. Temporomandibular joint and craniofacial pain: diagnosis and management. St Louis: Ishiyaku Euroamerica; 1988:46–47.

65. Cleland J, Palmer J. Effectiveness of Manual Physical Therapy, Therapeutic Exercise, and Patient Education on Bilateral Disc Displacement Without Reduction of the Temporomandibular Joint: A Single-Case Design. Journal of Orthopaedic & Sports Physical Therapy. 2004; 34(9):535–548.
.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

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
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – Pages 8-9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – Pages 7 and 9
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)
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – Pages 7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – Pages 9-11, Supplementary file
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – Page 12-13 (withdrawals)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – Page 12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – n/A

	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

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
	31b	Authorship eligibility guidelines and any intended use of professional writers – N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – N/A
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" license.