

# BMJ Open Prognostic factor analysis in patients with temporomandibular disorders after reversible treatment: study protocol for a prospective cohort study in China

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## ABSTRACT

**Introduction** Temporomandibular disorders (TMDs) are complex multifactorial disorders. Reversible treatment has been suggested for the initial management of TMD; however, comparable therapeutic effects of different reversible intervention modalities remain controversial. Various biopsychosocial factors, which may be putative prognostic factors that influence the response to reversible treatment for TMD, have been reported to increase the risk of developing first-onset TMD. However, there is a paucity of research that aims to identify prognostic factors associated with the clinical outcomes of reversible treatment in people with TMD. The objective of this prospective cohort study is to identify prognostic factors that are associated with clinical outcomes of reversible treatment in patients with TMD and to analyse the risk factors that influence the development of chronic TMD.

**Methods and analysis** We plan to recruit 834 patients with TMD who meet the inclusion criteria. Once informed consent is obtained, baseline data, including anamnestic data, physical assessments and self-report questionnaires, will be collected from participants at their first clinic visit; subsequently, they will receive 1–4 weeks of reversible treatment. The primary treatment outcome measures will be a change in the anterior maximum mouth opening, worsening of TMD pain scores assessed using a visual analogue scale (VAS) and a reduction in characteristic pain intensity. A good outcome will be defined as an anterior maximal opening  $\geq 35$  mm and at least a 30% reduction in VAS scores 3 months after baseline. The association between candidate prognostic factors and clinical outcomes of reversible TMD treatment will be analysed.

**Ethics and dissemination** The protocol has been approved by the Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, based on the guidelines outlined in the Declaration of Helsinki (SH9H-2019-T316-4). The results of this study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement. The authors intend to publish the results in a peer-reviewed journal.

**Trial registration number** ChiCTR2000033328.

## INTRODUCTION

Temporomandibular disorders (TMDs) are painful musculoskeletal conditions that are

## Strengths and limitations of this study

- A battery of assessments of demographic characteristics and biopsychosocial factors will be conducted to evaluate the associations between those variables and the prognosis of patients with temporomandibular disorder (TMD).
- Putative risk factors that are associated with the development of chronic TMD will be explored so that the heterogeneity of patient characteristics and psychosocial factors may be considered during treatment planning.
- Anterior maximal opening of the mouth and TMD pain will be included as outcome measures, providing evidence that will be useful for appropriately managing Chinese patients with TMD.
- As putative prognostic factors are selected based on current knowledge of risk factors associated with the development of TMD, some possible biopsychosocial factors may not be assessed in this study.
- Considering that the ethnic background of TMD patients may be associated with psychological variables, the influence of these psychological factors on the prognosis of patients with TMD may also differ based on ethnicity.

associated with pain and dysfunction of the temporomandibular joint (TMJ) and masticatory muscles.<sup>1 2</sup> Approximately 5%–12% of adults experience TMD.<sup>2</sup> The most common TMD symptoms and signs are facial pain, impaired jaw mobility, deviations of mandibular movements and TMJ sounds, affecting the patient's well-being and quality of life.<sup>3</sup>

TMD is a complex disorder associated with multiple physical, psychological, genetic, sensory processing and environmental domains, and clinical characteristics have been identified to predict the increased risk of developing TMD.<sup>4</sup> Previous reports from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study have concluded that numerous biopsychosocial factors increase the risk of developing

first-onset TMD.<sup>4–6</sup> The OPPERA study findings demonstrated that a complex pattern of considerable changes in psychological functioning (ie, perceived stress, depression and somatisation),<sup>7</sup> pain sensitivity,<sup>8</sup> clinical jaw function,<sup>9</sup> sleep disturbance and other health conditions<sup>10</sup> is associated with changes in the TMD status.

Various interventions have been suggested for TMD; although to date, the most effective treatment programme remains unclear.<sup>11–14</sup> These interventions are grouped into three categories based on the level of invasiveness, including reversible (eg, education, self-management, splint therapy and physiotherapy), minimally invasive (eg, arthrocentesis) and surgical (eg, arthroscopic and open joint surgeries) interventions.<sup>11</sup> A similar pain-reducing effect of physiotherapy and splint therapy has been confirmed in patients with myofascial TMD pain.<sup>14</sup> Diraçoğlu *et al*<sup>13</sup> concluded that neither reversible methods nor arthrocentesis was beneficial in the early treatment of TMD. A previous randomised controlled trial found no difference between medical management, non-surgical rehabilitation, arthroscopic surgery and arthroplasty in terms of TMJ pain and mandibular mobility at a 60-month follow-up.<sup>12</sup> The comparable therapeutic effects of different intervention modalities suggest that the least expensive, least invasive and simplest interventions should be employed for the initial management of TMD.<sup>11</sup>

Although promising outcomes have been reported with reversible treatment, the results remain controversial.<sup>15</sup> One prospective cohort study followed 40 TMD patients for 2.5 years and found that 43% of the patients were free of symptoms, 33% of the patients had decreased symptoms and 25% showed no improvement or required further treatment.<sup>15</sup> Similarly, nearly 50% of patients who received reversible treatment reported no pain 5 years later, although 14% of patients continued to report significant pain.<sup>16</sup> Little is known about the clinical characteristics of these TMD patients who experience a poor prognosis following reversible treatment. These findings suggest that prognostic information is critical when predicting the impact of reversible interventions in a population with TMD. However, there is a paucity of research that aims to identify prognostic factors associated with the clinical outcomes of reversible treatment in people with TMD.<sup>17–19</sup> Previous studies have concluded that numerous biopsychosocial factors increase the risk of developing first-onset TMD; therefore, we speculated that these factors may have a theoretical association with prognosis in individuals with TMD. Moreover, the TMD status changes substantially over time, and acute TMD becomes chronic in 25% of patients, as the course of TMD progression can be highly variable.<sup>20</sup> Long-term follow-up studies are needed to investigate the prognostic factors that influence the response to reversible treatment and the risk factors that are associated with the development of chronic TMD.

The aims of this prospective cohort study are: (1) to identify prognostic factors that are associated with clinical

outcomes of reversible treatment in patients with TMD; and (2) to analyse risk factors that influence the development of chronic TMD during a 1-year follow-up period. Based on current knowledge of risk factors for the development of TMD that have been reported in epidemiological studies, putative prognostic factors, including demographic data, data from self-report questionnaires and measures of physical function will be collected and analysed.

## Specific aims

### Aim 1

To determine whether demographic characteristics and biopsychosocial factors are associated with the prognosis of reversible treatment for TMD.

### Aim 2

To determine the risk factors associated with chronic TMD.

## TRIAL DESIGN AND METHODS

This clinical-based, prospective, cohort study will be conducted at Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. This protocol has been designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement and Prognosis Research Strategy (PROGRESS) guidelines.<sup>21</sup> The results of this study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>22</sup>

## Participants

We will recruit 834 patients with TMD presenting to the rehabilitation department. Consecutive eligible patients will receive 1–4 weeks of reversible treatment and will be followed up for 12 months after baseline measurements. The reversible treatment programme has been reproduced from a previous systematic review on patients with TMD.<sup>23</sup> The 1-year follow-up has been preregistered before patient enrolment. Study recruitment will commence in December 2020 and will be completed by December 2021.

The participants must meet the following inclusion criteria:

1. Patients aged 20–45 years.
2. Patients fulfilling the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).<sup>24</sup>
3. Patients with myofascial pain or reducible or non-reducible disc displacement.
4. Patients should have one of the following symptoms: (A): visual analogue scale (VAS) score for orofacial pain  $\geq 4$ ; (B): maximal mouth opening  $< 35$  mm.
5. Understanding of the survey and ability to independently complete the questionnaires.
6. Patients must volunteer to participate in the study and sign the consent form.

7. Patients receiving at least one type of reversible treatment (eg, education, self-management, medication, therapeutic exercise, manual therapy and occlusal splint therapy).

The participants will be excluded if they meet one of the following conditions at baseline:

1. History of traumatic facial injury or surgery.
2. Malignant disease, active rheumatic disease, haemorrhagic disease, heart disease or heart failure.
3. Pregnant or lactating women or women who plan to be pregnant within the next year.

Drop-out criteria: participants will have the right to drop out of the study at any time. Participants who meet one of the following conditions will be removed from the study:

1. The researcher believes that removal from the study will benefit the patient.
2. Failure to adhere to the follow-up time schedule or refusal to respond to the required questionnaires.

### Recruitment

Patients will be recruited from the rehabilitation department of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. We will recruit eligible patients at their first clinic visit. Prior to study initiation, training will be delivered to the clinical examiners working at the physiotherapy clinic to inform them of the study and how to screen patients for eligibility. LX will serve as the reference

examiner throughout the study. In a separate training session, each study examiner will conduct more than 10 blinded, replicated examinations of non-study volunteers. Data from the blinded, replicate examinations will be analysed for interexaminer reliability computed using the kappa statistic. Providers will have copies of the screening form to screen potential patients according to the inclusion and exclusion criteria. At the first outpatient visit, a potential patient will be informed about the study. All study participants will be required to provide written informed consent at the time of recruitment.

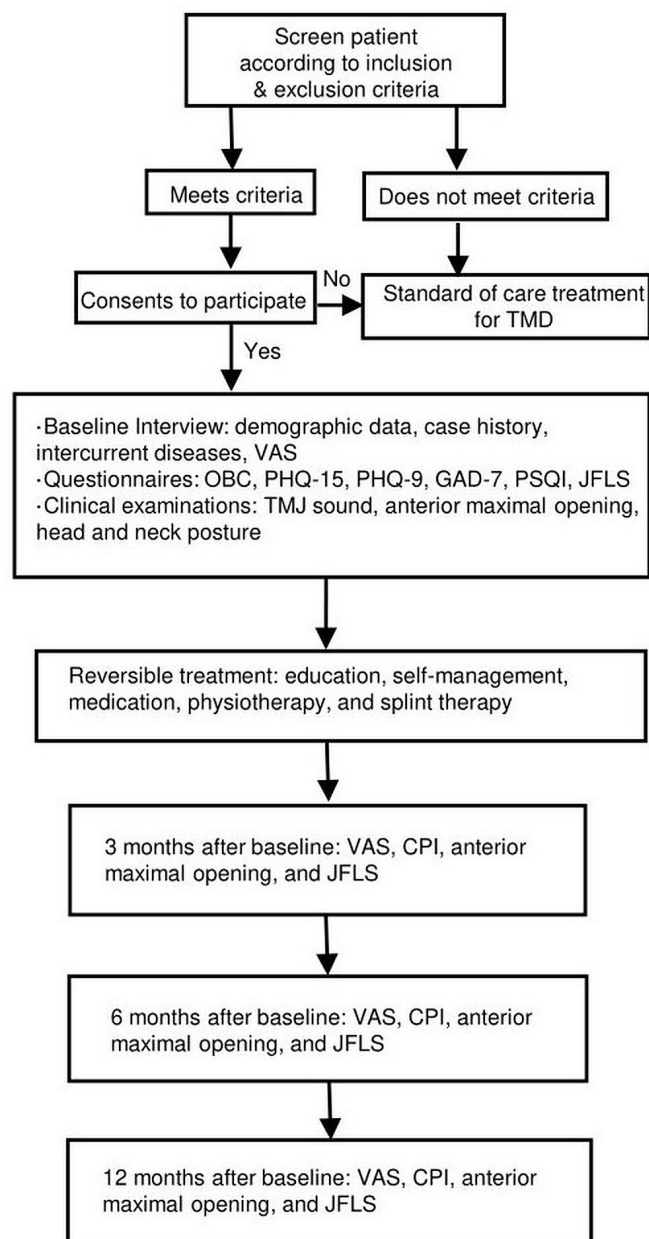
### Candidate prognostic factors

Owing to the lack of consensus on the prognostic factors that influence the response to reversible treatment for TMD, demographic data, physical measurements, data from self-report questionnaires and information about the type of treatment modality will be collected. Putative factors have been selected based on current knowledge of risk factors for the development of TMD from epidemiological studies that may have a theoretical association with prognosis in individuals with TMD, as confirmed by the biopsychosocial model of developing TMD. These selected factors are feasible to measure in clinical settings. The candidate prognostic factors are summarised in [table 1](#). All data collection will be standardised using clinical report forms and protocols.

**Table 1** Summary of measures that will be collected

Domain/candidate predictor	Baseline	Month 3	Month 6	Month 12
Fill out by clinicians				
Inclusion or exclusion standard table	√			
Sign informed notice	√			
Demographic data and case history	√			
Intercurrent diseases	√			
Anterior maximal opening	√	√	√	√
Head and neck posture	√			
Adverse events	√	√	√	√
Clinical routine inspection	√			
CPI		√	√	√
Filled out by subjects				
VAS score	√	√	√	√
OBC	√			
PHQ-15	√			
PHQ-9	√			
GAD-7	√			
PSQI	√			
JFLS	√	√	√	√

CPI, characteristic pain intensity; GAD, Generalized Anxiety Scale; JFLS, Jaw Functional Limitation Scale; OBC, Oral Behaviours Checklist; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; VAS, visual analogue scale.



**Figure 1** Participants recruitment and flow of the study. CPI, characteristic pain intensity; GAD, generalised anxiety disorder; JFLS, Jaw Functional Limitation Scale; OBC, Oral Behaviours Checklist; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; TMD, temporomandibular disorders; VAS, visual analogue scale; TMJ, temporomandibular joint.

### Data collection

Baseline data, including demographic data, data from self-report questionnaires and physical assessments, will be collected by a trained assessor at the first clinic visit. Patients will receive 1–4 weeks of reversible treatment within 2 weeks following recruitment, and the treatment modalities that patients receive will be recorded. Patients will be contacted by the same assessor by telephone 3, 6 and 12 months after baseline measurements

to complete the physical examination and functional questionnaires (figure 1).

### Baseline interview, self-report questionnaires and physical examination

During the first clinic visit, the researcher will collect each patient's demographic data (eg, sex, age distribution, educational attainment and marital status), case histories, intercurrent diseases (eg, pain related to the neck and TMJ region, and general musculoskeletal pain elsewhere) and use of medication. Anamnestic data will be collected at baseline, including the nature, duration and intensity of the pain. The intensity of the present facial pain, including masticatory muscle pain and TMJ pain at rest and during movements of the mandible according to the DC/TMD criteria, will be assessed with the VAS. The VAS scale is a measurement instrument that quantifies an attitude or characteristic that ranges across a continuum of values and cannot be directly measured.<sup>25</sup> Operationally, it is usually depicted using a horizontal line, 100 mm in length, with word descriptors at each end. The patient marks the point on the line that represents their current feelings. The VAS score, measured in millimetres, is determined as the distance from the left end to the point that the patient marks.

Patients will be asked to complete self-report questionnaires and will follow the procedure shown in table 1. Oral behaviours will be assessed at baseline using the Oral Behaviours Checklist, which is a self-report questionnaire comprising 21 items used to quantify the frequency of oral behaviours and has been evaluated as part of a larger study of the diagnostic validity and reliability of techniques for diagnosing TMD.<sup>26</sup>

The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for common mental disorders. The PHQ-15 assessed 15 somatic symptoms from the PHQ, and the PHQ-9 comprises nine items to establish a depressive disorder diagnosis, in addition to grading depressive symptom severity.<sup>27</sup> Generalised anxiety disorder (GAD) is a common mental disorder among TMD patients, and a seven-item anxiety scale (GAD-7) is a self-report scale to determine probable cases of GAD, with good reliability and procedural validity.<sup>28</sup>

The Pittsburgh Sleep Quality Index provides a valid, standardised, clinically useful measure of a variety of sleep disturbances that may affect sleep quality.<sup>29</sup>

The Jaw Functional Limitation Scale (JFLS) comprises 20 items used to assess limitations of jaw function in patients with TMD.<sup>30</sup>

Finally, a functional examination of the masticatory system and diagnosis of patients according to the DC/TMD criteria<sup>24</sup> will be conducted by the same clinician. Clinical stomatognathic assessments of TMD include the range of motion of the mandible, TMJ sounds and a patient's head and neck posture.<sup>31</sup> The range of motion of the mandible will be measured with a Vernier calliper.<sup>25</sup> When performing measurement of the anterior maximal opening, the examiner will ask the patient to place the

mandible in a comfortable position. The patient will be asked to open the mouth as far as possible without assistance. The edge of the millimetre ruler will be placed at the incisal edge of the maxillary central incisor for maximal vertical orientation to the labio-incisal edge of the opposing mandibular incisor. This measurement will be considered the interincisal opening. If subjects open their mouth less than 30 mm, the process will be repeated to ensure understanding. If the second opening is still less than 30 mm, the measurement will be recorded as the interincisal opening. To measure the vertical incisal overlap, the patient will be asked to perform the action of biting to bring the teeth together. The line where the incisal edge of the same previously measured maxillary central incisor overlaps the mandibular incisor will be marked with a pen. The distance from the mandibular incisal edge to the marked line will be recorded as the vertical incisal overlap. The anterior maximal opening will be considered as the sum of the interincisal opening and the vertical incisal overlap.<sup>32</sup>

The objective method of assessing head and neck posture will be to measure the craniocervical (CV) angle and the cranial rotation angle.<sup>33</sup> The CV angle will be defined as the angle between the horizontal plane (the line perpendicular to true vertical axis) and the line extending from the tragus of the ear to the C7 spinous process.<sup>34</sup> The cranial rotation angle will be formed by a line connecting the lateral canthus and the tragus with a horizontal line.<sup>34</sup> Measurement of the cervical angle will be performed using a protractor. The digitisation procedure has been proven to be highly reliable.<sup>33</sup> Sagittal plane imaging of the upper body of each patient will be conducted using a digital camera in a habitual relaxed, seated position. The patient will be asked to assume a comfortable habitual sitting position with the eyes focused toward the front, and the height of the chair will be 45 cm. Red markers will be placed over the tragus and C7 spinous process by the same examiner. To ensure consistency in the images, the distance between the camera and the patient will be 1.5 m, and the camera will be adjusted to remain aligned with the patient's shoulder.

### Interventions

Patients included in the study will be invited to attend a study session at the physiotherapy clinic. At this session, patients will receive a standardised reversible treatment programme within 2 weeks of recruitment and will be followed up for a period of 12 months after baseline. According to the recommendations from the current systematic reviews and meta-analyses, the least invasive, simplest and reversible interventions are considered as first-line therapy options for TMD. An experienced physiotherapist will design a reversible treatment programme according to each patient's clinical symptoms, characteristics and willingness. The programme will include education, self-management, medication, therapeutic exercise, manual therapy and occlusal splint therapy, as previously reported.<sup>23</sup> Patients will be informed of the reasoning

behind the treatment plan and provided detailed information about it.

For patients who meet the inclusion criteria but refuse to participate in the study, the standard of care treatment will be given. To promote patient retention, the researcher will inform the potential patient that although they can withdraw at any time, dropping out without a reason reduces the ability to answer the research question and, therefore, weakens the study. Patients will be advised to carry on with their usual daily routines, and any interventions received during reversible therapy sessions will be recorded for a descriptive analysis. The details of the treatment (eg, time, number, duration and modality) and the number of and reasons for dropouts will be documented and reported, as well as any adverse events during the study. Participants will be monitored during the 1–4 week programme and the 12-month follow-up period. Data from patients receiving monotherapy or adjuvant therapy will be analysed separately.

### Outcomes

The primary treatment outcome measures will be changes in the anterior maximal opening, worsening of TMD pain assessed using the VAS and changes in pain characteristics. A previous study concluded that the greatest improvement occurs between 3 and 4 months after baseline<sup>35</sup>; therefore, 3 months was chosen as the treatment outcome evaluation time point in this study. An anterior maximal opening of  $\geq 35$  mm and a reduction in VAS scores of at least 30% 3 months after baseline will be defined as good clinical outcomes.<sup>17</sup> Additional outcome measures will include changes in the frequency of TMD pain (recurrent, persistent and one-time experience), JFLS scores and the diagnosis of chronic TMD. The patients will be asked to report discomfort and complications associated with the reversible treatment and how often they perform the treatment. Additionally, all outcome measures will be evaluated 6 and 12 months after baseline measurements and will be assessed using predictive modelling.

### Data management

All data will be entered into the research folder, and a researcher will transfer them into the master data spreadsheet. Privacy of patient data will be maintained for all data handling procedures (collection transfer, storage and processing). The accuracy of the data will be guaranteed through a secondary review by study coauthors. Data recorded from each participant will be anonymised using research numbers and will be accessible only by members of this research team. A spreadsheet will be stored on a portable drive, and the research folders will be locked in a cabinet.

### Trial organisation and monitoring

The research team will consist of the authors listed in this article, in addition to administrative staff at the physiotherapy clinic who will assist with the entire process of

the study and data entry. The primary investigator will manage the study flow and perform inspections of enrolment, treatment and procedures throughout the entire study. Other investigators will monitor data collection and facilitate the maintenance of data integrity through periodic evaluations during the data collection phase.

### Data analysis

Numbers of individuals will be recorded, including those who are potentially eligible, confirmed eligible, recruited into the study, receiving reversible treatment and completing follow-up. Numbers related to withdrawals and loss to follow-up will be reported, along with reasons for removal from the study. Descriptive analyses of patients at baseline will include demographic, self-report questionnaire and physical assessment data.

All analyses will be performed using Statistical Package for the Social Sciences (SPSS) software (V.25.0). The Kolmogorov-Smirnov test will be performed to assess whether the data are normally distributed ( $p > 0.05$ ), considering that both parametric and non-parametric tests will be used in the data analyses. Linear regression, unpaired t-tests,  $\chi^2$  tests and logistic regression will be used depending on the analysis to be performed. A multiple linear regression analysis will be conducted to develop a linear model to determine the associations between candidate prognostic factors and the response to reversible treatment in patients with TMD, with anterior maximal opening and TMD pain as continuous dependent variables. For assessing risk factors for the development of chronic TMD, univariate associations between categorical variables (treatment, sex, etc) and the diagnosis of chronic TMD according to the DC/TMD criteria will be evaluated using  $\chi^2$  tests. Continuous variables (age, height, etc) and the diagnosis of chronic TMD according to the DC/TMD criteria will be evaluated using Student's unpaired t-tests with a Bonferroni correction. Multivariate analyses will be performed using binary logistic regression with forced entry of all independent variables. All analyses will be two tailed, with a threshold for statistical significance of  $p < 0.05$ .

### Sample size calculation

This prospective cohort study was designed with a target sample size of 834 enrolled patients with TMD to investigate the association between 20 candidate prognostic factors and the clinical outcome of reversible treatment in patients with TMD over the 1-year follow-up period, assuming 20% loss to follow-up. The researchers will ensure that there are at least 10 participants per prognostic factor to conduct an adequately powered linear regression analysis.<sup>36</sup> In a previous study, 70% of TMD patients who received reversible treatment reported good outcomes.<sup>12</sup> Therefore, a sample size of 834 participants will be adequate to power a linear regression analysis of 20 candidate prognostic factors.

### Management of missing data

For each variable of interest, the number of patients with missing data will be reported. Any potential bias due to

loss to follow-up will be assessed and compared using baseline data of patients who withdraw or are lost to follow-up.<sup>37</sup> Multiple imputation will be used to deal with missing outcome data, if necessary.<sup>38</sup> Participants will be excluded from the predictive model and subsequent analyses if they request to withdraw from the study following recruitment.<sup>37</sup>

### Patient and public involvement

No patients were involved with the design or will be involved in data collection, analysis or publication of the study.

## DISCUSSION

This will be the first protocol to describe methods and analysis for identifying prognostic factors associated with clinical outcomes of reversible treatment in individuals with TMD. In particular, self-report measures combined with physical examinations will be incorporated to predict poor outcomes of reversible treatments in individuals with TMD. The candidate prognostic factors have been selected based on current knowledge of risk factors for developing first-onset TMD and their possible utilisation in clinical practice. The knowledge gained through this study will provide a better understanding of how these prognostic factors can be used to improve clinical outcomes, including whether reversible treatment is useful in the clinical management of TMD patients.

This study will be conducted in accordance with the SPIRIT statement and PROGRESS framework.<sup>21 37</sup> The results of this study will provide new insights into who is likely to benefit from reversible treatment versus who is likely to develop chronic TMD. Between 57% and 71% of patients seeking treatment for acute TMD continue to report significant pain 6 months later.<sup>9 39</sup> Therefore, the evaluation of prognoses will be valuable for treatment planning for patients with TMD. In clinical practice, the heterogeneity of patient characteristics and psychosocial factors may be considered in treatment planning.

Despite the novelty of this trial, this study has some limitations. First, the candidate prognostic factors have been selected based on reported risk factors for developing first-onset TMD; however, some possible prognostic factors may be ignored. In future studies, we may include more candidate prognostic factors. Second, since the reversible treatment is a combined treatment, we cannot ascertain the effects of medication or manual therapy alone; however, we will explore the prognosis associated with each treatment component.

## ETHICS AND DISSEMINATION

The protocol was approved by the Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, based on the guidelines set forth in the Declaration of Helsinki (SH9H-2019-T316-4). An ethics review protects human medical

research participants to ensure compliance with federal regulations. Any modifications to the protocol that may impact study procedures or the conduct of the study will require approval by the Institutional Review Board and a formal amendment to the protocol. This clinical trial has been registered with the Chinese Clinical Trial Registry ([www.chictr.org.cn](http://www.chictr.org.cn)).

All study participants will provide written informed consent prior to randomisation. Patients included in this study have the right to withdraw at any time, and the reasons will be documented. If participants have trouble complying with the intervention or completing follow-up testing, they can discuss these challenges with the study coordinator. If participants miss measurement appointments, up to three reminders will be sent, and if necessary, the participant will be contacted by telephone to rearrange an appointment for measurements at an appropriate time. Regardless of the outcome, the results of the trial will be reported in accordance with the STROBE guidelines in a relevant scientific journal.

## TRIAL STATUS

Recruitment started in December 2020 and is estimated to be completed in December 2021.

**Contributors** All authors are involved in the design of the study. LX initiated the study. BC, LX, SL, LZ and SF contributed to the planning and design. LZ, BC and LX drafted the study protocol and design. WS and SF will perform the statistical analysis. LX, LZ, YY and SF are responsible for managing the research. LX is the supervisor of the project.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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