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# BMJ Open

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

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4 1 **Prognostic factor analysis in patients with**  
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6 2 **temporomandibular disorders after conservative treatment:**  
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9 3 **study protocol for a prospective cohort study in China**  
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50  
51 24 study; protocol

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57 27 **ABSTRACT**

58  
59 28 **Introduction:** Temporomandibular disorders (TMDs) are complex multifactorial disorders.  
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4 29 Conservative treatment has been suggested for the initial management of TMD; however,  
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6 30 comparable therapeutic effects of different conservative intervention modalities remain  
7  
8 31 controversial. Various biopsychosocial factors, which may be putative prognostic factors that  
9  
10 32 influence the response to conservative treatment for TMD, have been reported to increase the  
11  
12 33 risk of developing first-onset TMD. However, there is a paucity of research that aims to identify  
13  
14 34 prognostic factors associated with the clinical outcomes of conservative treatment in people  
15  
16 35 with TMD. The objective of this prospective cohort study is to identify prognostic factors that  
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18 36 are associated with clinical outcomes of conservative treatment in patients with TMD and to  
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20 37 analyse the risk factors that influence the development of chronic TMD.

21 38 **Methods and analysis:** We plan to recruit 834 patients with TMD who meet the inclusion  
22  
23 39 criteria. Following provision of informed consent, baseline data including anamnestic data,  
24  
25 40 physical assessments, and self-reported questionnaires will be collected from participants at  
26  
27 41 their first clinic visit, and then they will receive 1–4 weeks of conservative treatment. Primary  
28  
29 42 treatment outcome measures will be change in the anterior maximal opening, worse TMD pain  
30  
31 43 score registered on a visual analogue scale (VAS), and a reduction in characteristic pain  
32  
33 44 intensity. A good outcome will be defined as an anterior maximal opening  $\geq 35$  mm and at least  
34  
35 45 a 30% reduction on VAS post-treatment. The association between candidate prognostic factors  
36  
37 46 and clinical outcomes of conservative TMD treatment will be analysed.

38  
39 47 **Ethics and dissemination:** The protocol has been approved by the Ethics Committee of Ninth  
40  
41 48 People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, based  
42  
43 49 on the guidelines outlined in the Declaration of Helsinki (SH9H-2019-T316-4). The results of  
44  
45 50 this study will be reported in accordance with the Strengthening the Reporting of Observational  
46  
47 51 Studies in Epidemiology (STROBE) statement. The authors intend to publish the results in a  
48  
49 52 peer-reviewed source.

50 53 **Trial Registration Number:** ChiCTR2000033328.

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#### 53 55 **Strengths and limitations of this study**

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56 56 ■ This study will identify the prognostic factors that are associated with clinical outcomes of  
57  
58 57 conservative treatment in patients with TMD and analyse risk factors that influence the  
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58 development of chronic TMD.

59 ■ The heterogeneity of patient material and psychosocial factors may be considered in treatment  
60 planning.

61 ■ This study will provide evidence to appropriately manage Chinese patients with TMD.

62 ■ This study will be performed in China; thus, it limits applicability to other populations.

63

## 64 INTRODUCTION

65 Temporomandibular disorders (TMDs) are painful musculoskeletal conditions that are  
66 associated with pain and dysfunction of the temporomandibular joint (TMJ) and masticatory  
67 muscles.<sup>1 2</sup> Approximately 5% to 12% of adults experience TMD.<sup>2</sup> The most common TMD  
68 symptoms and signs are facial pain, impaired jaw mobility, deviations of mandibular  
69 movements, and TMJ sounds, affecting the patient's wellbeing and quality of life.<sup>3</sup>

70 TMD is a complex disorder resulting from multiple physical, psychological, genetic,  
71 sensory processing, and environmental domains, and clinical characteristics have been  
72 identified to predict the increased risk of developing TMD.<sup>4</sup> Previous reports from the Orofacial  
73 Pain: Prospective Evaluation and Risk Assessment (OPPERA) study have concluded that  
74 numerous biopsychosocial factors increase the risk of developing first-onset TMD.<sup>4-6</sup> The  
75 OPPERA study findings demonstrated that a complex pattern of considerable changes in  
76 psychologic functioning (i.e., perceived stress, depression, and somatisation),<sup>7</sup> pain sensitivity,<sup>8</sup>  
77 clinical jaw function,<sup>9</sup> sleep disturbance, and other health conditions<sup>10</sup> is associated with  
78 changes in the TMD status.

79 Various interventions have been suggested for TMD, but to date, the most effective  
80 treatment programme remains unclear.<sup>11-14</sup> These interventions are grouped into three  
81 categories based on the level of invasiveness, including conservative (e.g., education, self-  
82 management, splint therapy, and physiotherapy), minimally invasive (e.g., arthrocentesis), and  
83 surgical interventions (e.g., arthroscopic and open joint surgeries).<sup>11</sup> The similar pain-reducing  
84 effect of physiotherapy and splint therapy has been confirmed for patients with myofascial  
85 TMD pain.<sup>14</sup> Diraçoğlu et al.<sup>13</sup> concluded that neither conservative methods nor arthrocentesis  
86 is beneficial in the early treatment of TMD. A previous randomised controlled trial found no

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4 87 difference between medical management, non-surgical rehabilitation, arthroscopic surgery, and  
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6 88 arthroplasty relative to TMJ pain and mandibular mobility at a 60-month follow-up.<sup>12</sup> The  
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8 89 comparable therapeutic effects of different intervention modalities suggest that the least  
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10 90 expensive, least invasive, and simplest interventions should be employed for the initial  
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12 91 management of TMD.<sup>11</sup>

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14 92 Although promising outcomes have been reported with conservative treatment, the results  
15  
16 93 remain controversial.<sup>15</sup> One prospective cohort study followed 40 TMD patients for 2.5 years  
17  
18 94 and found that 43% of the patients were free of symptoms, 33% of the patients had decreased  
19  
20 95 symptoms, and 25% showed no improvement or required further treatment.<sup>15</sup> Similarly, nearly  
21  
22 96 50% of patients who received conservative treatment reported no pain 5 years later, and another  
23  
24 97 14% of patients continued to report significant pain.<sup>16</sup> Little is known about clinical  
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26 98 characteristics of these TMD patients with poor prognosis following conservative treatment.  
27  
28 99 These findings suggest that the prognostic information is critical when predicting the impact of  
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30 100 conservative interventions in a population with TMD. However, there is a paucity of research  
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32 101 that aims to identify prognostic factors associated with the clinical outcomes of conservative  
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34 102 treatment in people with TMD. Previous studies have concluded that numerous biopsychosocial  
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36 103 factors increase the risk of developing first-onset TMD; therefore, we speculated that these  
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38 104 factors may have a theoretical association with prognosis in individuals with TMD. Moreover,  
39  
40 105 the TMD status changes substantially over time, and acute TMD becomes chronic in 25% of  
41  
42 106 patients along the highly variable course of TMD.<sup>17</sup> Long-term follow-up studies are needed to  
43  
44 107 investigate the prognostic factors that influence the response to conservative treatment and the  
45  
46 108 risk factors that are associated with the development of chronic TMD.

47  
48 109 The aim of this prospective cohort study is 1) to identify prognostic factors that are  
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50 110 associated with clinical outcomes of conservative treatment in patients with TMD and 2) to  
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52 111 analyse risk factors that influence development of chronic TMD during the 1-year follow-up  
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54 112 period. Based on current knowledge of risk factors for the development of TMD that have been  
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56 113 reported in epidemiological studies, putative prognostic factors, including demographic data,  
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58 114 self-reported questionnaires, and measures of physical function, will be collected and analysed.

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4 116 **Specific aims**

5 117 **Aim 1:** To determine whether demographic characteristics and biopsychosocial factors are  
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7 118 associated with the prognosis of conservative treatment for TMD.

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9 119 **Aim 2:** To determine the risk factors associated with chronic TMD.  
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13 121 **TRIAL DESIGN AND METHODS**

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15 122 This population-based prospective cohort study will be conducted in Shanghai Ninth People's  
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17 123 Hospital, Shanghai Jiao Tong University School of Medicine. This protocol has been designed  
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19 124 in accordance with the Standard Protocol Items: Recommendations for Interventional Trials  
20  
21 125 (SPIRIT) 2013 statement and Prognosis Research Strategy (PROGRESS).<sup>18</sup> The results of this  
22  
23 126 study will be reported in accordance with the Strengthening the Reporting of Observational  
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25 127 Studies in Epidemiology (STROBE) statement.<sup>19</sup>  
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29 129 **Participants**

30  
31 130 We will recruit 834 patients with TMD presenting to the rehabilitation department. Consecutive  
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33 131 eligible patients will receive 1–4 weeks of conservative treatment and will be followed-up for  
34  
35 132 12 months post-treatment. The conservative treatment programme has been reproduced from a  
36  
37 133 previous systematic review on patients with TMD.<sup>20</sup> The 1-year follow-up has been pre-  
38  
39 134 registered before the patients participated. Study recruitment will commence on December  
40  
41 135 2020 and will be completed by December 2021.

42 136 The participants must meet the following criteria:

- 43  
44 137 1. Aged 12–75 years.  
45  
46 138 2. Fulfil the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).<sup>21</sup>  
47  
48 139 3. Maximal mouth opening < 35 mm and/or a visual analogue scale (VAS) score for orofacial  
49  
50 140 pain  $\geq$  4.  
51  
52 141 4. Understanding of the survey and independent completion of the questionnaires.  
53  
54 142 5. Volunteers to participate in the study and signs the consent form.

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56 143 The participants will be excluded if they meet one of the following conditions at baseline:

- 57  
58 144 1. History of traumatic facial injury or surgery.  
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4 145 2. Malignant disease, active rheumatologic disease, haemorrhagic disease, heart disease, or  
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6 146 heart failure.

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8 147 3. Pregnant or lactating women or women who plan to be pregnant within the next 1 year.

9  
10 148 Drop-out criteria: Participants will have the right to drop out of the study at any time.

11  
12 149 Participants who meet one of the following conditions will be removed from the study:

13  
14 150 1. The researcher believes that removal from the study will benefit the patient.

15  
16 151 2. Not following the follow-up time schedule or refusal to answer the required questionnaires.

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20 153 **Recruitment**

21  
22 154 Patients will be recruited from the rehabilitation department in Shanghai Ninth People's

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24 155 Hospital, Shanghai Jiao Tong University School of Medicine. We will recruit eligible patients

25  
26 156 at their first clinic visit. Prior to study initiation, training will be delivered to the clinical

27  
28 157 examiners working at the physiotherapy clinic to inform them of the study and how to screen

29  
30 158 patients for eligibility. X.L. will serve as the reference examiner throughout the study. In a

31  
32 159 separate training session, each study examiner will conduct more than 10 blinded, replicated

33  
34 160 examinations of non-study volunteers. Data from the blinded, replicate examinations will be

35  
36 161 analysed for interexaminer reliability computed using the Kappa statistic. Providers will have

37  
38 162 copies of the screening form to screen potential patients according to the inclusion and

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40 163 exclusion criteria. At the first outpatient visit, a potential patient will be informed about the

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42 164 study. All study patients will provide written informed consent at the time of recruitment.

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46 166 **Candidate prognostic factors**

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48 167 Owing to the lack of consensus on prognostic factors that influence the response to conservative

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50 168 treatment for TMD, demographic data, physical measures, self-reported questionnaires, and

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52 169 type of treatment modality will be collected. Putative factors have been selected based on

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54 170 current knowledge of risk factors for the development of TMD in epidemiological studies that

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56 171 may have a theoretical association with prognosis in individuals with TMD, as confirmed by

57  
58 172 the biopsychosocial model of developing TMD. These selected factors are feasible to measure

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60 173 in clinical settings. Candidate prognostic factors are summarised in Table 1. All data collection

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4 174 will be standardised using clinical report forms and protocols.

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8 176 **Data collection**

9 177 Baseline data including demographic data, self-reported questionnaires, and physical  
10 178 assessments will be collected by a trained assessor at the first clinic visit. Patients will receive  
11 179 1–4 weeks of conservative treatment within 2 weeks following recruitment, and treatment  
12 180 modalities that patients receive will be recorded. Patients will be contacted by the same assessor  
13 181 by telephone 3, 6, and 12 months after treatment to complete physical examination and  
14 182 functional questionnaires (Figure 1).

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23 184 **Baseline interview, self-reported questionnaires, and physical examination**

24 185 During the first clinic visit, the researcher will collect the patient's demographic data (e.g.,  
25 186 gender, age distribution, educational attainment, marital status), case histories, intercurrent  
26 187 diseases (e.g., pain related to the neck and TMJ region, general musculoskeletal pain elsewhere),  
27 188 and use of medication. Anamnestic data will be collected at baseline, including the nature,  
28 189 duration, and intensity of the pain. The intensity of the present facial pain, including masticatory  
29 190 muscle pain and TMJ pain at rest and during movements of the mandible according to the  
30 191 DC/TMD criteria, will be assessed with VAS. VAS is a measurement instrument that measures  
31 192 an attitude or characteristic that ranges across a continuum of values and cannot be directly  
32 193 measured.<sup>22</sup> Operationally, it usually takes the form of a horizontal line, 100 mm in length, with  
33 194 word descriptors at each end. The patient marks the point on the line that represents their current  
34 195 feelings. The VAS score, measured in millimetres, is determined from the left end to the point  
35 196 that the patient marks.

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48 197 Patients will be asked to complete self-reported questionnaires. The patients will follow  
49 198 the procedure shown in Table 1. The Oral Behaviors Checklist is a self-reported questionnaire  
50 199 with 21 items used to quantify the frequency of oral behaviours, which is considered as part of  
51 200 a larger study of diagnostic validity and reliability for TMD.<sup>23</sup>

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56 201 The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for  
57 202 common mental disorders. The PHQ-15 consists of 15 somatic symptoms from the PHQ, and

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4 203 the PHQ-9 comprises nine items to establish a depressive disorder diagnosis as well as grade  
5  
6 204 depressive symptom severity.<sup>24</sup> Generalised anxiety disorder (GAD) is a common mental  
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8 205 disorder among TMD patients, and a 7-item anxiety scale (GAD-7) is a self-reported scale to  
9  
10 206 determine probable cases of GAD with good reliability and procedural validity.<sup>25</sup>

11  
12 207 The Pittsburgh Sleep Quality Index provides a valid, standardised, clinically useful  
13  
14 208 measure of a variety of sleep disturbances that may affect sleep quality.<sup>26</sup>

15  
16 209 The Jaw Functional Limitation Scale (JFLS) comprises 20 items used to assess the  
17  
18 210 limitation of the jaw function in TMD patients.<sup>27</sup>

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20 211 Finally, a functional examination of the masticatory system and diagnosis of patients  
21  
22 212 according to the DC/TMD criteria<sup>21</sup> will be made by the same clinician. Clinical stomatognathic  
23  
24 213 assessments of TMD include the ranges of movements of the mandible, TMJ sounds, and  
25  
26 214 patients' head and neck posture.<sup>28</sup> The ranges of movements of the mandible will be measured  
27  
28 215 with a vernier caliper.<sup>22</sup> When performing measurement of the anterior maximal opening, the  
29  
30 216 examiner will ask the patient to place the mandible in a comfortable position. The patient will  
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32 217 be asked to open the mouth as far as possible without assistance. The edge of the millimetre  
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34 218 ruler will be placed at the incisal edge of the maxillary central incisor for maximal vertical  
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36 219 orientation to the labioincisal edge of the opposing mandibular incisor. This measurement will  
37  
38 220 be considered the interincisal opening. If subjects open their mouth less than 30 mm, the  
39  
40 221 opening will be repeated to insure understanding. If the second opening still produces an  
41  
42 222 opening less than 30 mm, the measurement will be recorded as the interincisal opening. To  
43  
44 223 measure the vertical incisal overlap, the patient will be asked to perform the action of biting to  
45  
46 224 bring the teeth together. The line where the incisal edge of the same maxillary central incisor  
47  
48 225 used before for measurements overlaps the mandibular incisor will be marked with a pen. The  
49  
50 226 distance from the mandibular incisal edge to the marked line will be recorded as the vertical  
51  
52 227 incisal overlap. The anterior maximal opening will be considered as the sum of the interincisal  
53  
54 228 opening and the vertical incisal overlap.<sup>29</sup>

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56 229 The objective method of assessing head and neck posture will be to measure the  
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58 230 craniovertebral (CV) angle and the cranial rotation angle.<sup>30</sup> The CV angle will be defined as the  
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60 231 angle between the horizontal plane (the line perpendicular to true vertical axis) and the line

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4 232 extending from the tragus of the ear to the C7 spinous process.<sup>31</sup> The cranial rotation angle will  
5  
6 233 be formed by a line connecting the lateral canthus and the tragus with a horizontal line.<sup>31</sup>  
7  
8 234 Measurement of the cervical angle will be performed using a protractor. The digitisation  
9  
10 235 procedure has been proven to be highly reliable.<sup>30</sup> The sagittal plane images of the upper body  
11  
12 236 of each patient will be taken using a digital camera in a habitual relaxation sitting position. The  
13  
14 237 patient will be asked to assume a comfortable habitual sitting position with the eyes focused  
15  
16 238 towards the front, and the height of the chair will be 45 cm. Red markers will be placed over  
17  
18 239 the tragus and C7 spinous process by the same examiner. To ensure consistency in images, the  
19  
20 240 distance between the camera and the patient will be 1.5 m and the camera will be adjusted to  
21  
22 241 keep with the patient's shoulder.

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### 25 243 **Interventions**

26  
27 244 Patients included in the study will be invited to attend a study session at the physiotherapy clinic.  
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29 245 At this session, patients will receive a standardised conservative treatment programme within  
30  
31 246 2 weeks of recruitment and will be followed-up for a period of 12 months after treatment.  
32  
33 247 According to the recommendations from the current systematic reviews and meta-analyses, the  
34  
35 248 least invasive, simplest, and reversible interventions are considered as first-line therapy for  
36  
37 249 TMD. An experienced physiotherapist will design a conservative treatment programme  
38  
39 250 according to each patient's clinical symptoms, characteristics, and willingness. The programme  
40  
41 251 will include education, self-management, medication, therapeutic exercise, manual therapy,  
42  
43 252 and occlusal splint therapy, as previously reported.<sup>20</sup> Patients will be informed of the reasoning  
44  
45 253 behind the treatment plan and provided detailed information about the treatment programme.

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47 254 For those patients who meet the inclusion criteria but refuse to participate in the study, the  
48  
49 255 standard of care treatment will be given. To promote patient retention, the researcher will  
50  
51 256 inform the potential patient that although they can withdraw at any time, dropping out without  
52  
53 257 reason reduces the ability to answer the research question and therefore weakens the study.  
54  
55 258 Patients will be advised to carry on with their usual daily routines, and any interventions  
56  
57 259 received during conservative therapy sessions will be recorded for a descriptive analysis. The  
58  
59 260 detail of treatment (eg, time, number, duration, modality), leave requests and reasons will be

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4 261 documented and reported, as well as any adverse events during the study. Participants will be  
5 262 monitored during the 1 to 4-week programme and 12-month follow-up.  
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#### 10 264 **Outcomes**

11 265 The primary treatment outcome measures will be change in the anterior maximal opening,  
12 266 worse TMD pain registered on the VAS, and characteristic pain intensity. An anterior maximal  
13 267 opening  $\geq 35$  mm and at least 30% reduction on VAS post-treatment will be defined as good  
14 268 outcomes. Additional outcome measures will include change in frequency of TMD pain  
15 269 (recurrent, persistent, and one-time experience), the JFLS scores, and diagnosis of chronic  
16 270 TMD. The patients will be asked to report discomfort and complications associated with the  
17 271 conservative treatment and how often they perform the treatment. Additionally, all outcome  
18 272 measures will be collected 3, 6, and 12 months after treatment and assessed for the prediction  
19 273 model.  
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#### 30 275 **Data management**

31 276 All data will be entered into the research folder, and a researcher will transfer them into the  
32 277 master data spreadsheet. Privacy of patient data will be maintained through data handling  
33 278 (collection transfer, storage, and processing). Accuracy of data will be guaranteed by a  
34 279 secondary review by co-authors. Data from each participant will be recorded by research  
35 280 numbers and will be accessible only by members of this research team. A spreadsheet will be  
36 281 stored on a portable drive, and the research folders will be locked in a cabinet.  
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#### 47 283 **Trial organisation and monitoring**

48 284 The research team will consist of the authors listed in this article, in addition to administrative  
49 285 staff at the physiotherapy clinic who will assist with the entire process of the study and data  
50 286 entry. The primary investigator will manage the study flow and perform inspections of  
51 287 enrolment, treatment, and procedures throughout the entire study. Other investigators will  
52 288 monitor data collection and facilitate data integrity performed with periodic evaluations during  
53 289 the data collection phase.  
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5 291 **Data analysis**

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7 292 Numbers of individuals will be recorded, including those potentially eligible, confirmed  
8  
9 293 eligible, recruited into the study, receiving conservative treatment, and completing follow-up.  
10  
11 294 Withdrawals and loss to follow-up will be reported with reasons. Descriptive analyses of  
12  
13 295 patients at baseline will include demographics, self-reported questionnaires, and physical  
14  
15 296 assessment data.

16  
17 297 All analyses will be performed with the use of SPSS software (version 25.0). All analyses  
18  
19 298 will be conducted with a 2-sided significance level, with a threshold of  $P < 0.05$ . Linear  
20  
21 299 regression analysis, as the primary analysis, will be used to develop a linear model to determine  
22  
23 300 the association between candidate prognostic factors and the response to conservative treatment  
24  
25 301 in patients with TMD. For risk factors for the development of chronic TMD, univariate  
26  
27 302 associations between categorical variables (treatment, sex et.) and the diagnose of chronic TMD  
28  
29 303 according to DC/TMD will be tested using  $\chi^2$  tests. Continuous variable (age, height et.) and  
30  
31 304 the diagnose of chronic TMD according to DC/TMD will be tested using students unpaired t  
32  
33 305 tests. Multivariable analyses will be performed using binary logistic regression with forced  
34  
35 306 entry of all independent variables.

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37 307

38 308 **Sample size calculation**

39  
40 309 This prospective cohort study was designed with a target sample size of 834 enrolled patients  
41  
42 310 with TMD. This is expected to investigate the association between 20 candidate prognostic  
43  
44 311 factors and the clinical outcome of conservative treatment in patients with TMD over the 1-  
45  
46 312 year follow-up, assuming 20% loss to follow-up. The researchers will ensure at least 10  
47  
48 313 participants per prognostic factor to develop an adequately powered linear regression analysis.<sup>33</sup>  
49  
50 314 In a previous study, 70% of TMD patients who received conservative treatment reported good  
51  
52 315 outcomes.<sup>12</sup> Therefore, a sample size of 834 participants will be adequate to power a linear  
53  
54 316 regression analysis of 20 candidate prognostic factors.

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58 318 **Management of missing data**

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4 319 For each variable of interest, numbers of patients with missing data will be reported. Any  
5  
6 320 potential bias due to loss to follow-up will be assessed and compared using baseline data of  
7  
8 321 patients who withdraw or were lost to follow-up.<sup>32</sup> Multiple imputation will be used to deal  
9  
10 322 with missing outcome data, if necessary.<sup>34</sup> Participants will be excluded from the predictive  
11  
12 323 model and subsequent analyses if they request to withdraw from the study following  
13  
14 324 recruitment.<sup>32</sup>

15 325

### 17 326 **Patient and public involvement**

18  
19 327 No patients were involved with the design or will be involved in data provision, analysis, or  
20  
21 328 publication of the study.

22  
23 329

### 25 330 **DISCUSSION**

26  
27 331 This will be the first protocol to describe the methods and analysis for identifying prognostic  
28  
29 332 factors for clinical outcomes of conservative treatment in individuals with TMD. In particular,  
30  
31 333 self-reported measures together with physical examination will be incorporated to predict poor  
32  
33 334 outcome of conservative treatment in individuals with TMD. The candidate prognostic factors  
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35 335 have been selected based on current knowledge of risk factors for developing first-onset TMD  
36  
37 336 and its possible utilisation in clinical practice. The knowledge gained through this study will  
38  
39 337 provide a better understanding of how these prognostic factors can be used to improve clinical  
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41 338 outcomes, including whether conservative treatment is useful in the clinical management of  
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43 339 TMD patients.

44  
45 340 This study will be conducted in accordance with the SPIRIT statement and PROGRESS  
46  
47 341 framework.<sup>18,32</sup> The results from this study will provide new insights into who is likely to benefit  
48  
49 342 from conservative treatment versus who is likely to develop chronic TMD. Between 57% and  
50  
51 343 71% of patients seeking treatment for acute TMD continue to report significant pain 6 months  
52  
53 344 later.<sup>9, 35</sup> Therefore, the evaluation of prognoses will be valuable for treatment planning of  
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55 345 patients with TMD. In clinical practice, the heterogeneity of the patient material and  
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57 346 psychosocial factors may be considered in treatment planning.

58 347 Despite the novelty of this trial, this study has some limitations. First, the candidate

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4 348 prognostic factors are selected based on those reported risk factors for developing first-onset  
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6 349 TMD, however, some possible prognostic factors may be ignored. For future studies, we may  
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8 350 include more candidate prognostic factors. Second, since the conservative treatment is a  
9  
10 351 combined treatment, we cannot ascertain the effects of medication only or manual therapy only;  
11  
12 352 however, we will explore the prognose of each treatment component.

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14 353

#### 15 354 **ETHICS AND DISSEMINATION**

16  
17 355 The protocol was approved by the Ethics Committee of Ninth People's Hospital, Shanghai Jiao  
18  
19 356 Tong University School of Medicine, Shanghai, China, based on the guidelines set forth in the  
20  
21 357 Declaration of Helsinki (SH9H-2019-T316-4). An ethics review protects human medical  
22  
23 358 research participants to ensure compliance with federal regulations. Any modifications to the  
24  
25 359 protocol which may impact study procedures or the conduct of the study will require approval  
26  
27 360 by the Institutional Review Board and a formal amendment to the protocol. This clinical trial  
28  
29 361 has been registered with Chinese Clinical Trial Registry ([www.chictr.org.cn](http://www.chictr.org.cn)) with a registration  
30  
31 362 number ChiCTR2000033328.

32  
33 363 All study participants will provide written informed consent prior to randomisation.  
34  
35 364 Patients included in this study have rights to withdraw at any time, and the reasons will be  
36  
37 365 documented. If participants have trouble complying with the intervention or completing follow-  
38  
39 366 up testing, they can discuss these challenges with the study coordinator. If participants miss  
40  
41 367 measurement appointments, up to three reminders will be sent, and if needed, the participant  
42  
43 368 will be contacted by telephone to rearrange measurements at an appropriate time. Regardless  
44  
45 369 of the outcome, the results of the trial will be reported following the STROBE statement in a  
46  
47 370 relevant scientific journal.

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#### 50 372 **TRIAL STATUS**

51  
52 373 Recruitment started in December 2020 and is estimated to be completed in December 2021.

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55  
56 375 **Contributors** All authors are involved in the design of the study. LX initiated the study. BC,  
57  
58 376 LX, SL, LZ and SF contributed to planning and design. LZ, BC and LX drafted the study  
59  
60



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4 377 protocol and design. SW and SF perform statistical analysis. LX and ZF are responsible for  
5 378 communications through different centres and research management. LX is the supervisor of  
6  
7 379 the project.

8  
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11  
12 382 **Competing interests** None declared.

13  
14 383 **Patient consent for publication** Obtained.

15  
16 384 **Ethics approval** Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University  
17 385 School of Medicine, Shanghai, China (SH9H-2019-T316-4).

18  
19 386 **Provenance and peer review** Not commissioned; externally peer reviewed.

20  
21 387 **Data availability statement** Data are available on reasonable request.

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Table 1 Summary of measures that will be collected					
Domain/candidate predictor	Baseline	After treatment	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	✓	✓	✓	✓	✓

474 CPI, characteristic pain intensity; VAS, visual analogue scale; OBC, Oral Behaviors Checklist; PHQ,  
 475 Patient Health Questionnaire; GAD, generalized anxiety scale; PSQI, Pittsburgh Sleep Quality  
 476 Index; JFLS, Jaw Functional Limitation Scale

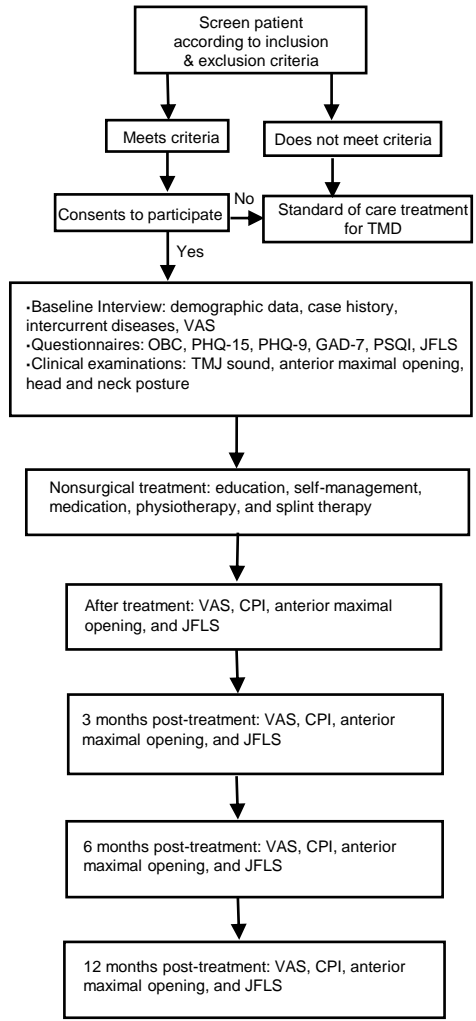
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#### 478 **Figure Legends**

479 **Figure 1** Participants recruitment and flow of the study.

480 TMD, temporomandibular disorders; VAS, visual analogue scale; OBC, Oral Behaviors Checklist;  
 481 PHQ, Patient Health Questionnaire; GAD, generalized anxiety disorder; PSQI, Pittsburgh Sleep  
 482 Quality Index; JFLS, Jaw Functional Limitation Scale; TMJ, temporomandibular joint; CPI,  
 483 characteristic pain intensity

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# 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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<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Dentistry and oral medicine, Rehabilitation medicine, Public health, Research methods
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4 1 **Prognostic factor analysis in patients with**  
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6 2 **temporomandibular disorders after reversible treatment:**  
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9 3 **study protocol for a prospective cohort study in China**  
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13 5 Ling Zhang<sup>a</sup>, MPE, Wentao Shi<sup>b</sup>, PhD, Shenji Lu<sup>a</sup>, PhD, Bin Cai<sup>a</sup>, PhD, Shuai Fan<sup>a</sup>,  
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15 6 MPT, Yang Yang<sup>a</sup>, MPE, Lili Xu<sup>a</sup>, PhD  
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48  
49 23 **Keywords:** prognostic factor; temporomandibular disorders; reversible treatment; cohort  
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51 24 study; protocol

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53 25 **Total word count:** 3720  
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59 28 **ABSTRACT**  
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4 29 **Introduction:** Temporomandibular disorders (TMDs) are complex multifactorial disorders.  
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6 30 Reversible treatment has been suggested for the initial management of TMD; however,  
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8 31 comparable therapeutic effects of different reversible intervention modalities remain  
9  
10 32 controversial. Various biopsychosocial factors, which may be putative prognostic factors that  
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12 33 influence the response to reversible treatment for TMD, have been reported to increase the  
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14 34 risk of developing first-onset TMD. However, there is a paucity of research that aims to  
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16 35 identify prognostic factors associated with the clinical outcomes of reversible treatment in  
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18 36 people with TMD. The objective of this prospective cohort study is to identify prognostic  
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20 37 factors that are associated with clinical outcomes of reversible treatment in patients with  
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22 38 TMD and to analyse the risk factors that influence the development of chronic TMD.

23 39 **Methods and analysis:** We plan to recruit 834 patients with TMD who meet the inclusion  
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25 40 criteria. Once informed consent is obtained, baseline data, including anamnestic data, physical  
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27 41 assessments, and self-report questionnaires, will be collected from participants at their first  
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29 42 clinic visit; subsequently, they will receive 1–4 weeks of reversible treatment. The primary  
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31 43 treatment outcome measures will be a change in the anterior maximum mouth opening,  
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33 44 worsening of TMD pain scores assessed using a visual analogue scale (VAS), and a reduction  
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35 45 in characteristic pain intensity. A good outcome will be defined as an anterior maximal  
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37 46 opening  $\geq 35$  mm and at least a 30% reduction in VAS scores 3 months after baseline. The  
38  
39 47 association between candidate prognostic factors and clinical outcomes of reversible TMD  
40  
41 48 treatment will be analysed.

42 49 **Ethics and dissemination:** The protocol has been approved by the Ethics Committee of  
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44 50 Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai,  
45  
46 51 China, based on the guidelines outlined in the Declaration of Helsinki (SH9H-2019-T316-4).  
47  
48 52 The results of this study will be reported in accordance with the Strengthening the Reporting  
49  
50 53 of Observational Studies in Epidemiology (STROBE) statement. The authors intend to  
51  
52 54 publish the results in a peer-reviewed journal.

53 54 **Trial Registration Number:** ChiCTR2000033328.

#### 54 55 **Strengths and limitations of this study**

55 56 ■ A battery of assessments of demographic characteristics and biopsychosocial factors will be  
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4 58 conducted to evaluate the associations between those variables and the prognosis of patients  
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6 59 with TMD.

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8 60 ■ Putative risk factors that are associated with the development of chronic TMD will be  
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10 61 explored so that the heterogeneity of patient characteristics and psychosocial factors may be  
11  
12 62 considered during treatment planning.

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14 63 ■ Anterior maximal opening of the mouth and TMD pain will be included as outcome  
15  
16 64 measures, providing evidence that will be useful for appropriately managing Chinese patients  
17  
18 65 with TMD.

19  
20 66 ■ As putative prognostic factors are selected based on current knowledge of risk factors  
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22 67 associated with the development of TMD, some possible biopsychosocial factors may not be  
23  
24 68 assessed in this study.

25  
26 69 ■ Considering that the ethnic background of TMD patients may be associated with  
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28 70 psychological variables, the influence of these psychological factors on the prognosis of  
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30 71 patients with TMD may also differ based on ethnicity.

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### 33 73 **INTRODUCTION**

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35 74 Temporomandibular disorders (TMDs) are painful musculoskeletal conditions that are  
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37 75 associated with pain and dysfunction of the temporomandibular joint (TMJ) and masticatory  
38  
39 76 muscles.<sup>1,2</sup> Approximately 5% to 12% of adults experience TMD.<sup>2</sup> The most common TMD  
40  
41 77 symptoms and signs are facial pain, impaired jaw mobility, deviations of mandibular  
42  
43 78 movements, and TMJ sounds, affecting the patient's well-being and quality of life.<sup>3</sup>

44  
45 79 TMD is a complex disorder associated with multiple physical, psychological, genetic,  
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47 80 sensory processing, and environmental domains, and clinical characteristics have been  
48  
49 81 identified to predict the increased risk of developing TMD.<sup>4</sup> Previous reports from the  
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51 82 Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study have  
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53 83 concluded that numerous biopsychosocial factors increase the risk of developing first-onset  
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55 84 TMD.<sup>4,6</sup> The OPPERA study findings demonstrated that a complex pattern of considerable  
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57 85 changes in psychological functioning (i.e., perceived stress, depression, and somatisation),<sup>7</sup>  
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59 86 pain sensitivity,<sup>8</sup> clinical jaw function,<sup>9</sup> sleep disturbance, and other health conditions<sup>10</sup> is

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4 87 associated with changes in the TMD status.

5 88 Various interventions have been suggested for TMD, although to date, the most effective  
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7 89 treatment programme remains unclear.<sup>11-14</sup> These interventions are grouped into three  
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9 90 categories based on the level of invasiveness, including reversible (e.g., education,  
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11 91 self-management, splint therapy, and physiotherapy), minimally invasive (e.g.,  
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13 92 arthrocentesis), and surgical (e.g., arthroscopic and open joint surgeries) interventions.<sup>11</sup> A  
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15 93 similar pain-reducing effect of physiotherapy and splint therapy has been confirmed in  
16  
17 94 patients with myofascial TMD pain.<sup>14</sup> Diraçoğlu et al.<sup>13</sup> concluded that neither reversible  
18  
19 95 methods nor arthrocentesis was beneficial in the early treatment of TMD. A previous  
20  
21 96 randomised controlled trial found no difference between medical management, non-surgical  
22  
23 97 rehabilitation, arthroscopic surgery, and arthroplasty in terms of TMJ pain and mandibular  
24  
25 98 mobility at a 60-month follow-up.<sup>12</sup> The comparable therapeutic effects of different  
26  
27 99 intervention modalities suggest that the least expensive, least invasive, and simplest  
28  
29 100 interventions should be employed for the initial management of TMD.<sup>11</sup>

30  
31 101 Although promising outcomes have been reported with reversible treatment, the results  
32  
33 102 remain controversial.<sup>15</sup> One prospective cohort study followed 40 TMD patients for 2.5 years  
34  
35 103 and found that 43% of the patients were free of symptoms, 33% of the patients had decreased  
36  
37 104 symptoms, and 25% showed no improvement or required further treatment.<sup>15</sup> Similarly,  
38  
39 105 nearly 50% of patients who received reversible treatment reported no pain five years later,  
40  
41 106 although 14% of patients continued to report significant pain.<sup>16</sup> Little is known about the  
42  
43 107 clinical characteristics of these TMD patients who experience a poor prognosis following  
44  
45 108 reversible treatment. These findings suggest that prognostic information is critical when  
46  
47 109 predicting the impact of reversible interventions in a population with TMD. However, there is  
48  
49 110 a paucity of research that aims to identify prognostic factors associated with the clinical  
50  
51 111 outcomes of reversible treatment in people with TMD.<sup>17-19</sup> Previous studies have concluded  
52  
53 112 that numerous biopsychosocial factors increase the risk of developing first-onset TMD;  
54  
55 113 therefore, we speculated that these factors may have a theoretical association with prognosis  
56  
57 114 in individuals with TMD. Moreover, the TMD status changes substantially over time, and  
58  
59 115 acute TMD becomes chronic in 25% of patients, as the course of TMD progression can be  
60

1  
2  
3  
4 116 highly variable.<sup>20</sup> Long-term follow-up studies are needed to investigate the prognostic factors  
5  
6 117 that influence the response to reversible treatment and the risk factors that are associated with  
7  
8 118 the development of chronic TMD.

9  
10 119 The aims of this prospective cohort study are: 1) to identify prognostic factors that are  
11  
12 120 associated with clinical outcomes of reversible treatment in patients with TMD; and 2) to  
13  
14 121 analyse risk factors that influence the development of chronic TMD during a 1-year follow-up  
15  
16 122 period. Based on current knowledge of risk factors for the development of TMD that have  
17  
18 123 been reported in epidemiological studies, putative prognostic factors, including demographic  
19  
20 124 data, data from self-report questionnaires, and measures of physical function will be collected  
21  
22 125 and analysed.

23  
24 126

### 25 127 **Specific aims**

26  
27 128 **Aim 1:** To determine whether demographic characteristics and biopsychosocial factors are  
28  
29 129 associated with the prognosis of reversible treatment for TMD.

30  
31 130 **Aim 2:** To determine the risk factors associated with chronic TMD.

32  
33 131

### 34 35 132 **TRIAL DESIGN AND METHODS**

36  
37 133 This clinical-based, prospective, cohort study will be conducted at Shanghai Ninth People's  
38  
39 134 Hospital, Shanghai Jiao Tong University School of Medicine. This protocol has been  
40  
41 135 designed in accordance with the Standard Protocol Items: Recommendations for  
42  
43 136 Interventional Trials (SPIRIT) 2013 statement and Prognosis Research Strategy  
44  
45 137 (PROGRESS) guidelines.<sup>21</sup> The results of this study will be reported in accordance with the  
46  
47 138 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)  
48  
49 139 statement.<sup>22</sup>

50  
51 140

### 52 141 **Participants**

53  
54 142 We will recruit 834 patients with TMD presenting to the rehabilitation department.  
55  
56 143 Consecutive eligible patients will receive 1–4 weeks of reversible treatment and will be  
57  
58 144 followed up for 12 months after baseline measurements. The reversible treatment programme

1  
2  
3  
4 145 has been reproduced from a previous systematic review on patients with TMD.<sup>23</sup> The 1-year  
5 146 follow-up has been pre-registered before patient enrolment. Study recruitment will commence  
6  
7 147 in December 2020 and will be completed by December 2021.

8  
9 148 The participants must meet the following inclusion criteria:

- 10  
11 149 1. Patients aged 20–45 years.  
12  
13 150 2. Patients fulfilling the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).<sup>24</sup>  
14  
15 151 3. Patients with myofascial pain or reducible or non-reducible disc displacement.  
16  
17 152 4. Patients should have one of the following symptoms:  
18  
19 153 a: visual analogue scale (VAS) score for orofacial pain  $\geq 4$ ;  
20  
21 154 b: maximal mouth opening  $< 35$  mm.  
22  
23 155 5. Understanding of the survey and ability to independently complete the questionnaires.  
24  
25 156 6. Patients must volunteer to participate in the study and sign the consent form.  
26  
27 157 7. Patients receiving at least one type of reversible treatment (e.g., education,  
28  
29 158 self-management, medication, therapeutic exercise, manual therapy, and occlusal splint  
30  
31 159 therapy).

32  
33 160 The participants will be excluded if they meet one of the following conditions at baseline:

- 34  
35 161 1. History of traumatic facial injury or surgery.  
36  
37 162 2. Malignant disease, active rheumatologic disease, haemorrhagic disease, heart disease, or  
38  
39 163 heart failure.  
40  
41 164 3. Pregnant or lactating women or women who plan to be pregnant within the next year.

42  
43 165 Drop-out criteria: Participants will have the right to drop out of the study at any time.

44  
45 166 Participants who meet one of the following conditions will be removed from the study:

- 46  
47 167 1. The researcher believes that removal from the study will benefit the patient.  
48  
49 168 2. Failure to adhere to the follow-up time schedule or refusal to respond to the required  
50  
51 169 questionnaires.

52  
53 170

## 54 171 **Recruitment**

55  
56 172 Patients will be recruited from the rehabilitation department of Shanghai Ninth People's  
57  
58 173 Hospital, Shanghai Jiao Tong University School of Medicine. We will recruit eligible patients

1  
2  
3  
4 174 at their first clinic visit. Prior to study initiation, training will be delivered to the clinical  
5  
6 175 examiners working at the physiotherapy clinic to inform them of the study and how to screen  
7  
8 176 patients for eligibility. X.L. will serve as the reference examiner throughout the study. In a  
9  
10 177 separate training session, each study examiner will conduct more than 10 blinded, replicated  
11  
12 178 examinations of non-study volunteers. Data from the blinded, replicate examinations will be  
13  
14 179 analysed for inter-examiner reliability computed using the Kappa statistic. Providers will have  
15  
16 180 copies of the screening form to screen potential patients according to the inclusion and  
17  
18 181 exclusion criteria. At the first outpatient visit, a potential patient will be informed about the  
19  
20 182 study. All study participants will be required to provide written informed consent at the time  
21  
22 183 of recruitment.

23  
24 184

### 25 185 **Candidate prognostic factors**

26  
27 186 Owing to the lack of consensus on the prognostic factors that influence the response to  
28  
29 187 reversible treatment for TMD, demographic data, physical measurements, data from  
30  
31 188 self-report questionnaires, and information about the type of treatment modality will be  
32  
33 189 collected. Putative factors have been selected based on current knowledge of risk factors for  
34  
35 190 the development of TMD from epidemiological studies that may have a theoretical  
36  
37 191 association with prognosis in individuals with TMD, as confirmed by the biopsychosocial  
38  
39 192 model of developing TMD. These selected factors are feasible to measure in clinical settings.  
40  
41 193 The candidate prognostic factors are summarised in Table 1. All data collection will be  
42  
43 194 standardised using clinical report forms and protocols.

44  
45 195

### 46 196 **Data collection**

47  
48 197 Baseline data, including demographic data, data from self-report questionnaires, and physical  
49  
50 198 assessments will be collected by a trained assessor at the first clinic visit. Patients will receive  
51  
52 199 1–4 weeks of reversible treatment within 2 weeks following recruitment, and the treatment  
53  
54 200 modalities that patients receive will be recorded. Patients will be contacted by the same  
55  
56 201 assessor by telephone 3, 6, and 12 months after baseline measurements to complete the  
57  
58 202 physical examination and functional questionnaires (Figure 1).

203

**204 Baseline interview, self-report questionnaires, and physical examination**

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

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

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

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

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



1  
2  
3  
4 232 Finally, a functional examination of the masticatory system and diagnosis of patients  
5  
6 233 according to the DC/TMD criteria<sup>24</sup> will be conducted by the same clinician. Clinical  
7  
8 234 stomatognathic assessments of TMD include the range of motion of the mandible, TMJ  
9  
10 235 sounds, and a patient's head and neck posture.<sup>31</sup> The range of motion of the mandible will be  
11  
12 236 measured with a Vernier caliper.<sup>25</sup> When performing measurement of the anterior maximal  
13  
14 237 opening, the examiner will ask the patient to place the mandible in a comfortable position.  
15  
16 238 The patient will be asked to open the mouth as far as possible without assistance. The edge of  
17  
18 239 the millimetre ruler will be placed at the incisal edge of the maxillary central incisor for  
19  
20 240 maximal vertical orientation to the labio-incisal edge of the opposing mandibular incisor. This  
21  
22 241 measurement will be considered the interincisal opening. If subjects open their mouth less  
23  
24 242 than 30 mm, the process will be repeated to ensure understanding. If the second opening is  
25  
26 243 still less than 30 mm, the measurement will be recorded as the interincisal opening. To  
27  
28 244 measure the vertical incisal overlap, the patient will be asked to perform the action of biting to  
29  
30 245 bring the teeth together. The line where the incisal edge of the same previously measured  
31  
32 246 maxillary central incisor overlaps the mandibular incisor will be marked with a pen. The  
33  
34 247 distance from the mandibular incisal edge to the marked line will be recorded as the vertical  
35  
36 248 incisal overlap. The anterior maximal opening will be considered as the sum of the  
37  
38 249 interincisal opening and the vertical incisal overlap.<sup>32</sup>

39 250 The objective method of assessing head and neck posture will be to measure the  
40  
41 251 craniovertebral (CV) angle and the cranial rotation angle.<sup>33</sup> The CV angle will be defined as  
42  
43 252 the angle between the horizontal plane (the line perpendicular to true vertical axis) and the  
44  
45 253 line extending from the tragus of the ear to the C7 spinous process.<sup>34</sup> The cranial rotation  
46  
47 254 angle will be formed by a line connecting the lateral canthus and the tragus with a horizontal  
48  
49 255 line.<sup>34</sup> Measurement of the cervical angle will be performed using a protractor. The  
50  
51 256 digitisation procedure has been proven to be highly reliable.<sup>33</sup> Sagittal plane imaging of the  
52  
53 257 upper body of each patient will be conducted using a digital camera in a habitual relaxed,  
54  
55 258 seated position. The patient will be asked to assume a comfortable habitual sitting position  
56  
57 259 with the eyes focused toward the front, and the height of the chair will be 45 cm. Red markers  
58  
59 260 will be placed over the tragus and C7 spinous process by the same examiner. To ensure  
60

261 consistency in the images, the distance between the camera and the patient will be 1.5 m, and  
262 the camera will be adjusted to remain aligned with the patient's shoulder.

263

### 264 **Interventions**

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

276 For patients who meet the inclusion criteria but refuse to participate in the study, the  
277 standard of care treatment will be given. To promote patient retention, the researcher will  
278 inform the potential patient that although they can withdraw at any time, dropping out without  
279 a reason reduces the ability to answer the research question and, therefore, weakens the study.  
280 Patients will be advised to carry on with their usual daily routines, and any interventions  
281 received during reversible therapy sessions will be recorded for a descriptive analysis. The  
282 details of the treatment (e.g., time, number, duration, modality) and the number of and  
283 reasons for dropouts will be documented and reported, as well as any adverse events during  
284 the study. Participants will be monitored during the 1- to 4-week programme and the  
285 12-month follow-up period. Data from patients receiving monotherapy or adjuvant therapy  
286 will be analysed separately.

287

### 288 **Outcomes**

289 The primary treatment outcome measures will be changes in the anterior maximal opening,

1  
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3  
4 290 worsening of TMD pain assessed using the VAS, and changes in pain characteristics. A  
5  
6 291 previous study concluded that the greatest improvement occurs between 3 and 4 months after  
7  
8 292 baseline;<sup>35</sup> therefore, 3 months was chosen as the treatment outcome evaluation time point in  
9  
10 293 this study. An anterior maximal opening of  $\geq 35$  mm and a reduction in VAS scores of at least  
11  
12 294 30% three months after baseline will be defined as good clinical outcomes.<sup>17</sup> Additional  
13  
14 295 outcome measures will include changes in the frequency of TMD pain (recurrent, persistent,  
15  
16 296 and one-time experience), JFLS scores, and the diagnosis of chronic TMD. The patients will  
17  
18 297 be asked to report discomfort and complications associated with the reversible treatment and  
19  
20 298 how often they perform the treatment. Additionally, all outcome measures will be evaluated 6  
21  
22 299 and 12 months after baseline measurements and will be assessed using predictive modelling.

23  
24  
25 300

#### 301 **Data management**

26  
27 302 All data will be entered into the research folder, and a researcher will transfer them into the  
28  
29 303 master data spreadsheet. Privacy of patient data will be maintained for all data handling  
30  
31 304 procedures (collection transfer, storage, and processing). The accuracy of the data will be  
32  
33 305 guaranteed through a secondary review by study co-authors. Data recorded from each  
34  
35 306 participant will be anonymized using research numbers and will be accessible only by members  
36  
37 307 of this research team. A spreadsheet will be stored on a portable drive, and the research  
38  
39 308 folders will be locked in a cabinet.

40  
41  
42 309

#### 310 **Trial organisation and monitoring**

43  
44 311 The research team will consist of the authors listed in this article, in addition to administrative  
45  
46 312 staff at the physiotherapy clinic who will assist with the entire process of the study and data  
47  
48 313 entry. The primary investigator will manage the study flow and perform inspections of  
49  
50 314 enrolment, treatment, and procedures throughout the entire study. Other investigators will  
51  
52 315 monitor data collection and facilitate the maintenance of data integrity through periodic  
53  
54 316 evaluations during the data collection phase.

55  
56  
57 317

#### 318 **Data analysis**

1  
2  
3  
4 319 Numbers of individuals will be recorded, including those who are potentially eligible,  
5 320 confirmed eligible, recruited into the study, receiving reversible treatment, and completing  
6  
7 321 follow-up. Numbers related to withdrawals and loss to follow-up will be reported, along with  
8  
9 322 reasons for removal from the study. Descriptive analyses of patients at baseline will include  
10  
11 323 demographic, self-report questionnaire, and physical assessment data.

12  
13 324 All analyses will be performed using Statistical Package for the Social Sciences (SPSS)  
14  
15 325 software (version 25.0). The Kolmogorov–Smirnov test will be performed to assess whether  
16  
17 326 the data are normally distributed ( $p>0.05$ ), considering that both parametric and  
18  
19 327 non-parametric tests will be used in the data analyses. Linear regression, unpaired *t*-tests, chi  
20  
21 328 square tests, and logistic regression will be used depending on the analysis to be performed. A  
22  
23 329 multiple linear regression analysis will be conducted to develop a linear model to determine  
24  
25 330 the associations between candidate prognostic factors and the response to reversible treatment  
26  
27 331 in patients with TMD, with anterior maximal opening and TMD pain as continuous dependent  
28  
29 332 variables. For assessing risk factors for the development of chronic TMD, univariate  
30  
31 333 associations between categorical variables (treatment, sex, etc.) and the diagnosis of chronic  
32  
33 334 TMD according to the DC/TMD criteria will be evaluated using  $\chi^2$  tests. Continuous  
34  
35 335 variables (age, height, etc.) and the diagnosis of chronic TMD according to the DC/TMD  
36  
37 336 criteria will be evaluated using student's unpaired *t*-tests with a Bonferroni correction.  
38  
39 337 Multivariate analyses will be performed using binary logistic regression with forced entry of  
40  
41 338 all independent variables. All analyses will be two-tailed, with a threshold for statistical  
42  
43 339 significance of  $P < 0.05$ .

44  
45 340

#### 46 341 **Sample size calculation**

47  
48 342 This prospective cohort study was designed with a target sample size of 834 enrolled patients  
49  
50 343 with TMD to investigate the association between 20 candidate prognostic factors and the  
51  
52 344 clinical outcome of reversible treatment in patients with TMD over the 1-year follow-up  
53  
54 345 period, assuming 20% loss to follow-up. The researchers will ensure that there are at least 10  
55  
56 346 participants per prognostic factor to conduct an adequately powered linear regression  
57  
58 347 analysis.<sup>36</sup> In a previous study, 70% of TMD patients who received reversible treatment

1  
2  
3  
4 348 reported good outcomes.<sup>12</sup> Therefore, a sample size of 834 participants will be adequate to  
5  
6 349 power a linear regression analysis of 20 candidate prognostic factors.  
7

8 350

9  
10 351 **Management of missing data**

11 352 For each variable of interest, the number of patients with missing data will be reported. Any  
12  
13 353 potential bias due to loss to follow-up will be assessed and compared using baseline data of  
14  
15 354 patients who withdraw or are lost to follow-up.<sup>37</sup> Multiple imputation will be used to deal  
16  
17 355 with missing outcome data, if necessary.<sup>38</sup> Participants will be excluded from the predictive  
18  
19 356 model and subsequent analyses if they request to withdraw from the study following  
20  
21 357 recruitment.<sup>37</sup>  
22

23 358

24  
25 359 **Patient and public involvement**

26  
27 360 No patients were involved with the design or will be involved in data collection, analysis, or  
28  
29 361 publication of the study.  
30

31 362

32  
33 363 **DISCUSSION**

34  
35 364 This will be the first protocol to describe methods and analysis for identifying prognostic  
36  
37 365 factors associated with clinical outcomes of reversible treatment in individuals with TMD. In  
38  
39 366 particular, self-report measures combined with physical examinations will be incorporated to  
40  
41 367 predict poor outcomes of reversible treatments in individuals with TMD. The candidate  
42  
43 368 prognostic factors have been selected based on current knowledge of risk factors for  
44  
45 369 developing first-onset TMD and their possible utilisation in clinical practice. The knowledge  
46  
47 370 gained through this study will provide a better understanding of how these prognostic factors  
48  
49 371 can be used to improve clinical outcomes, including whether reversible treatment is useful in  
50  
51 372 the clinical management of TMD patients.

52  
53 373 This study will be conducted in accordance with the SPIRIT statement and PROGRESS  
54  
55 374 framework.<sup>21 37</sup> The results of this study will provide new insights into who is likely to benefit  
56  
57 375 from reversible treatment versus who is likely to develop chronic TMD. Between 57% and  
58  
59 376 71% of patients seeking treatment for acute TMD continue to report significant pain 6 months  
60

1  
2  
3  
4 377 later.<sup>9 39</sup> Therefore, the evaluation of prognoses will be valuable for treatment planning for  
5  
6 378 patients with TMD. In clinical practice, the heterogeneity of patient characteristics and  
7  
8 379 psychosocial factors may be considered in treatment planning.

9  
10 380 Despite the novelty of this trial, this study has some limitations. Firstly, the candidate  
11  
12 381 prognostic factors have been selected based on reported risk factors for developing first-onset  
13  
14 382 TMD; however, some possible prognostic factors may be ignored. In future studies, we may  
15  
16 383 include more candidate prognostic factors. Secondly, since the reversible treatment is a  
17  
18 384 combined treatment, we cannot ascertain the effects of medication or manual therapy alone;  
19  
20 385 however, we will explore the prognosis associated with each treatment component.

21  
22 386

### 23 387 **ETHICS AND DISSEMINATION**

24  
25 388 The protocol was approved by the Ethics Committee of Ninth People's Hospital, Shanghai  
26  
27 389 Jiao Tong University School of Medicine, Shanghai, China, based on the guidelines set forth  
28  
29 390 in the Declaration of Helsinki (SH9H-2019-T316-4). An ethics review protects human  
30  
31 391 medical research participants to ensure compliance with federal regulations. Any  
32  
33 392 modifications to the protocol that may impact study procedures or the conduct of the study  
34  
35 393 will require approval by the Institutional Review Board and a formal amendment to the  
36  
37 394 protocol. This clinical trial has been registered with the Chinese Clinical Trial Registry  
38  
39 395 ([www.chictr.org.cn](http://www.chictr.org.cn)), with the registration number ChiCTR2000033328.

40  
41 396 All study participants will provide written informed consent prior to randomisation.  
42  
43 397 Patients included in this study have the right to withdraw at any time, and the reasons will be  
44  
45 398 documented. If participants have trouble complying with the intervention or completing  
46  
47 399 follow-up testing, they can discuss these challenges with the study coordinator. If participants  
48  
49 400 miss measurement appointments, up to three reminders will be sent, and, if necessary, the  
50  
51 401 participant will be contacted by telephone to rearrange an appointment for measurements at  
52  
53 402 an appropriate time. Regardless of the outcome, the results of the trial will be reported in  
54  
55 403 accordance with the STROBE guidelines in a relevant scientific journal.

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57 404

### 58 405 **TRIAL STATUS**

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4 406 Recruitment started in December 2020 and is estimated to be completed in December 2021.

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6 407

7 408 **Authors' contributions** All authors are involved in the design of the study. LX initiated the  
8 study. BC, LX, SL, LZ and SF contributed to the planning and design. LZ, BC and LX  
9 409 drafted the study protocol and design. WS and SF will perform the statistical analysis. LX,  
10 410 LZ, YY and SF are responsible for managing the research. LX is the supervisor of the project.  
11  
12 411  
13  
14 412

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16  
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18 414 and the Shanghai Municipal Science and Technology Major Project (Grant No.  
19 415 19441908400).  
20  
21  
22

23 416

24  
25 417 **Competing interests** None declared.  
26

27 418

28  
29 419 **Patient consent for publication** Obtained.  
30

31 420

32  
33 421 **Ethics approval** Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong  
34 422 University School of Medicine, Shanghai, China (SH9H-2019-T316-4).  
35  
36

37 423

38 424 **Provenance and peer review** Not commissioned; externally peer reviewed.  
39

40 425

41 426 **Data availability statement** Data are available upon reasonable request.  
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For peer review only

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Table 1 Summary of measures that will be collected

Domain/candidate predictor	Baseline	Month 3	Month 6	Month 12
<b>Fill out by clinicians</b>				
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		✓	✓	✓
<b>Filled out by subjects</b>				
VAS score	✓	✓	✓	✓
OBC	✓			
PHQ-15	✓			
PHQ-9	✓			
GAD-7	✓			
PSQI	✓			
JFLS	✓	✓	✓	✓

554 CPI, characteristic pain intensity; VAS, visual analogue scale; OBC, Oral Behaviors Checklist;

555 PHQ, Patient Health Questionnaire; GAD, generalized anxiety scale; PSQI, Pittsburgh Sleep

556 Quality Index; JFLS, Jaw Functional Limitation Scale

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8 **559 Figure Legends**

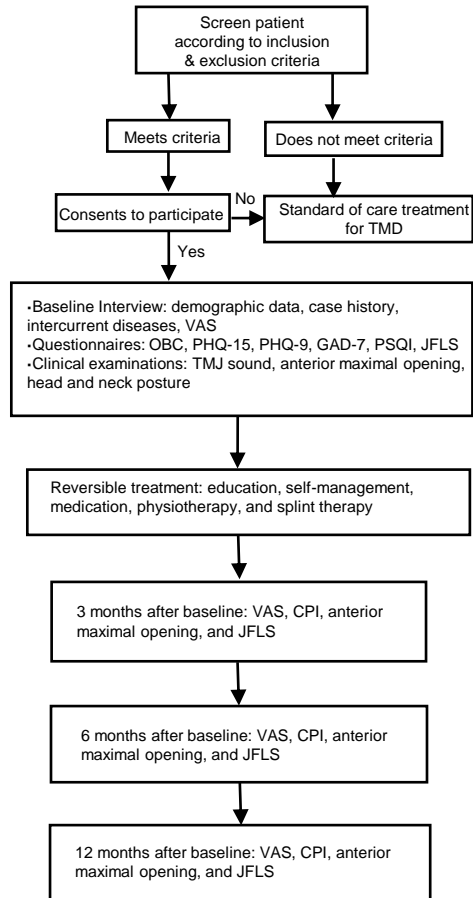
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10 **560 Figure 1** Participants recruitment and flow of the study.

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12 561 TMD, temporomandibular disorders; VAS, visual analogue scale; OBC, Oral Behaviors Checklist;

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14 562 PHQ, Patient Health Questionnaire; GAD,generalized anxiety disorder; PSQI, Pittsburgh Sleep

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16 563 Quality Index; JFLS, Jaw Functional Limitation Scale; TMJ, temporomandibular joint; CPI,

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6 6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	11 11 11 11 11
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	None
Outcome data	15*	Report numbers of outcome events or summary measures over time	None

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	None
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	None
5	<b>Discussion</b>			
6	Key results	18	Summarise key results with reference to study objectives	N/A
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
10	<b>Other information</b>			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.