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## Effectiveness of ultrasound therapy for the treatment of carpal tunnel syndrome (the USTINCTS trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

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**TITLE PAGE**

**Title**

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## Author Contributions

CS and SZY are the primary investigators.

CS, SZY, LWX, ZYY, FCY participated in the development of the study design.

CS, SZY, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the study conduct.

CS, SZY and LWX drafted the manuscript under FCY's supervision.

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51FCY contributed to applying for and gaining funding.

52All authors contributed to the content and critical revision and approved the final

53draft of the manuscript.

54

55**Conflict of interests**

56The authors, their immediate families, and any research foundation with which

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60

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## 77 **ETHICS**

78 The Ethics Committee of the 4 clinical centers have approved this study. The  
79 Ethics Committee approval number of the leading clinical center (Shanghai Sixth  
80 People's Hospital) is 2021-152. The research registry number is ChiCTR2100050701  
81 at <http://www.chictr.org.cn>. Data will be analyzed anonymously; all patients will  
82 approve the results of this study by oral consent. The oral consent approval will be  
83 documented in the patients' files. All clinical investigations will be conducted in  
84 accordance with the guidelines of the Declaration of Helsinki.

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86     **ABSTRACT**

87     **Introduction**

88           There has no consensus on optimal management of carpal tunnel syndrome  
89     (CaTS), the most common compression neuropathy. Conservative therapy is generally  
90     accepted as first-line intervention. Ultrasound (US) therapy has been widely reported  
91     to be treatment beneficial in nerve regeneration and conduction, and further accelerate  
92     compression recovery. The purpose of this study is to investigate the effectiveness of  
93     US for CaTS treatment.

94     **Methods and analysis**

95           This study protocol entails a three-arm, prospective, multicenter, randomised  
96     controlled trial. 63 eligible participants diagnosed with CaTS will be assigned to either  
97     (1) US, (2) night splint or (3) combined group. Primary outcome is Symptom Severity  
98     Scale of Boston Carpal Tunnel Questionnaire (BCTQ-SSS). Secondary outcomes  
99     include Functional Status Scale of BCTQ, numerical rating scale for hand-wrist  
100    symptom intensity, shortened version of the Disabilities of the Arm, Shoulder and Hand  
101    for upper limb disability, sleep questionnaire for interrupted sleep, EuroQol-5D for  
102    general health, Hospital Anxiety and Depression Scale for mental status, Work  
103    Limitations Questionnaire-25 for functional limitations at work, Global Rating of  
104    Change for treatment success and recurrence rate, Likert scale for participant's  
105    satisfaction, physical examination, electrophysiological and ultrasound parameters.  
106    Intention-to-treat analyses will be used.

107    **Ethics and dissemination**

108           Ethics Committees of all clinical centers have approved this study. The leading  
109    center is Shanghai Sixth People's Hospital, whose approval number is 2021-152. New  
110    versions with appropriate amendments will be submitted to the committee for further

111 approval. Study results will be published in peer-reviewed journals and presented at  
112 local, national and international conferences.

113 **Trial registration number**

114 ChiCTR2100050701.

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For peer review only



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**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- Ultrasound (US) as independent or adjunct therapy in treating carpal tunnel syndrome (CaTS).
- The first randomised controlled trial (RCT) to compared the efficacy between US and night splint in CaTS treatment.
- Multicenter RCT with blinded outcome assessor and statistician.
- Use of several patient-reported outcome measures as well as objective parameters.
- Participants and treating surgeons not blinded.

## INTRODUCTION

Carpal tunnel syndrome (CaTS), the most common compression neuropathy, results from median nerve entrapment in the carpal tunnel, accounting for about 90% of all such disorders.<sup>1,2</sup> The clinically confirmed CaTS prevalence was 9.6% in the general population of China,<sup>3</sup> with a yearly incidence rate of 2.76%, and women is more susceptible than men.<sup>2,4</sup> CaTS has significant impact on daily life and ability to work,<sup>5</sup> and causes great burden on social economy, with an annual associated costs estimated at \$13 billion.<sup>6</sup> Classically, CaTS causes discomfort, paraesthesia and numbness in the median nerve distribution; and nocturnal symptoms are often clinically significant causing sleep disturbance.<sup>7</sup> Patients can be diagnosed by clinical history and physical examination; while electrophysiological methods will be additional for insufficient diagnosis by clinical findings and severe cases that need surgical management.<sup>8</sup>

In general, the severity of CaTS can be classified into mild, moderate and severe.<sup>9</sup> Non-surgical interventions are suggested to be the first choice to treat mild and moderate CaTS.<sup>10</sup> To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. A consensus of multidisciplinary treatment guideline from the European HANDGUIDE Study suggests that “education” should be included as the first-line management approach, which has the advantages of low cost, high efficacy and non-invasive.<sup>7,11</sup> In addition, “night splint (NS)” and “corticosteroid injection (CI)” are also recommended in guidelines of American Academy of Orthopaedic Surgeons (AAOS) and American Physical Therapy Association (APTA).<sup>12,13</sup> One recent RCT published in Lancet compares both two methods, and finds that CI has superior clinical effectiveness at 6 weeks than NS, but no differences at 6 months; while CI may bring adverse events like thinning, lightening

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or darkening of the skin at the injection site, hot flushes and even more pain.<sup>9</sup>  
Systematic reviews have also shown that the effects of other conservative treatments  
like acupuncture,<sup>14</sup> exercise and mobilization interventions,<sup>15</sup> laser,<sup>16</sup> extracorporeal  
shockwave therapy<sup>17</sup> and platelet-rich plasma injection<sup>18</sup> still remain controversial or  
provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct  
to physiotherapy. With an intensity range of 0.5-2.0 W/cm<sup>2</sup>, US may have the potential  
to induce various biophysical effects within tissue.<sup>19</sup> Experiments of US on nerve  
conduction and stimulation of nerve regeneration,<sup>20,21</sup> and findings of its anti-  
inflammatory effects<sup>22</sup> all support that US might facilitate recovery for nerve  
compression. An RCT published in BMJ showed more pronounced subjective  
symptoms and electroneurographic variables for US treatment than sham control in  
patients with mild to moderate CaTS.<sup>23</sup> However, to our best of knowledge, no study  
has compared the efficacy between NS and US in CaTS treatment yet. Additionally,  
some studies have also reported the efficacy of US to be used as part of a multi-  
intervention approach, but with low grade of study design and data<sup>24-29</sup>. Therefore, the  
role of US in CaTS treatment still needs to be further explored by high-quality study.

Therefore, the purpose of the current three-arm, prospective, randomized,  
multicenter trial is to examine the effectiveness of US in treatment for CaTS, that is,  
NS+US versus NS versus US, on clinical and functional outcomes, including Boston  
Carpal Tunnel Questionnaire (BCTQ) in patients diagnosed with CaTS.

## **METHODS**

### **Study design**

The design of this study is a three-arm, prospective, multicenter, randomised controlled trial, that will enroll participants with a diagnosis of mild to moderate CaTS from 4 municipal tertiary hospitals (Shanghai Sixth People's Hospital, Shanghai Tenth People's Hospital, Shanghai East Hospital, and Pudong New Area People's Hospital of Shanghai). This manuscript is written according to the SPIRIT guidelines.<sup>30</sup>

### **Participant and public involvement**

This study was done without participant involvement. Participants were not invited to comment on the design and not consulted to develop patient-relevant outcomes. Participants will not be invited to contribute to the writing or editing of this manuscript for readability or accuracy. The resulting publications will be disseminated to public via mass media. Participants as a whole will be acknowledged in the end of our publications and presentations.

### **Participant recruitment**

**Figure 1** shows the participant flow chart throughout the study. Participants will be recruited over a period of 5 months, from the intake clinics of 4 principals of each sub-centers. Additionally, we will recruit participants through other physicians and healthcare professionals, via the hospital intranet, community and medical association newsletters, etc. Those interested will contact the research assist who will provide further information about the study objectives and procedures and will perform an initial eligibility screening interview by telephone.

### **Medical evaluation and enrolment procedure**

Participants found to be eligible will be invited to attend a medical examination, to confirm the CaTS diagnosis and assess eligibility to participate in the research project.

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- Inclusion criteria
1. Age  $\geq$ 18 years old;
2. Clinical diagnosis based on presenting symptoms, clinical history and physical tests, by using criteria developed from a consensus survey by the UK Primary Care Rheumatology Society;<sup>31</sup>
3. Mild to moderate CaTS,<sup>9</sup> with symptoms longer than 6 weeks duration; participants with bilateral CaTS will be designated their study hand based on the most severe symptoms;
- Mild: intermittent paraesthesia in the distribution of the median nerve
- Moderate: constant paraesthesia, and reversible numbness or pain of idiopathic nature
- Severe: constant pain, numbness or sensory loss in the wrist and hand (specifically palm, index, or middle finger, or thumb), or thenar muscle atrophy
4. Able to read and write in simplified Chinese (Mainland), understand and complete the questionnaire, and should provide informed consent.
- Exclusion criteria
- CaTS secondary to wrist deformity, trauma, mass, pregnancy, hypothyroidism, or inflammatory arthropathy;
- Treatment by NS, US or injection within the past 6 months, or previous carpal tunnel surgery;
- Previous surgery on the affected wrist (or study wrist if bilateral CaTS);
- Unable to tolerate the study interventions;
- Trauma to the affected upper limb requiring immobilization or surgery within the past 12 months;

- 222 ■ Inter-current illness including, poorly controlled thyroid disease or diabetes mellitus,  
223 vibration-induced neuropathy, inflammatory joint disease, osteoarthritis, suspected  
224 complex neurological and musculoskeletal conditions, et al.;
- 225 ■ Known abuse of drugs or alcohol;
- 226 ■ Allergy to any of the splint materials;
- 227 ■ Contraindications to US, including dermatological conditions, abnormal sensation  
228 in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy  
229 or breastfeeding, et al.

230 Following the medical evaluation, a research assistant will meet with the eligible  
231 participants and obtain written informed consent. Demographic variables will be  
232 reported before treatment (baseline) of all participants regarding age, sex, body mass  
233 index, affected elbow (whether bilateral), dominant arm, lifestyle (smoking and  
234 drinking), and previous medical history. Participants will also be asked relevant  
235 questions about duration of symptoms and previous treatments (rehabilitation exercises,  
236 injections or others). Others like occupation, employment characteristics (full-time or  
237 part-time work, manual or non-manual labor), employment status (whether on sickness  
238 absence), and professional activity characteristics (repetitive movements for >4  
239 hours/day; wrist flexion for >2 hours/day and use of computer keyboard/ mouse [how  
240 many hours/day]) will be also collected.

#### 241 **Randomization and blinding**

242 Participants will be randomized in three intervention groups (either US or NS or  
243 US+NS arm) in a ratio of 1:1:1, using a computer-generated randomized sequence with  
244 varying unknown block sizes (either 3 or 6) for all study centers, without stratification.  
245 A research assistant with no involvement in the clinical care and evaluations of  
246 participants will prepare sequentially numbered, opaque, sealed envelopes according to

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the randomization lists, with security in place to ensure allocation data cannot be accessed or influenced by any person. At the appropriate time, this assistant will open the envelope and assure coordination of the therapeutic interventions.

The outcome assessor and statistician will be blinded to group allocation and not involved in treatment procedures.

**Intervention**

At the beginning, all participants will attend a 20-30 minutes group education presentation by the research assistant on the same day as their baseline assessment. This presentation will cover the pathophysiology, treatment options, posture and activity modification principles of CaTS. This information will also be provided in the form of education booklets, encouraging participants to review at home. Changes in habits include limitation of wrist movement and reduction of heavy work activities, and the use of ergonomically friendly work tools can be useful in reducing median nerve stress.<sup>32,33</sup>

Participants in the [US group] will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm<sup>2</sup> for 15 minutes in 5 days per week for 6 weeks to the area over the carpal tunnel.

Participants allocated to the [NS group] will receive a splint to wear at night for 6 weeks. The splint immobilizes the wrist in a neutral or slightly extended position (20° from neutral) in order to avoid movement of the wrist, which increases carpal tunnel pressure.<sup>34</sup> Each splint will be fitted according to the size of the participant's hand and arm using standard splints of differing sizes. Participants will be shown how to fit and remove the wrist splint according to a standardized trial protocol. Adherence will be encouraged and reinforced by verbal instruction from the clinician on how and when to use the splint and this will be supported by written information, detailing care, fitting

272 and use of the splint. Participants will be instructed to perform gentle range-of-motion  
273 exercises when removing the splint to prevent stiffness.

274 Participants randomized to the [US+NS group] will receive both US for 6 weeks  
275 as in the [US group] and NS for 6 weeks as in the [NS group].

276 For participants with bilateral CTS, the non-study hand will be treated according  
277 to normal clinical protocols in use at the research site.

278 We discouraged additional treatments to that assigned (that is, not per protocol)  
279 during the intervention period, but we allowed the use of simple analgesics as needed.  
280 Participants reported all not per protocol treatments, such as drugs, in a diary.

## 281 **Data management**

282 Data will be collected during the participants' visits to the hospital at baseline, 3  
283 weeks, 6 weeks and 3 months after random assignment (**Table 1**). In order to maximize  
284 participant compliance in follow-up completion, reminder emails and a telephone call  
285 by the research assistant will be programmed. Registered participants will be withdrawn  
286 from the study if: (1) participant withdraws his/her consent, and (2) exclusion criteria  
287 is discovered after registration. The reason and date of discontinuation will be recorded.  
288 Consent to use the data already collected prior to a participant's withdrawal will be  
289 included in the consent form.

## 290 **Primary outcome measure**

291 The primary outcome measure will be the difference in Symptom Severity Scale  
292 of the Boston Carpal Tunnel Questionnaire (BCTQ-SSS). The BCTQ is a disease-  
293 specific questionnaire referring to a typical 24-hour period in the past two weeks,<sup>35</sup> and  
294 has been shown to be highly reproducible, internally consistent, valid and responsive  
295 to clinical change in CaTS.<sup>36</sup> It consists of two different subscales: Symptom Severity  
296 Scale (11 items, about symptom severity) and Functional Status Scale (8 items, about



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the degrees of difficulty on daily activities), both rated on a five-point scale, with final scores for each subscale result in mean scores between 1 and 5. The overall score is calculated as the mean of all 19 items. Higher scores represent more severe symptoms and functional impairment. We use a validated Chinese version<sup>37</sup> of the BCTQ in this study.

**Secondary outcome**

Secondary outcome measures will be the differences in Functional Status Scale of the Boston Carpal Tunnel Questionnaire (BCTQ-FSS), numerical rating scale (NRS)<sup>38,39</sup> for hand-wrist symptom intensity, shortened version of the Disabilities of the Arm, Shoulder and Hand (quick-DASH)<sup>40</sup> for upper limb disability, sleep questionnaire for interrupted sleep<sup>41</sup>, EuroQol-5D (EQ-5D)<sup>42</sup> for life quality and health status, Hospital Anxiety and Depression Scale (HADS)<sup>43</sup> for anxiety and depression status, Work Limitations Questionnaire (WLQ)-25<sup>44</sup> for functional limitations at work, Global Rating of Change (GROC) for treatment success and recurrence rate, Likert scale for participant’s satisfaction, physical function examination as well as various electrophysiology and ultrasound parameters.

■ Hand-wrist symptom intensity (pain severity and paresthesia/dysthesia)

The NRS will be used for symptom intensity evaluation, which is a 0-10 numerical rating scale. 0 point represents “no pain”, and 10 points represents “extremely severe pain”.<sup>38,39</sup> A minimum decrease of 1.3 points or 25% reduction in NRS is considered the minimal clinically important difference.<sup>45,46</sup>

■ Upper limb disability

The well-validated simplified Chinese (Mainland) version of Quick-DASH<sup>47</sup> will be used for elbow function evaluation, which consists of eleven questions scored on a 5-point scale similar to the DASH.<sup>40</sup> Total and individual module scores will be

calculated out of 100, with a higher score indicating a worse status. A minimal clinically important difference of 15.91 points has been reported.<sup>48</sup>

#### ■ Interrupted sleep

Sleep questionnaire will be used for sleep quality evaluation, which consists of 4 questions, asking about how many times during the last month participants have experienced.<sup>41</sup> Six response categories are available for each question, and are coded on a 0-5 scale in sequence: not at all, 1-3, 4-7, 8-14, 15-21 and 22-31 days. All questions are equally weighted and summed. Higher scores represent more interrupted sleep.

#### ■ Life quality and health status

The EQ-5D is one of the widely validated generic health-related quality of life (HRQoL) measures known as its simplicity.<sup>42</sup> It contains a five-dimension descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS, ranging from 0 to 1, in which 1 represents perfect health. All the dimensions are grouped into three levels (no problem, some problem and extreme problem). We used a validated Chinese version<sup>49,50</sup> of the EQ-5D, which has been recommended by China Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQoL and health utility.<sup>51</sup>

#### ■ Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders - anxiety and depression.<sup>43</sup> There is evidence of increased levels of anxiety and depression in people with LET.<sup>52</sup> HADS is a 14-item scale independent of somatic symptoms, which consists of two 7-item subscales measuring depression and anxiety respectively. A 4-point scale (from 0 representing absence of symptoms, to 3 representing maximum symptomatology) is used. The total scores for each subscale range from 0 to 21, with higher scores indicating higher levels of disorder.

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HADS has two cut offs for categorization: 0-7, “non-case”; 8-10, “possible or doubtful case”; 11-21, “probable or definite case”.<sup>53</sup>

■ Functional limitations at work

In order to gather information that is complementary to the pain and disability scales, functional limitations at work will be measured with the WLQ-25. It contains 25 items arranged under four subscales addressing four dimensions of job demands, those are, time demands, physical demands, mental/interpersonal demands, and output demands.<sup>44</sup> A five-level ordinal response scale ranging from 0 (all of the time) to 4 (none of the time) with an additional sixth option (does not apply to my job) is used. The total scores range from 0-100 points, and a 13-point (out of 100) improvement for the summed score is established for clinically important differences.<sup>54</sup>

■ Treatment success and recurrence rate

Participants’ treatment impression of change regarding their condition will be recorded on a 6-point Likert scale (from “completely recovered”, “much improved”, “somewhat improved”, “same”, “worse” to “much worse”). Success rates will be calculated by dichotomizing responses. Participants who report their overall condition as “completely recovered” or “much improved” since the beginning of the study will be counted as successes, while other responses will be counted as failures.<sup>55,56</sup> Recurrence will primarily be defined as occurring when a participant rates a success at 3 weeks and a failure at 6 weeks or 3 months on GROC.<sup>55,56</sup>

■ Participants’ satisfaction

Similarly, participants’ level of satisfaction on the evolution of their condition will be determined on a validated 5-point Likert scale ranging from “very satisfied”, “quite satisfied”, “no opinion”, “not very satisfied” to “not at all satisfied”.<sup>57,58</sup>

■ Physical function examination

372 The physical examinations will include measurement of 2-point discrimination  
373 (performed on the radial and ulnar aspects of each digit), grip strength with a  
374 dynamometer (CAMRY, City of Industry, CA, USA), and pinch strength with the pinch  
375 gauge (three trials for each hand). The affected side will be measured first and then the  
376 unaffected side. The measurement readings will be not revealed to the subjects until the  
377 completion of the test. The mean of three consecutive trials, separated by a 20s pause,  
378 will be calculated. Results will be presented as a ratio of values of the symptomatic  
379 side/ asymptomatic side $\times 100$ .<sup>59</sup>

380 2 point discrimination testing was started with a distance of 4 mm and successively  
381 increased if necessary by 2 mm. Grip strength and 3 point pinch strength, measured  
382 with the Baseline dynamometer and pinch gauge (Chattanooga Group, Hixson,  
383 Tennessee, USA), respectively, were recorded (three trials for each hand).

#### 384 ■ Electrophysiological Study

385 Median nerve distal motor latency (DML), compound muscle action potential  
386 (CMAP), sensory nerve conduction velocity (SNCV) and sensory nerve action potential  
387 (SNAP) amplitudes will be recorded.<sup>55,56</sup> DML and CMAP were measured by placing  
388 surface electrodes on the abductor pollicis brevis muscle, and stimulation was applied  
389 8 cm proximal to the active recording electrode. SNAP and SNCV were obtained by  
390 using a ring electrode, which was placed on the proximal and distal interphalangeal  
391 joints of the index finger. The sensory conduction study was stimulated antidromically  
392 14 cm proximal to the active electrode. Motor study was performed by supramaximal  
393 stimulation while the amplitude was measured an average of 10 times for the sensory  
394 study. All measurements will be made 3 times, and the values obtained will be averaged  
395 for analysis.

#### 396 ■ US parameters

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The cross-sectional area (CSA) was measured using an electronic caliper at the scaphoid-pisiform level.<sup>38,39</sup> The measurements will be made 3 times, and the values obtained will be averaged for analysis.

**Adverse events**

All adverse events, defined as any negative or unwanted reactions to intervention, will be recorded through the symptoms reported by the patients, and observations by a researcher at every visit. US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. NS treatment may cause skin allergy, wrist stiffness, et al. The participants will be instructed to do gentle range of motion exercises when removing the splint to prevent stiffness and reinforced adherence by verbal instruction.

**Sample size calculation**

Sample size and power calculation are based on the primary outcome of BCTQ score. All sample size calculations assume two-sided analysis with a power of 90% (1- $\beta=0.90$ ) at a significant level of  $\alpha=0.05$ . Based on previous trial, a standard deviation (SD) of 0.38-point on BCTQ-SSS score will be used.<sup>60</sup> To detect a minimum clinically significant difference of 0.8-point<sup>58</sup> (superiority margin) between US+NS and NS groups (assuming a true difference of 1.18-point<sup>27,60</sup>), a total of 18 participants in each group is required. Allowing for an up to 15% drop out rate, we aim to enroll at least 21 participants in each group to complete the study.

**Analysis plan**

Baseline characteristics will be summarized for the three treatment groups using appropriate descriptive statistics. Both primary and secondary analysis will be conducted blind to treatment allocation and analyzed on intention-to-treat (ITT)<sup>61</sup> approach with all randomized participants retaining their original randomized group.

Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and non-responses if these missing data are judged to be random.

The primary comparisons for BCTQ-SSS scores will be made using linear regression. In secondary analyses, repeated measures mixed model<sup>62</sup> will also be used to examine the associations between treatments and repeated outcome measures, with terms of treatment, time, trial center and corresponding baseline values as covariates (age, gender, body mass index, et al.). Linear regression will be used for numerical outcomes, and logistic/ordinal regression for any categorical outcomes.

#### **Quality assurance/monitoring/management**

A Manual of Operations and Procedures (MOP) and case report form will be developed as per protocol to standardize all procedures and staff training in areas such as patient recruitment, outcome measurement, data entry, management, analysis, and security, which also include the monitoring plans to assure patient protection and data integrity, thus facilitating consistency in protocol implementation and data collection. The investigators, physicians, research assistants, outcome assessors and statisticians are different people, and should receive Good Clinical Practice training. A trained project manager will visit each center for monitoring to ensure data quality and compliance with trial protocol.

All data obtained will be kept strict and stored electronically on a database with secured and restricted access. An encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

#### **Study duration**

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Recruitment of the trial will begin in the November of 2021 and 3-month follow-up for all participants is anticipated to be completed by June 2022. See **Table 1** for time points and recruitment progress.

**Ethics and dissemination**

The study has been approved by all 4 Medical Ethics Committees (the approval number of the leading clinical center [Shanghai Sixth People’s Hospital] is 2021-152) and will be conducted according to the principle of the Declaration of Helsinki (64th, 2013). All requirements regarding the welfare, rights and privacy of participants are fulfilled. The potential risks of this clinical trial are considered to be minimal and are addressed in the protocol and consent forms. A written consent will be obtained by clinical practitioners from each participant. The trial was registered on [www.chictr.org](http://www.chictr.org) website (registration number ChiCTR2100050701). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

## DISCUSSION

CaTS is a highly prevalent compression neuropathy, which results in significant paraesthesia and numbness in the median nerve distribution, especially nocturnal symptoms causing sleep disturbance, causing great socioeconomic burden. Up till now, there is still no consensus on the optimal management, and nonoperative treatment is generally accepted as the first-line intervention for mild and moderate CaTS. Multiple methods have been studied and reviewed in the recent decades, however, the exact efficacy still remains controversial.

In an RCT published in BMJ for mild to moderate CaTS, active US treatment (1 MHz, 1.0 W/cm<sup>2</sup>) was applied to the area over the carpal tunnel in the experimental group, and indistinguishable sham US treatment was applied in the control group.<sup>23</sup> At 6 months' follow up, satisfactory improvement or complete remission of symptoms was observed in 74% receiving active treatment, which is significantly higher than those receiving sham treatment (20%). As for electroneurography, DML and SNCV improved significantly with active treatment while remained unchanged with sham treatment. Hand grip and finger pinch strength in physical examination also improved significantly with active treatment. All results suggested satisfying effects from US treatment for CaTS.

US can also be used as part of a multi-intervention approach. Some studies have compared NS alone to NS combined with US in treatment of CaTS, while the effects were different, and the grades of study design and data were low. Dincer U et al.<sup>26</sup> found that the improvements in the combined group were statistically significantly better ( $p=0.043$ ) than those in NS alone group in BCTQ-SSS, as well as BCTQ-FSS ( $p<0.001$ ), and VAS for pain ( $p<0.001$ ). Similar results were also reported by Baysal O et al.<sup>63</sup>;



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while Jothi KP et al.<sup>27</sup>, Sim SE et al.<sup>28</sup> and Armagan O et al.<sup>29</sup> found US therapy may add no benefit to splinting in CaTS.

In this study, to the best of our knowledge, it is the first to compared the efficacy between US [US group] and NS [NS group] in CaTS treatment. What's more, the additional effects of US [US+NS group] in a multi-intervention approach will be compared with NS alone [NS group]. In clinic, US is less invasive, less expensive, safer and more portable than other nonoperative therapy like drug injections for compression neuropathy and, if proved to be effective, could be offered to selected patients as part of non-operative therapy.

There are some on-going clinical trials on CaTS treatment recent years,<sup>64-67</sup> and our prospective randomized study proposes to complement and add to this relevant and much needed scientific effort.

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683 **Figure Legends**

684 **Figure 1** Participant flow chart

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**Table 1** Study evaluation procedures and timeline

Study procedure	Medical evaluation	Enrolment visit	3 weeks	6 weeks	3 months
Determine eligibility	√	√			
Obtain signed consent		√			
Obtain medical and demographic data		√			
Give instructions for Pain medication diary		√			
Outcome measures					
Boston Carpal Tunnel Questionnaire		√	√	√	√
Numerical rating scale for hand-wrist symptom intensity		√	√	√	√
Shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire		√	√	√	√
Interrupted sleep questionnaire		√	√	√	√
EuroQol-5D		√	√	√	√
Hospital Anxiety and Depression Scale		√	√	√	√
Work Limitations Questionnaire-25		√	√	√	√
Treatment success rate				√	√
Treatment recurrence rate				√	√

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Participants' satisfaction

✓ ✓ ✓

Physical examination

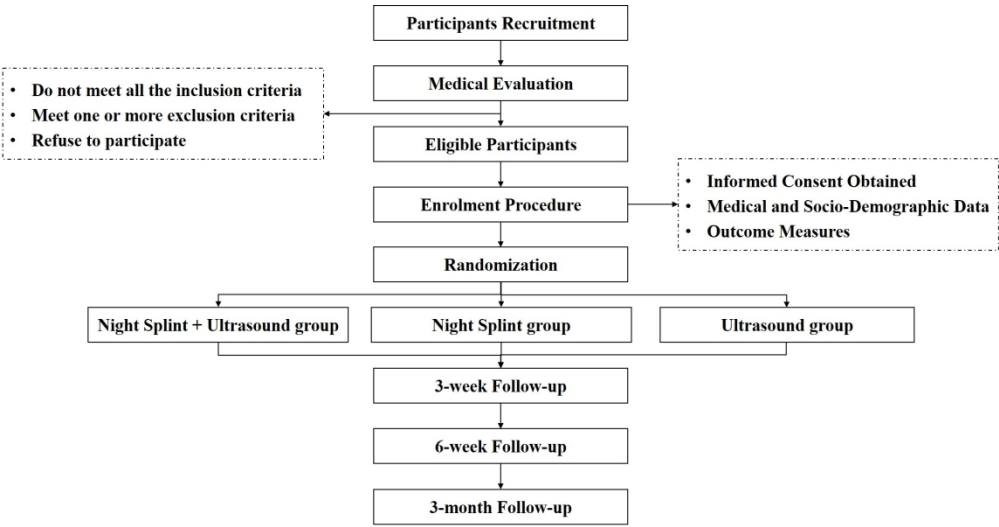
✓ ✓ ✓

Electrophysiological and ultrasound parameters

✓ ✓ ✓

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Participant flow chart

365x190mm (150 x 150 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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			Page
Reporting Item			Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered,	4/6

1		name of intended registry	
2			
3			
4	Trial registration: data	<a href="#">#2b</a> All items from the World Health Organization Trial	4/6
5			
6	set	Registration Data Set	
7			
8			
9	Protocol version	<a href="#">#3</a> Date and version identifier	5
10			
11			
12	Funding	<a href="#">#4</a> Sources and types of financial, material, and other support	3
13			
14			
15	Roles and	<a href="#">#5a</a> Names, affiliations, and roles of protocol contributors	2
16			
17	responsibilities:		
18			
19	contributorship		
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22			
23	Roles and	<a href="#">#5b</a> Name and contact information for the trial sponsor	2
24			
25	responsibilities:		
26			
27	sponsor contact		
28			
29	information		
30			
31			
32	Roles and	<a href="#">#5c</a> Role of study sponsor and funders, if any, in study design;	2
33			
34	responsibilities:	collection, management, analysis, and interpretation of	
35			
36	sponsor and funder	data; writing of the report; and the decision to submit the	
37		report for publication, including whether they will have	
38		ultimate authority over any of these activities	
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44	Roles and	<a href="#">#5d</a> Composition, roles, and responsibilities of the coordinating	2
45			
46	responsibilities:	centre, steering committee, endpoint adjudication	
47			
48	committees	committee, data management team, and other individuals	
49		or groups overseeing the trial, if applicable (see Item 21a	
50		for data monitoring committee)	
51			
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57	Introduction		
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Background and rationale	<a href="#">#6a</a>	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-9
Background and rationale: choice of comparators	<a href="#">#6b</a>	Explanation for choice of comparators	8-9
Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	10
Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	10
<b>Methods:</b>			
<b>Participants, interventions, and outcomes</b>			
Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	11-12



1		surgeons, psychotherapists)	
2			
3			
4	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	13-14
5			
6	description	replication, including how and when they will be	
7			
8		administered	
9			
10			
11	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated	13-14
12			
13	modifications	interventions for a given trial participant (eg, drug dose	
14			
15		change in response to harms, participant request, or	
16		improving / worsening disease)	
17			
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20			
21	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols,	13-14
22			
23	adherence	and any procedures for monitoring adherence (eg, drug	
24			
25		tablet return; laboratory tests)	
26			
27			
28			
29	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are	13-14
30			
31	concomitant care	permitted or prohibited during the trial	
32			
33			
34	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the	14-19
35			
36		specific measurement variable (eg, systolic blood	
37			
38		pressure), analysis metric (eg, change from baseline, final	
39			
40		value, time to event), method of aggregation (eg, median,	
41			
42		proportion), and time point for each outcome. Explanation	
43			
44		of the clinical relevance of chosen efficacy and harm	
45			
46		outcomes is strongly recommended	
47			
48			
49			
50			
51	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any	20-21
52			
53		run-ins and washouts), assessments, and visits for	
54			
55		participants. A schematic diagram is highly recommended	
56			
57		(see Figure)	
58			
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Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
<b>Methods: Assignment of interventions (for controlled trials)</b>			
Allocation: sequence generation	<a href="#">#16a</a>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12-13
Allocation concealment mechanism	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-13
Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12-13

1	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	12-13
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
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6				
7				
8	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	12-13
9	emergency		permissible, and procedure for revealing a participant's	
10	unblinding		allocated intervention during the trial	
11				
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16	<b>Methods: Data</b>			
17	<b>collection,</b>			
18	<b>management, and</b>			
19	<b>analysis</b>			
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26	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	14, 19-
27			and other trial data, including any related processes to	21
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
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43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-	14, 19-
44	retention		up, including list of any outcome data to be collected for	21
45			participants who discontinue or deviate from intervention	
46			protocols	
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53	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	14, 19-
54			including any related processes to promote data quality	21
55			(eg, double data entry; range checks for data values).	
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		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
Statistics: additional analyses	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-20
<b>Methods: Monitoring</b>			
Data monitoring: formal committee	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14, 19-21
Data monitoring: interim analysis	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14, 19-21
Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	19

1		conduct	
2			
3			
4	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any,	19
5			
6		and whether the process will be independent from	
7			
8		investigators and the sponsor	
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11	Ethics and		
12			
13	dissemination		
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16	Research ethics	<a href="#">#24</a> Plans for seeking research ethics committee / institutional	21
17			
18	approval	review board (REC / IRB) approval	
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21			
22	Protocol	<a href="#">#25</a> Plans for communicating important protocol modifications	21
23			
24	amendments	(eg, changes to eligibility criteria, outcomes, analyses) to	
25			
26		relevant parties (eg, investigators, REC / IRBs, trial	
27			
28		participants, trial registries, journals, regulators)	
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32	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or assent from potential	21
33			
34		trial participants or authorised surrogates, and how (see	
35			
36		Item 32)	
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39	Consent or assent:	<a href="#">#26b</a> Additional consent provisions for collection and use of	21
40			
41	ancillary studies	participant data and biological specimens in ancillary	
42			
43		studies, if applicable	
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47	Confidentiality	<a href="#">#27</a> How personal information about potential and enrolled	21
48			
49		participants will be collected, shared, and maintained in	
50			
51		order to protect confidentiality before, during, and after the	
52			
53		trial	
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57	Declaration of	<a href="#">#28</a> Financial and other competing interests for principal	21
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interests		investigators for the overall trial and each study site	
Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14, 19-21
Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19-21
Dissemination policy: trial results	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19-21
Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	19-21
Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19-21
<b>Appendices</b>			
Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	/
Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	/

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# BMJ Open

## Effectiveness of ultrasound therapy for the treatment of carpal tunnel syndrome (the USTINCTS trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057541.R1
Article Type:	Protocol
Date Submitted by the Author:	19-Jan-2022
Complete List of Authors:	Chen, Shuai; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration, Sun, Ziyang; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration Liu, Weixuan; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration Sun, Guixin; Shanghai East Hospital, Tongji University School of Medicine, Department of Orthopaedics Liu, Junjian; Shanghai Tenth People's Hospital, Wang, Jian; Pudong New Area People's Hospital, Department of Orthopedics Wang, Wei; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration Zheng, Yuanyi; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Ultrasound in Medicine Fan, Cunyi; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration
<b>Primary Subject Heading</b>:	Sports and exercise medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	REHABILITATION MEDICINE, SPORTS MEDICINE, Hand & wrist < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY

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# **TITLE PAGE**

## **Title**

Effectiveness of ultrasound therapy for the treatment of carpal tunnel syndrome (the USTINCTS trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

## **Running Title**

study protocol of USTINCTS trial for carpal tunnel syndrome

## **Keywords**

Carpal tunnel syndrome, randomised controlled trial, ultrasound therapy, night splint, Boston Carpal Tunnel Questionnaire

## **Word count**

3958 words

## **Authors and information**

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**Author Contributions**

46

CS and SZY are the primary investigators.

47

CS, SZY, LWX, ZYY, FCY participated in the development of the study design.

48

CS, SZY, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the study

49

conduct.

50

CS, SZY and LWX drafted the manuscript under FCY's supervision.

FCY contributed to applying for and gaining funding.

All authors contributed to the content and critical revision and approved the final draft of the manuscript.

### **Conflict of interests**

The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

The authors declare no competing financial interests.

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76 Innovation Studio of Shanghai Jiao Tong University School of Medicine.

77

78 **ETHICS**

79 The study has been approved by all 4 Medical Ethics Committees, those are,  
80 Ethics Committee of Shanghai Sixth People’s Hospital (the leading clinical center,  
81 approval No. 2021-152), Ethics Committee of Shanghai East Hospital  
82 (EC.D(BG).016.03.1-2021-095), Ethics Committee of Shanghai Tenth People’s  
83 Hospital (SHSY-IEC-4.1/21-194/01), and Ethics Committee of Pudong New Area  
84 People’s Hospital (IRBY2021-006). The research registry number is  
85 ChiCTR2100050701 at <http://www.chictr.org.cn>. Data will be analyzed anonymously;  
86 all patients will approve the results of this study by written consent. The written  
87 consent approval will be documented in the patients’ files. All clinical investigations  
88 will be conducted in accordance with the guidelines of the Declaration of Helsinki.

89

## 90 **ABSTRACT**

### 91 **Introduction**

92 There has no consensus on optimal management of carpal tunnel syndrome  
93 (CaTS), the most common compression neuropathy. Conservative therapy is generally  
94 accepted as first-line intervention. Ultrasound (US) therapy has been widely reported  
95 to be treatment beneficial in nerve regeneration and conduction, and further accelerate  
96 compression recovery. The purpose of this study is to investigate the effectiveness of  
97 US for CaTS treatment.

### 98 **Methods and analysis**

99 This study protocol entails a three-arm, prospective, multicenter, randomised  
100 controlled trial. 162 eligible adult participants diagnosed with mild to moderate CaTS  
101 by using criteria developed from a consensus survey by the UK Primary Care  
102 Rheumatology Society will be assigned to either (1) US, (2) night splint (NS) or (3)  
103 US+NS (combined) group. Primary outcome will be difference in Symptom Severity  
104 Scale of Boston Carpal Tunnel Questionnaire (BCTQ-SSS) at 6-week between NS  
105 and US+NS groups. Secondary outcomes include Functional Status Scale of BCTQ,  
106 numerical rating scale for hand-wrist symptom intensity, shortened version of the  
107 Disabilities of the Arm, Shoulder and Hand for upper limb disability, sleep  
108 questionnaire for interrupted sleep, EuroQol-5D for general health, Hospital Anxiety  
109 and Depression Scale for mental status, Work Limitations Questionnaire-25 for  
110 functional limitations at work, Global Rating of Change for treatment success and  
111 recurrence rate, Likert scale for participant's satisfaction, physical examination,  
112 electrophysiological and ultrasound parameters. Intention-to-treat analyses will be  
113 used.

### 114 **Ethics and dissemination**

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115 Ethics Committees of all clinical centers have approved this study. The leading  
116 center is Shanghai Sixth People’s Hospital, whose approval number is 2021-152. New  
117 versions with appropriate amendments will be submitted to the committee for further  
118 approval. Final results will be published in peer-reviewed journals and presented at  
119 local, national and international conferences.

120 **Trial registration number**

121 ChiCTR2100050701.

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## 123 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 124 ● Ultrasound (US) as independent or adjunct therapy in treating carpal tunnel  
125 syndrome (CaTS).
- 126 ● The first randomised controlled trial (RCT) to compared the efficacy between US  
127 and night splint in CaTS treatment.
- 128 ● Multicenter RCT with blinded outcome assessor and statistician.
- 129 ● Use of several patient-reported outcome measures as well as objective  
130 parameters.
- 131 ● Participants and treating surgeons not blinded.

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**INTRODUCTION**

Carpal tunnel syndrome (CaTS), the most common compression neuropathy, results from median nerve entrapment in the carpal tunnel, accounting for about 90% of all such disorders.<sup>1,2</sup> The clinically confirmed CaTS prevalence was 9.6% in the general population of China,<sup>3</sup> with a yearly incidence rate of 2.76%, and women is more susceptible than men.<sup>2,4</sup> CaTS has significant impact on daily life and ability to work,<sup>5</sup> and causes great burden on social economy, with an annual associated costs estimated at \$13 billion.<sup>6</sup> Classically, CaTS causes discomfort, paraesthesia and numbness in the median nerve distribution; and nocturnal symptoms are often clinically significant causing sleep disturbance.<sup>7</sup> Patients can be diagnosed by clinical history and physical examination; while electrophysiological methods will be additional for insufficient diagnosis by clinical findings and severe cases that need surgical management.<sup>8</sup>

In general, the severity of CaTS can be classified into mild, moderate and severe.<sup>9</sup> Non-surgical interventions are suggested to be the first choice to treat mild and moderate CaTS.<sup>10</sup> To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. A consensus of multidisciplinary treatment guideline from the European HANDGUIDE Study suggests that “education” should be included as the first-line management approach, which has the advantages of low cost, high efficacy and non-invasive.<sup>7,11</sup> In addition, “night splint (NS)” and “corticosteroid injection (CI)” are also recommended in guidelines of American Academy of Orthopaedic Surgeons (AAOS) and American Physical Therapy Association (APTA).<sup>12,13</sup> One recent RCT published in Lancet compares both two methods, and finds that CI has superior clinical effectiveness at 6 weeks than NS, but no differences at 6 months; while CI may bring adverse events

like thinning, lightening or darkening of the skin at the injection site, hot flushes and even more pain.<sup>9</sup> Systematic reviews have also shown that the effects of other conservative treatments like acupuncture,<sup>14</sup> exercise and mobilization interventions,<sup>15</sup> laser,<sup>16</sup> extracorporeal shockwave therapy<sup>17</sup> and platelet-rich plasma injection<sup>18</sup> still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. In the intensity range of 0.5-2.0 W/cm<sup>2</sup>, US may have the potential to induce a variety of biophysical effects in tissues.<sup>19</sup> US experiments on stimulation of nerve conduction and regeneration,<sup>20,21</sup> and discoveries of its anti-inflammatory effects<sup>22</sup> all support that US may promote recovery of nerve compression. An RCT published in BMJ showed more pronounced subjective symptoms and electroneurographic variables for US treatment than sham control in patients with mild to moderate CaTS.<sup>23</sup> However, to our best of knowledge, no study has compared the efficacy between NS and US in CaTS treatment yet. Additionally, some studies have also reported the efficacy of US to be used as part of a multi-intervention approach, but with low grade of study design and data<sup>24-29</sup>. Therefore, the role of US in CaTS treatment still needs to be further explored by high-quality study.

Therefore, the purpose of the current three-arm, prospective, randomized, multicenter trial is to examine the effectiveness of US in treatment for CaTS, that is, NS+US (combined) versus NS versus US, on clinical and functional outcomes, including Boston Carpal Tunnel Questionnaire (BCTQ) in patients diagnosed with CaTS.

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**METHODS**

**Study design**

This study is a three-arm, prospective, multicenter, randomized controlled trial that will recruit participants from 4 municipal tertiary hospitals with a diagnosis of mild to moderate CaTS. The multi-centres are Shanghai Sixth People’s Hospital, Shanghai Tenth People’s Hospital, Shanghai East Hospital, and Pudong New Area People’s Hospital of Shanghai, respectively. This manuscript is written according to the SPIRIT guidelines.<sup>30</sup>

**Participant and public involvement**

There was no participant involvement in this study. Participants were not invited to make comments or suggestions on the protocol, were not consulted about the selection of patient-relevant evaluation outcomes, or were invited to participate in writing or editing the manuscript to improve readability or accuracy. The final findings will be disseminated to the public through mass media. Our published papers and conference presentations also acknowledge all participants as a whole.

**Participant recruitment**

**Figure 1** shows the participant flow chart throughout the study. Participants will be recruited over a 5-month period from outpatient clinics of 4 principals in each sub-centre. In addition, recruitment can also be through other doctors and healthcare professionals. Interested participants can contact the research assistant, who will provide more information about the study purpose and protocol, and conduct an initial eligibility screening by phone.

**Medical evaluation and enrolment procedure**

Eligible participants will be invited to participate in a physical examination to confirm CaTS diagnosis and assess eligibility to participate in the program.

206 Inclusion criteria

207 ■ Age  $\geq 18$  years old;

208 ■ Clinical diagnosis on the basis of clinical symptoms, history and physical  
209 examination, using criteria developed from a consensus survey by the UK Primary  
210 Care Rheumatology Society;<sup>31</sup>

211 ■ Mild to moderate CaTS,<sup>9</sup> with symptoms longer than 6 weeks duration;  
212 participants with bilateral CaTS will be designated their study hand based on the  
213 most severe symptoms;

214 ■ Mild: intermittent paraesthesia in the distribution of the median nerve

215 ■ Moderate: constant paraesthesia, and reversible numbness or pain of  
216 idiopathic nature

217 ■ Severe: constant pain, numbness or sensory loss in the wrist and hand  
218 (specifically palm, index, or middle finger, or thumb), or thenar muscle  
219 atrophy

220 ■ Able to read and write in simplified Chinese (Mainland), understand and complete  
221 the questionnaire, and should provide informed consent.

222 Exclusion criteria

223 ■ CaTS secondary to wrist deformity, trauma, mass, pregnancy, hypothyroidism, or  
224 inflammatory arthropathy;

225 ■ Treatment by NS, US or injection within the past 6 months, or previous carpal  
226 tunnel surgery;

227 ■ Previous surgery on the affected wrist (or study wrist if bilateral CaTS);

228 ■ Unable to tolerate the study interventions;

229 ■ Trauma to the affected upper limb requiring operation or immobilization within  
230 the past 12 months;

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- 231 ■ Inter-current illness including, poorly controlled diabetes mellitus or thyroid
- 232 disease, vibration-induced neuropathy, osteoarthritis or inflammatory joint
- 233 disease, suspected complex neurological and musculoskeletal conditions, et al.;
- 234 ■ Known drugs or alcohol abuse;
- 235 ■ Allergy to any of the splint materials;
- 236 ■ Contraindications to US, including dermatological conditions, abnormal sensation
- 237 in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy
- 238 or breastfeeding, et al.
- 239 Following the medical evaluation, a research assistant will meet with the eligible
- 240 participants and obtain their written informed consent. Demographic variables such as
- 241 age, sex, body mass index, affected elbow (whether bilateral), dominant arm, lifestyle
- 242 (smoking and alcohol use), and medical history of all participants will be collected
- 243 prior to treatment (baseline). Participants will also be asked relevant questions about
- 244 symptoms duration and previous treatments (rehabilitation exercises, injections or
- 245 others). Others like occupation, employment characteristics (full-time or part-time
- 246 work, manual or non-manual labor), employment status (whether on sickness
- 247 absence), and professional activity characteristics (repetitive movements for >4
- 248 hours/day; wrist flexion and extension for >2 hours/day and use of computer
- 249 keyboard/ mouse [how many hours/day]) will be also collected.

250 **Randomization and blinding**

251 Participants will be randomized in three intervention groups (either US or NS or

252 US+NS arm) in a ratio of 1:1:1, using a computer-generated randomized sequence

253 with varying unknown block sizes (either 3 or 6) for all study centres, without

254 stratification. A research assistant who are not involved in clinical care and participant

255 evaluations will prepare sequentially numbered, opaque, sealed envelopes based on a

random list, and ensure that the allocation data will not be accessed or influenced by anyone. When appropriate, the assistant will open envelopes and ensure coordination of therapeutic interventions.

The outcome assessor and statistician will be blinded to group allocation and not involved in treatment procedures.

## **Intervention**

At the beginning, all participants will participate in an about 30-minute group educational presentation by a research assistant on the same day as the baseline assessment. This presentation will cover the pathophysiology, treatment options, posture and activity modification principles of CaTS. The above information will also be provided to participants in the form of education booklets, to encourage them to review at home. Habits changes include limited wrist movement and a reduction in strenuous work activities, and the use of ergonomically friendly work tools helps reduce median nerve pressure.<sup>32,33</sup>

Participants in the [US group] will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm<sup>2</sup> for 15 minutes in 5 days per week for 6 weeks to the area over the carpal tunnel.

Participants allocated to the [NS group] will receive a splint to wear at night for 6 weeks. The splint holds the wrist in a neutral position or slightly extended 20° from the neutral position to avoid wrist movement, which can increase pressure on the carpal tunnel.<sup>34</sup> The choose of each splint will be based on the size of individual participant's hands and arms. Participants will be shown how to fit and remove the wrist splint according to a standardized trial protocol. Oral guidance from the clinician on how and when to use splints will encourage and reinforce compliance, which will be also supported by written information, detailed care, and splint fitting

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281 and use. Participants will be instructed to perform gentle range-of-motion exercises  
282 when removing the splint to prevent stiffness.

283 Participants randomized to the [US+NS group] will receive both US for 6 weeks  
284 as in the [US group] and NS for 6 weeks as in the [NS group].

285 For participants with bilateral CTS, the non-study hand will be treated according  
286 to normal clinical protocols in use at the research site.

287 We discouraged additional treatments to that assigned (that is, not per protocol)  
288 during the intervention period, but we allowed the use of simple analgesics as needed.  
289 Participants reported all not per protocol treatments, such as drugs, in a diary.

290 **Data management**

291 Data will be collected during the participants' visits to the hospital at baseline, 6  
292 weeks, 3 months, 6 months, and one-year after random assignment (**Table 1**).  
293 Reminder emails and phone calls from the research assistants will be programmed to  
294 maximize participant compliance in subsequent completion. A registered participant  
295 will withdraw from the study if (1) the participant withdraws his/her consent, and (2)  
296 exclusion criteria is found after registration. The cause and date of suspension will be  
297 recorded. Consent to use data that has been collected before the participant's  
298 withdrawal will be included in the consent form.

299 **Primary outcome measure**

300 The primary outcome measure will be the difference in Symptom Severity Scale  
301 of the Boston Carpal Tunnel Questionnaire (BCTQ-SSS) at 6-week. The BCTQ is a  
302 disease-specific questionnaire referring to a typical 24-hour period in the past two  
303 weeks,<sup>35</sup> and has been shown to be highly reproducible, internally consistent, valid  
304 and responsive to clinical change in CaTS.<sup>36</sup> It consists of two different subscales:  
305 Symptom Severity Scale (11 items, about symptom severity) and Functional Status

Scale (8 items, about the degrees of difficulty on daily activities), both rated on a five-point scale, with final scores for each subscale result in mean scores between 1 and 5. The overall score is calculated as the mean of all 19 items. Higher scores represent more severe symptoms and functional impairment. We use a validated Chinese version<sup>37</sup> of the BCTQ in this study.

### Secondary outcome

Secondary outcome measures will be the differences in Functional Status Scale of the Boston Carpal Tunnel Questionnaire (BCTQ-FSS), numerical rating scale (NRS)<sup>38,39</sup> for hand-wrist symptom intensity, shortened version of the Disabilities of the Arm, Shoulder and Hand (quick-DASH)<sup>40</sup> for upper limb disability, sleep questionnaire for interrupted sleep<sup>41</sup>, EuroQol-5D (EQ-5D)<sup>42</sup> for life quality and health status, Hospital Anxiety and Depression Scale (HADS)<sup>43</sup> for anxiety and depression status, Work Limitations Questionnaire (WLQ)-25<sup>44</sup> for functional limitations at work, Global Rating of Change (GROC) for treatment success and recurrence rate, Likert scale for participant's satisfaction, physical function examination as well as various electrophysiology and ultrasound parameters.

#### ■ Hand-wrist symptom intensity (pain severity and paresthesia/dysthesia)

The NRS will be used for symptom intensity evaluation, which is a 0-10 numerical rating scale. 0 point represents "no symptom", and 10 points represents "extremely severe symptom".<sup>38,39</sup> A minimum decrease of 1.3 points or 25% reduction in NRS is considered the minimal clinically important difference.<sup>45,46</sup>

#### ■ Upper limb disability

Elbow function assessment will be conducted using a well-validated Simplified Chinese (Mainland) Version of Quick-DASH,<sup>47</sup> consisting of 11 questions on a 5-point scale similar to the DASH.<sup>40</sup> The overall score and individual modules will be



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calculated out of 100 points, with higher scores indicating worse status. The minimal clinically important difference was reported to be 15.91 points.<sup>48</sup>

■ Interrupted sleep

The sleep questionnaire, which will be used to assess sleep quality, consists of four questions asking participants how many times they have experienced it in the last month.<sup>41</sup> Each question has six response categories and are coded in 0-5 order: not at all, 1-3, 4-7, 8-14, 15-21 and 22-31 days. All questions have equal weights and add up. Higher scores are associated with more disrupted sleep.

■ Life quality and health status

EQ-5D has been widely validated and used to measure generic health-related quality of life (HRQoL) due to its simplicity.<sup>42</sup> It consists of a five-dimensional description system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS that scales from 0 to 1, where 1 represents perfect health. All dimensions are divided into three levels (no problem, some problem and extreme problem). We used a validated Chinese version<sup>49,50</sup> of EQ-5D, which has been recommended by Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQoL and health utility.<sup>51</sup>

■ Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders - anxiety and depression.<sup>43</sup> There is evidence of increased anxiety and depression in LET patients.<sup>52</sup> The HADS is a 14-item scale independent of physical symptoms and consists of two 7-item subscales measuring depression and anxiety, respectively. A 4-point scale (0 for absence of symptoms, and 3 for maximum symptomatology) is used. Each subscale has an overall score ranging from 0 to 21, with a higher score indicating a higher degree of impairment. HADS has two

cut offs for categorization: 0-7, “non-case”; 8-10, “possible or doubtful case”; 11-21, “probable or definite case”.<sup>53</sup>

#### ■ Functional limitations at work

To gather information that is complementary to the pain and disability scales, functional limitations at work will be measured using WLQ-25. It contains 25 items, arranged under four sub-scales, covering four dimensions of job demands, namely time demands, physical demands, mental/interpersonal demands, and output demands.<sup>44</sup> A five-level ordinal response scale ranging from 0 (all of the time) to 4 (none of the time) with an additional sixth option (does not apply to my job) is used. The overall score ranges from 0 to 100, with an increase of 13 points (out of 100) for clinically important differences.<sup>54</sup>

#### ■ Treatment success and recurrence rate

Participants' treatment impressions of changes in their condition (ranging from “completely recovered”, “much improved”, “somewhat improved”, “same”, “worse” to “much worse”) will be recorded on a six-level Likert scale. The success rate will be calculated by dichotomizing the response. Participants who report “completely recovered” or “much improved” in their overall condition since the study beginning will be considered successful, while other responses will be considered failures.<sup>55,56</sup> Recurrence will be defined primarily as when a participant rates a success at 6 weeks and a failure at 3 months, 6 months or one-year on GROC.<sup>55,56</sup>

#### ■ Participants' satisfaction

Similarly, participants' level of satisfaction on the evolution of their condition will be determined on a validated 5-point Likert scale ranging from “very satisfied”, “quite satisfied”, “no opinion”, “not very satisfied” to “not at all satisfied”.<sup>57,58</sup>

#### ■ Physical function examination

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The physical examinations will include measurement of 2-point discrimination (performed on the radial and ulnar aspects of each digit), grip strength with a dynamometer (CAMRY, City of Industry, CA, USA), and pinch strength with the pinch gauge (three trials for each hand). The affected side will be measured first and then the unaffected side. The measurement readings will be not revealed to the subjects until the completion of the test. The mean of three consecutive trials, separated by a 20s pause, will be calculated. Results will be presented as a ratio of values of the symptomatic side/ asymptomatic side $\times 100$ .<sup>59</sup>

The 2-point discrimination test starts at a distance of 4 mm and increases continuously by 2 mm as necessary. Grip strength and 3-point pinching force (3 tests per hand) as measured with baseline dynamometer and pinch gauge (Chattanooga Group, Hixson, Tennessee, USA) will be recorded.

■ Electrophysiological Study

Median nerve distal motor latency (DML), compound muscle action potential (CMAP), sensory nerve conduction velocity (SNCV) and sensory nerve action potential (SNAP) amplitudes will be recorded.<sup>55,56</sup> DML and CMAP will be measured by placing surface electrodes on the abductor pollicis brevis muscle, and stimulation applied 8 cm proximal to the active recording electrode. SNAP and SNCV will be obtained using ring electrodes placed on the proximal and distal interphalangeal joints of the index finger. Sensory conduction will be studied by antidromically stimulation at 14 cm proximal to the active electrode. Motor study will be performed by supramaximal stimulation while the amplitude will be measured an average of 10 times for the sensory study. All measurements will be made 3 times, and the values obtained will be averaged for analysis.

■ US parameters

The cross-sectional area (CSA) will be measured using an electronic caliper at the scaphoid-pisiform level.<sup>38,39</sup> The measurements will be made 3 times, and the values obtained will be averaged for analysis.

#### **Adverse events**

All adverse events, defined as any negative or unwanted reactions to intervention, will be recorded through the symptoms reported by the patients, and observations by a researcher at every visit. US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. NS treatment may cause skin allergy, wrist stiffness, et al. The participants will be instructed to do gentle range-of-motion exercises when removing the splint to prevent stiffness and reinforced adherence by verbal instruction.

#### **Sample size calculation**

Sample size and power calculation are based on the primary outcome of BCTQ-SSS score at 6-week. All sample size calculations assume two-sided analysis with a power of 90% ( $1-\beta=0.90$ ) at a significant level of  $\alpha=0.05$ . Based on a published RCT trial ([Lancet. 2018;392:1423-1433], the authors compared corticosteroid injection and NS for CaTS, and participants in the NS group had a standard deviation [SD] of 0.76 points for BCTQ-SSS at their 6-week followup, ["6-week" was the primary endpoint in this study]),<sup>9</sup> a SD of 0.76-point on BCTQ-SSS score will be used. To detect a minimum clinically significant difference of 0.8-point<sup>58</sup> (superiority margin) between US+NS and NS groups (assuming a true difference of 1.19-point<sup>9,60</sup>), a total of 48 participants in each group is required. Allowing for an up to 10% drop out rate, we aim to enroll at least 54 participants in each group to complete the study.

#### **Analysis plan**

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431 Baseline characteristics of the three treatment groups will be summarized using  
432 appropriate descriptive statistics. Both the primary and secondary analyses will be  
433 blind analyses of treatment assignments and will be performed using the intention-to-  
434 treat (ITT)<sup>61</sup> method, with all randomized participants retaining their original assigned  
435 group. Multiple imputation by chained equations will be used to address missing data  
436 caused by lost access and non-response if these missing data are judged to be random.

437 The primary comparisons for BCTQ-SSS scores will be made using linear  
438 regression. In secondary analyses, repeated measures mixed model<sup>62</sup> will also be used  
439 to examine the associations between treatments and repeated outcome measures, with  
440 terms of treatment, time, trial center and corresponding baseline values as covariates  
441 (age, gender, body mass index, et al.). Bonferroni method will be used to adjust for  
442 multiplicity.<sup>63,64</sup> Linear regression will be used for numerical outcomes, and  
443 logistic/ordinal regression for any categorical outcomes.

444 **Quality assurance/monitoring/management**

445 In order to standardize the procedures of staff training and learning, such as  
446 participants recruitment, outcome measures, data import, security, management and  
447 analysis, a Manual of Operations and Procedures and a case report form will be  
448 developed as per protocol, which also include the monitoring plans to assure  
449 participant protection and data integrity, thus facilitating consistency in protocol  
450 implementation and data collection. The investigators, physicians, research assistants,  
451 outcome assessors and statisticians are different people and should be trained in good  
452 clinical practice. Trained project managers will visit each centre for monitoring to  
453 ensure data quality and compliance with the trial protocol.

454 All data obtained will be stored electronically and strictly in a database with  
455 secure and restricted access. Encryption will be used for data transmission, with

removal for any information that can identify individuals. Data will only be de-identified for analysis at the completion of this study.

### **Study duration**

Recruitment of the trial will begin in the November of 2021 and one-year follow-up for all participants is anticipated to be completed by June 2023. See **Table 1** for time points and recruitment progress.

### **Ethics and dissemination**

This study has been approved by the Ethics Committee of Shanghai Sixth People's Hospital (lead Clinical Center, approval No. 2021-152), Ethics Committee of Shanghai East Hospital (EC.D(BG).016.03.1-2021-095), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-194/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-006). The potential risks of this clinical trial are considered minimal and are addressed in the protocol and consent form. A written consent (**Supplemental file 1**) will be obtained by clinical practitioners from each participant. The trial was registered on [www.chictr.org](http://www.chictr.org) website (registration number ChiCTR2100050701). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

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**DISCUSSION**

CaTS is a highly prevalent compression neuropathy, which results in significant paraesthesia and numbness in the median nerve distribution, especially nocturnal symptoms causing sleep disturbance, causing great socioeconomic burden. Up till now, there is still no consensus on the optimal management, and nonoperative treatment is generally accepted as the first-line intervention for mild and moderate CaTS. Multiple methods have been studied and reviewed in the recent decades, however, the exact efficacy still remains controversial.

In an RCT published in BMJ for mild to moderate CaTS, active US treatment (1 MHz, 1.0 W/cm<sup>2</sup>) was applied to the area over the carpal tunnel in the experimental group, and indistinguishable sham US treatment was applied in the control group.<sup>23</sup> At 6 months' follow up, satisfactory improvement or complete remission of symptoms was observed in 74% receiving active treatment, which is significantly higher than those receiving sham treatment (20%). As for electroneurography, DML and SNCV improved significantly with active treatment while remained unchanged with sham treatment. Hand grip and finger pinch strength in physical examination also improved significantly with active treatment. All results suggested satisfying effects from US treatment for CaTS.

US can also be used as part of a multi-intervention approach. Some studies have compared NS alone to NS combined with US in treatment of CaTS, while the effects were different, and the grades of study design and data were low. Dincer U et al.<sup>26</sup> found that the improvements in the combined group were statistically significantly better (p=0.043) than those in NS alone group in BCTQ-SSS, as well as BCTQ-FSS (p<0.001), and VAS for pain (p<0.001). Similar results were also reported by Baysal

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3 498 O et al.<sup>65</sup>; while Jothi KP et al.<sup>27</sup>, Sim SE et al.<sup>28</sup> and Armagan O et al.<sup>29</sup> found US  
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5 499 therapy may add no benefit to splinting in CaTS.  
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8 500 In this study, to the best of our knowledge, it is the first to compared the efficacy  
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10 501 between US [US group] and NS [NS group] in CaTS treatment. What's more, the  
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12 502 additional effects of US [US+NS group] in a multi-intervention approach will be  
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14 503 compared with NS alone [NS group]. In clinic, US is less invasive, less expensive,  
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16 504 safer and more portable than other nonoperative therapy like drug injections for  
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18 505 compression neuropathy and, if proved to be effective, could be offered to selected  
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20 506 patients as part of non-operative therapy.  
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24 507 There are some on-going clinical trials on CaTS treatment recent years,<sup>66-69</sup> and  
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26 508 our prospective randomized study proposes to complement and add to this relevant  
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710 **Figure Legends**

711 **Figure 1** Participant flow chart

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Table 1 Study evaluation procedures and timeline						
Study procedure	Medical evaluation	Enrolment visit	6 weeks	3 months	6 months	One year
Determine eligibility	√	√				
Obtain signed consent		√				
Obtain medical and demographic data		√				
Give instructions for Pain medication diary		√				
Outcome measures						
Boston Carpal Tunnel Questionnaire		√	√	√	√	√
Numerical rating scale for hand-wrist symptom intensity		√	√	√	√	√
Shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire		√	√	√	√	√
Interrupted sleep questionnaire		√	√	√	√	√
EuroQol-5D		√	√	√	√	√
Hospital Anxiety and Depression Scale		√	√	√	√	√
Work Limitations Questionnaire-25		√	√	√	√	√
Treatment success rate			√	√	√	√
Treatment recurrence rate				√	√	√
Participants' satisfaction			√	√	√	√

Physical examination

✓

✓

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✓

Electrophysiological and ultrasound parameters

✓

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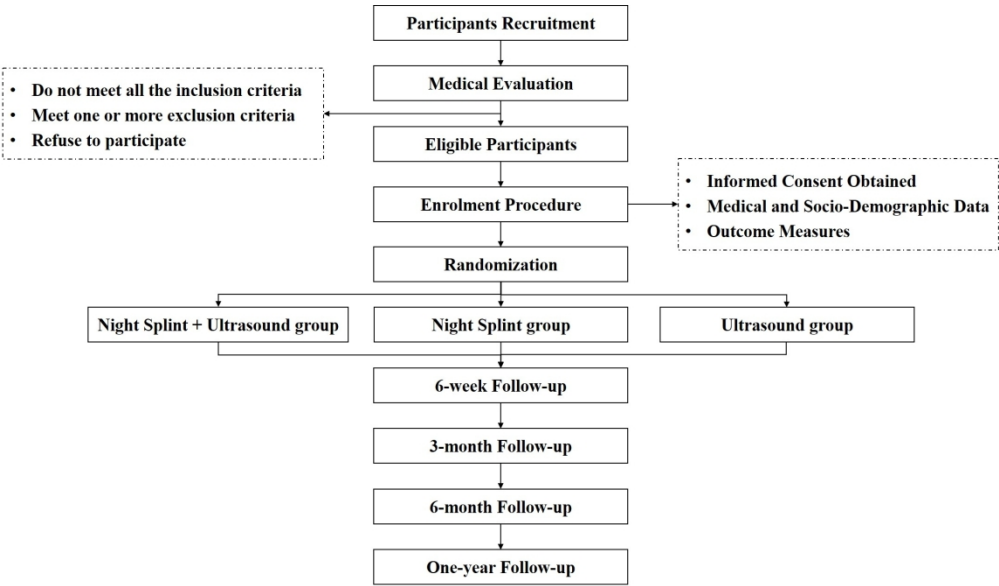


Figure 1 Participant flow chart  
365x212mm (150 x 150 DPI)

# INFORMED CONSENT FORM

(English Version)

## Participant Information Page

**Study Title** : Effectiveness of ultrasound therapy for the treatment of carpal tunnel syndrome  
**Principal Investigator** : Cunyi Fan  
**Sponsor** : Shanghai Sixth People's Hospital

Dear participant:

You have been diagnosed with lateral elbow tendinopathy, and will be invited to participate in the study named "Effectiveness of ultrasound therapy for the treatment of carpal tunnel syndrome". The study is conducted by the researchers themselves. Please read this informed consent carefully and make the decision whether to participate in this study or not. Participation in this study is entirely your choice. As a participant, you must give your written consent prior to joining the clinical study. When your doctor or researcher discusses informed consent with you, you can ask him or her to explain to you what you don't understand. We encourage you to discuss this thoroughly with your family and friends before making any decision to participate in this study. You have the right to refuse to participate in the study or withdraw from the study at any time without being penalized or losing your rights. If you are participating in another study, please inform your study doctor or investigator. The background, purpose, process and other important information of this study are as follows:

### 1. BACKGROUND

Carpal tunnel syndrome (CaTS), the most common compression neuropathy, results from median nerve entrapment in the carpal tunnel, accounting for about 90% of all such disorders. The clinically confirmed CaTS prevalence was 9.6% in the general population of China, with a yearly incidence rate of 2.76%, and women is more susceptible than men. CaTS has significant impact on daily life and ability to work, and causes great burden on social economy, with an annual associated cost estimated at \$13 billion. Classically, CaTS causes discomfort, paraesthesia and numbness in the median nerve distribution; and nocturnal symptoms are often clinically significant causing sleep disturbance. Patients can

be diagnosed by clinical history and physical examination; while electrophysiological methods will be additional for insufficient diagnosis by clinical findings and severe cases that need surgical management.

In general, the severity of CaTS can be classified into mild, moderate and severe. Non-surgical interventions are suggested to be the first choice to treat mild and moderate CaTS. To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. A consensus of multidisciplinary treatment guideline from the European HANDGUIDE Study suggests that “education” should be included as the first-line management approach, which has the advantages of low cost, high efficacy and non-invasive. In addition, “night splint (NS)” and “corticosteroid injection (CI)” are also recommended in guidelines of American Academy of Orthopaedic Surgeons (AAOS) and American Physical Therapy Association (APTA). One recent RCT published in Lancet compares both two methods, and finds that CI has superior clinical effectiveness at 6 weeks than NS, but no differences at 6 months; while CI may bring adverse events like thinning, lightening or darkening of the skin at the injection site, hot flushes and even more pain. Systematic reviews have also shown that the effects of other conservative treatments like acupuncture, exercise and mobilization interventions, laser, extracorporeal shockwave therapy and platelet-rich plasma injection still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. In the intensity range of 0.5-2.0 W/cm<sup>2</sup>, US may have the potential to induce a variety of biophysical effects in tissues. US experiments on stimulation of nerve conduction and regeneration, and discoveries of its anti-inflammatory effects all support that US may promote recovery of nerve compression. An RCT published in BMJ showed more pronounced subjective symptoms and electroneurographic variables for US treatment than sham control in patients with mild to moderate CaTS. However, to our best of knowledge, no study has compared the efficacy between NS and US in CaTS treatment yet. Additionally, some studies have also reported the efficacy of US to be used as part of a multi-intervention approach, but with low grade of study design and data. Therefore, the role of US in CaTS treatment still needs to be further explored by high-quality study.

**2. STUDY PURPOSE**

The purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for CaTS, that is, NS+US (combined) versus NS versus US, on clinical and functional outcomes, including Boston Carpal Tunnel

Questionnaire (BCTQ).

### 3. STUDY PROCESS

#### (1) How many people will participate in the study?

About 162 people will participate in the study at 4 municipal tertiary hospitals: Shanghai Sixth People's Hospital (leader unit), Shanghai East Hospital (participating unit), Shanghai Tenth People's Hospital (participating unit) and Pudong New Area People's Hospital of Shanghai (participating unit).

#### (2) What are the study procedures?

Before you are enrolled in the study, your medical history will be asked, and you will be screened for carpal tunnel syndrome by using criteria developed from a consensus survey by the UK Primary Care Rheumatology Society.

After determining that you are eligible to participate in the study based on inclusion and exclusion criteria, you will be collected and randomly assigned to treatment:

##### *A. Characteristic features collection*

You will be asked for your age, sex, body mass index, affected elbow (whether bilateral), dominant arm, lifestyle (smoking and alcohol use), and medical history. As well as relevant questions about symptoms duration and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-time work, manual or non-manual labor), employment status (whether on sickness absence), professional activity characteristics, and sports activities will be also collected.

##### *B. Clinical features collection*

You will complete the following questionnaires, including Boston Carpal Tunnel Questionnaire (BCTQ) for wrist function and symptom, numerical rating scale (NRS) for hand-wrist symptom intensity, shortened version of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH) for upper limb disability, EuroQol-5D (EQ-5D) for life quality and health status, Hospital Anxiety and Depression Scale (HADS) for anxiety and depression status, Work Limitations Questionnaire (WLQ)-25 for functional limitations at work, Global Rating of Change (GROC) for treatment success and recurrence rate, Likert scale for participant's satisfaction, as well as physical function examination and various electrophysiology and ultrasound parameters.

##### *C. Treatment by group*

At the beginning, all participants will participate in an about 30-minute group



educational presentation by a research assistant on the same day as the baseline assessment. This presentation will cover the pathophysiology, treatment options, posture and activity modification principles of CaTS. The above information will also be provided to participants in the form of education booklets, to encourage them to review at home. Habits changes include limited wrist movement and a reduction in strenuous work activities, and the use of ergonomically friendly work tools helps reduce median nerve pressure.

You will be randomly assigned to one of three groups, [US group] vs. [NS group] vs. [US+NS group]:

(a) If you are assigned in the [US group], you will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm<sup>2</sup> for 15 minutes in 5 days per week for 6 weeks to the area over the carpal tunnel.

(b) If you are allocated to the [NS group], you will receive a splint to wear at night for 6 weeks. The splint holds the wrist in a neutral position or slightly extended 20° from the neutral position to avoid wrist movement, which can increase pressure on the carpal tunnel. The choose of each splint will be based on the size of each of your hands and arms. You will be shown how to fit and remove the wrist splint according to a standardized trial protocol. Oral guidance from the clinician on how and when to use splints will encourage and reinforce compliance, which will be also supported by written information, detailed care, and splint fitting and use. You will be instructed to perform gentle range-of-motion exercises when removing the splint to prevent stiffness.

(c) If you are randomized to the [US+NS group], you will receive both US for 6 weeks as in the [US group] and NS for 6 weeks as in the [NS group].

We discourage additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allowed the use of simple analgesics as needed. You will report all not per protocol treatments, such as drugs, in a diary.

*D. Follow-up features collection*

Follow-up data will be collected during your visits to the hospital at 6 weeks, 3 and 6 months, and one year after random assignment.

**(3) How long will the study last?**

This study will continue for 1 year from the time you receive treatment, and we will collect follow-up information from you at 6 weeks, 3 months, 6 months, and one year at your regular outpatient review.

You may drop out of the study at any time without losing any benefits to which you are entitled. However, if you decide to withdraw during the study, you are encouraged to talk to your doctor first. If you experience a serious adverse event, or if your study doctor

feels it is not in your best interest to continue in the study, he or she may decide to withdraw you from the study. The sponsor or regulatory agency may also terminate during the study period. However, your withdrawal will not affect your normal medical treatment and rights.

If you withdraw from the study for any reason, you may be asked about your participation in the study. You may also be asked for a medical examination and follow-up questionnaire if your doctor deems it necessary.

#### **(4) Information and biological specimens collected during the study**

Biological specimens are not involved in this study, and the information collected is basic characteristics features, preoperative and follow-up clinical features (see the study procedures for details).

All data obtained will be kept strict and stored electronically on a database with secured and restricted access. An encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

### **4. RISKS AND BENEFITS**

#### **(1) What are the risks of participating in this study?**

The risks you may incur by participating in this study are as follows. You should discuss these risks with your study doctor or, if you prefer, with your regular care provider.

US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. The occurrence of these reactions depends on the dose of treatment, the extent of the lesion, and the individual patient, and usually does not require special treatment. Severe adverse reactions can be treated locally, or prolong the interval of treatment, reduce the intensity of treatment. If the treatment does not improve or abnormal conditions occur, the treatment should be stopped and immediately go to the hospital.

NS treatment may cause skin allergy, wrist stiffness, et al. You will be instructed to do gentle range-of-motion exercises when removing the splint to prevent stiffness and reinforced adherence by verbal instruction.

If you experience any discomfort, new changes, or any unexpected conditions during the study period, whether or not related to the study, you should inform your doctor in a timely manner, and he/she will judge and administer appropriate medical treatment.

During the study period, you need to visit the hospital on time and do some examinations, which will take up some of your time and may cause trouble or

inconvenience to you.

**(2) What are the benefits of participating in the study?**

If you agree to participate in this study, you may receive direct medical benefits, such as accelerated relief of symptoms of CaTS. You can also have a deeper understanding of diseases and so on. In addition, we hope that the information gained from your participation in this study will benefit you or other patients with similar conditions in the future.

**5. ALTERNATIVE TREATMENT OPTIONS**

In addition to participating in this study, you may receive the other treatments provided by your doctor: corticosteroid injection, acupuncture, exercise and mobilization interventions, laser, extracorporeal shockwave therapy and platelet-rich plasma injection, and surgery, etc.

Please discuss these and other possible options with your doctor.

In general, the severity of CaTS can be classified into mild, moderate and severe. Non-surgical interventions are suggested to be the first choice to treat mild and moderate CaTS. To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. A consensus of multidisciplinary treatment guideline from the European HANDGUIDE Study suggests that “education” should be included as the first-line management approach, which has the advantages of low cost, high efficacy and non-invasive. In addition, “night splint (NS)” and “corticosteroid injection (CI)” are also recommended in guidelines of American Academy of Orthopaedic Surgeons (AAOS) and American Physical Therapy Association (APTA). One recent RCT published in Lancet compares both two methods, and finds that CI has superior clinical effectiveness at 6 weeks than NS, but no differences at 6 months; while CI may bring adverse events like thinning, lightening or darkening of the skin at the injection site, hot flushes and even more pain. Systematic reviews have also shown that the effects of other conservative treatments like acupuncture, exercise and mobilization interventions, laser, extracorporeal shockwave therapy and platelet-rich plasma injection still remain controversial or provide little to no benefit.

**6. USE OF RESEACH RESULTS AND CONFIDENTIALITY OF PERSONAL INFORMATION**

Results conducted through this program may be published in medical journals with

the understanding and assistance of you and other participants, but we will keep your study records confidential as required by law.

The personal information of study participants will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws.

If necessary, government administrative departments, hospital ethics committees and other relevant researchers can access your data according to regulations.

## **7. RESEARCH EXPENSES AND RELATED COPENSAATION**

### **(1) Cost of drugs/instruments used in the study and related examinations**

There are no potential additional costs for this study. Routine outpatient fees include registration, examination for CaTS, oral non-steroidal anti-inflammatory drugs, etc. The expenses related to US and NS will be borne by our research group and funding. In addition, you will be solely responsible for the expenses incurred by you for any treatment other than this study, as well as for the routine treatment and examination required for any concurrent disease.

### **(2) Compensation for participation in the study**

There are no additional compensation costs for this study.

### **(3) Compensation/compensation after damage**

For participants who suffer damage related to this study, the sponsor Shanghai Sixth People's Hospital will bear the treatment cost and corresponding economic compensation in accordance with Chinese laws and regulations.

## **8. RIGHTS OF PARTICIPANTS AND RELEVANT MATTERS NEEDING ATTENTION**

### **(1) Your rights**

Your participation in the study is voluntary throughout the entire process.

If you decide not to participate in this study, it will not affect other treatments you should receive.

If you decide to participate, you will be asked to sign this written informed consent. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your medical treatment and rights will not be affected.

### **(2) Matters needing attention**

As a subject, you are required to provide true information about your medical history and current medical condition;

Inform the study doctor of any discomfort observed during the study;

Do not take any restricted drugs, food, etc. as advised by your doctor;

Tell the study doctor if you have recently participated in or are currently participating in other studies.

During the intervention, we discouraged additional therapy (i.e., not according to the grouping protocol), but we permitted the use of analgesics when needed (only acetaminophen and NSAIDs).

For medications taken, the name, dose, frequency and duration will be recorded at all follow-up visits.

**9. RELEVANT CONTACT INFORMATION**

If there is any significant new information during the study that may affect your willingness to continue to participate, your doctor will inform you promptly. If you are interested in your own study data, or you would like to know the findings after this study, you may ask any questions about this study at any time and receive answers accordingly, Please contact doctor Shuai Chen at \*\*\*\*\*.

## Participant Signature Page

### Informed Consent Statement:

I have been informed of the purpose, background, process, risks and benefits of this study. I have plenty of time and opportunity to ask questions, and I am satisfied with the answers.

I am also told who to contact when I have questions, want to report difficulties, concerns, suggestions for research, or want further information, or to help with research.

I have read this informed consent and agree to participate in this study.

I understand that I may choose not to participate in the study or withdraw from the study at any time during the study without any reason.

I already know that if I get worse, or if I have a serious adverse event, or if my study doctor decides it's not in my best interest to continue, he or she will decide to withdraw me from the study. The funder or regulatory agency may terminate during the study without my consent. If this happens, the doctor will inform me and the study doctor will discuss other options with me.

I will be provided with a copy of the informed consent which contains my signature and that of the investigator.

Participant Signature: \_\_\_\_\_

Date: \_\_\_\_\_

(NOTE: If participant has no capacity/limited capacity, legal representative signature and date will be required)

Legal Representative's Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Investigator Signature: \_\_\_\_\_

Date: \_\_\_\_\_

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

			Page
Reporting Item			Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered,	4/6



		name of intended registry	
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	4/6
Protocol version	<a href="#">#3</a>	Date and version identifier	5
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	2
Roles and responsibilities: sponsor contact information	<a href="#">#5b</a>	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2

## Introduction



1	Background and	<a href="#">#6a</a>	Description of research question and justification for	8-9
2				
3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	8-9
12				
13	rationale: choice of			
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15	comparators			
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18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	10
19				
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21				
22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	10
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
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32	Methods:			
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34	Participants,			
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36	interventions, and			
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38	outcomes			
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41				
42	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	10
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
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52	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	11-12
53			applicable, eligibility criteria for study centres and	
54			individuals who will perform the interventions (eg,	
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surgeons, psychotherapists)

Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-14
description			
Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	13-14
modifications			
Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
adherence			
Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
concomitant care			
Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-19
Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	20-21

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BMJ Open

1	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
2				
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11	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
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16	<b>Methods: Assignment</b>			
17	<b>of interventions (for</b>			
18	<b>controlled trials)</b>			
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24	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12-13
25	generation			
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41	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-13
42	concealment			
43				
44	mechanism			
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51	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12-13
52	implementation			
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1	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	12-13
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
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8	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	12-13
9	emergency		permissible, and procedure for revealing a participant's	
10	unblinding		allocated intervention during the trial	
11				
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16	<b>Methods: Data</b>			
17	<b>collection,</b>			
18	<b>management, and</b>			
19	<b>analysis</b>			
20				
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26	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	14, 19-
27			and other trial data, including any related processes to	21
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
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43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-	14, 19-
44	retention		up, including list of any outcome data to be collected for	21
45			participants who discontinue or deviate from intervention	
46			protocols	
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53	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	14, 19-
54			including any related processes to promote data quality	21
55			(eg, double data entry; range checks for data values).	
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1			Reference to where details of data management	
2			procedures can be found, if not in the protocol	
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5				
6	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	19-20
7			outcomes. Reference to where other details of the	
8			statistical analysis plan can be found, if not in the protocol	
9				
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13	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and	19-20
14	analyses		adjusted analyses)	
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18	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	19-20
19	population and		adherence (eg, as randomised analysis), and any statistical	
20	missing data		methods to handle missing data (eg, multiple imputation)	
21				
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26	<b>Methods: Monitoring</b>			
27				
28				
29	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);	14, 19-
30	formal committee		summary of its role and reporting structure; statement of	21
31			whether it is independent from the sponsor and competing	
32			interests; and reference to where further details about its	
33			charter can be found, if not in the protocol. Alternatively, an	
34			explanation of why a DMC is not needed	
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44	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping	14, 19-
45	interim analysis		guidelines, including who will have access to these interim	21
46			results and make the final decision to terminate the trial	
47				
48				
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51	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	19
52			solicited and spontaneously reported adverse events and	
53			other unintended effects of trial interventions or trial	
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		conduct	
Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
<b>Ethics and dissemination</b>			
Research ethics approval	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21
Consent or assent: ancillary studies	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	21

1	interests		investigators for the overall trial and each study site	
2				
3				
4	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	14, 19-
5				
6			and disclosure of contractual agreements that limit such	21
7				
8			access for investigators	
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11	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	19-21
12				
13	trial care		compensation to those who suffer harm from trial	
14				
15			participation	
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19	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	19-21
20				
21	trial results		results to participants, healthcare professionals, the public,	
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23			and other relevant groups (eg, via publication, reporting in	
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25			results databases, or other data sharing arrangements),	
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27			including any publication restrictions	
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31	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	19-21
32				
33	authorship		professional writers	
34				
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36	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	19-21
37				
38	reproducible research		participant-level dataset, and statistical code	
39				
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41				
42	Appendices			
43				
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45	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given	21
46				
47	materials		to participants and authorised surrogates	
48				
49				
50	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	/
51				
52			biological specimens for genetic or molecular analysis in	
53				
54			the current trial and for future use in ancillary studies, if	
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56			applicable	
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For peer review only



# BMJ Open

## Effectiveness of therapeutic ultrasound for the treatment of carpal tunnel syndrome (the USTINCTS trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057541.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Mar-2022
Complete List of Authors:	Chen, Shuai; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration, Qian, Yun; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration Sun, Ziyang; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration Liu, Weixuan; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration Sun, Guixin; Shanghai East Hospital, Tongji University School of Medicine, Department of Orthopaedics Liu, Junjian; Shanghai Tenth People's Hospital, Wang, Jian; Pudong New Area People's Hospital, Department of Orthopedics Wang, Wei; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration Zheng, Yuanyi; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Ultrasound in Medicine Fan, Cunyi; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Orthopedics; Shanghai Engineering Research Center for Orthopaedic Material Innovation and Tissue Regeneration
<b>Primary Subject Heading</b>:	Sports and exercise medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	REHABILITATION MEDICINE, SPORTS MEDICINE, Hand & wrist < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY



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# **TITLE PAGE**

## **Title**

Effectiveness of therapeutic ultrasound for the treatment of carpal tunnel syndrome (the USTINCTS trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

## **Running Title**

study protocol of USTINCTS trial for carpal tunnel syndrome

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45 **Author Contributions**

46 CS, QY and SZY are the primary investigators.

47 CS, QY, SZY, LWX, ZYY, FCY participated in the development of the study

48 design.

49 CS, QY, SZY, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the

50 study conduct.

CS, QY, SZY and LWX drafted the manuscript under FCY's supervision.

FCY and QY contributed to applying for and gaining funding.

All authors contributed to the content and critical revision and approved the final draft of the manuscript.

## **Conflict of interests**

The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

The authors declare no competing financial interests.

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## **Acknowledgments**

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79  
80 **ETHICS**

81 The study has been approved by all 4 Medical Ethics Committees, those are,  
82 Ethics Committee of Shanghai Sixth People’s Hospital (the leading clinical center,  
83 approval No. 2021-152), Ethics Committee of Shanghai East Hospital  
84 (EC.D(BG).016.03.1-2021-095), Ethics Committee of Shanghai Tenth People’s  
85 Hospital (SHSY-IEC-4.1/21-194/01), and Ethics Committee of Pudong New Area  
86 People's Hospital (IRBY2021-006). The research registry number is  
87 ChiCTR2100050701 at <http://www.chictr.org.cn>. Data will be analyzed anonymously;  
88 all patients will approve the results of this study by written consent. The written  
89 consent approval will be documented in the patients’ files. All clinical investigations  
90 will be conducted in accordance with the guidelines of the Declaration of Helsinki.

91

## 92 **ABSTRACT**

### 93 **Introduction**

94 There has no consensus on optimal management of carpal tunnel syndrome  
95 (CTS), the most common compression neuropathy. Conservative therapy is generally  
96 accepted as first-line intervention. Therapeutic ultrasound has been widely reported to  
97 be treatment beneficial in nerve regeneration and conduction, and further accelerate  
98 compression recovery. The purpose of this study is to investigate the effectiveness of  
99 therapeutic ultrasound for CTS treatment.

### 100 **Methods and analysis**

101 This study protocol entails a three-arm, prospective, multicenter, randomised  
102 controlled trial. 162 eligible adult participants diagnosed with mild to moderate CTS  
103 by using criteria developed from a consensus survey by the UK Primary Care  
104 Rheumatology Society will be assigned to either (1) therapeutic ultrasound, (2) night  
105 splint or (3) therapeutic ultrasound + night splint (combined) group. Primary outcome  
106 will be difference in Symptom Severity Scale of Boston Carpal Tunnel Questionnaire  
107 (BCTQ-SSS) at 6-week between night splint and therapeutic ultrasound + night splint  
108 groups. Secondary outcomes include Functional Status Scale of BCTQ, sleep  
109 questionnaire for interrupted sleep, EuroQol-5D for general health, Hospital Anxiety  
110 and Depression Scale for mental status, Work Limitations Questionnaire-25 for  
111 functional limitations at work, Global Rating of Change for treatment success and  
112 recurrence rate, physical examination, electrophysiological and ultrasound  
113 parameters. Intention-to-treat analyses will be used.

### 114 **Ethics and dissemination**

115 Ethics Committees of all clinical centers have approved this study. The leading  
116 center is Shanghai Sixth People's Hospital, whose approval number is 2021-152. New

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117 versions with appropriate amendments will be submitted to the committee for further  
118 approval. Final results will be published in peer-reviewed journals and presented at  
119 local, national and international conferences.

120 **Trial registration number**

121 ChiCTR2100050701.

122

For peer review only



## 123 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 124 ● Therapeutic ultrasound as independent or adjunct therapy in treating carpal tunnel  
125 syndrome (CTS).
- 126 ● The first randomised controlled trial (RCT) to compared the efficacy between  
127 therapeutic ultrasound and night splint in CTS treatment.
- 128 ● Multicenter RCT with blinded outcome assessor and statistician.
- 129 ● Use of several patient-reported outcome measures as well as objective  
130 parameters.
- 131 ● Participants and treating surgeons not blinded.

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**INTRODUCTION**

Carpal tunnel syndrome (CTS), the most common compression neuropathy, results from median nerve entrapment in the carpal tunnel, accounting for about 90% of all such disorders.<sup>1,2</sup> The clinically confirmed CTS prevalence was 9.6% in the general population of China,<sup>3</sup> with a yearly incidence rate of 2.76%, and women is more susceptible than men.<sup>2,4</sup> CTS has significant impact on daily life and ability to work,<sup>5</sup> and causes great burden on social economy, with an annual associated costs estimated at \$13 billion.<sup>6</sup> Classically, CTS causes discomfort, paraesthesia and numbness in the median nerve distribution; and nocturnal symptoms are often clinically significant causing sleep disturbance.<sup>7</sup> Patients can be diagnosed by clinical history and physical examination; while electrophysiological methods will be additional for insufficient diagnosis by clinical findings and severe cases that need surgical management.<sup>8</sup>

In general, the severity of CTS can be classified into mild, moderate and severe.<sup>9</sup> Non-surgical interventions are suggested to be the first choice to treat mild and moderate CTS.<sup>10</sup> To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. A consensus of multidisciplinary treatment guideline from the European HANDGUIDE Study suggests that “education” should be included as the first-line management approach, which has the advantages of low cost, high efficacy and non-invasiveness.<sup>7,11</sup> In addition, “night splint” and “corticosteroid injection” are also recommended in guidelines of American Academy of Orthopaedic Surgeons (AAOS) and American Physical Therapy Association (APTA).<sup>12,13</sup> One recent RCT published in Lancet compares both two methods, and finds that corticosteroid injection has superior clinical effectiveness at 6 weeks than night splint, but no differences at 6 months;

158 while corticosteroid injection may bring adverse events like thinning, lightening or  
159 darkening of the skin at the injection site, hot flushes and even more pain.<sup>9</sup> Systematic  
160 reviews have also shown that the effects of other conservative treatments like  
161 acupuncture,<sup>14</sup> exercise and mobilization interventions,<sup>15</sup> laser,<sup>16</sup> extracorporeal  
162 shockwave therapy<sup>17</sup> and platelet-rich plasma injection<sup>18</sup> still remain controversial or  
163 provide little to no benefit.

164 Therapeutic ultrasound is widely used for imaging purposes and regarded as an  
165 adjunct to physiotherapy. In the intensity range of 0.5-2.0 W/cm<sup>2</sup>, therapeutic  
166 ultrasound may have the potential to induce a variety of biophysical effects in  
167 tissues.<sup>19</sup> Therapeutic ultrasound experiments on stimulation of nerve conduction and  
168 regeneration,<sup>20,21</sup> and discoveries of its anti-inflammatory effects<sup>22</sup> all support that  
169 therapeutic ultrasound may promote recovery of nerve compression. An RCT  
170 published in BMJ showed more pronounced subjective symptoms and  
171 electroneurographic variables for therapeutic ultrasound than sham control in patients  
172 with mild to moderate CTS.<sup>23</sup> However, to our best of knowledge, no study has  
173 compared the efficacy between night splint and therapeutic ultrasound in CTS  
174 treatment yet. Additionally, some studies have also reported the efficacy of US to be  
175 used as part of a multi-intervention approach, but with low grade of study design and  
176 data<sup>24-29</sup>. Therefore, the role of therapeutic ultrasound in CTS treatment still needs to  
177 be further explored by high-quality study.

178 Therefore, the purpose of the current three-arm, prospective, randomized,  
179 multicenter trial is to examine the effectiveness of therapeutic ultrasound in treatment  
180 for CTS, that is, night splint + therapeutic ultrasound (combined) versus night splint  
181 versus therapeutic ultrasound, on clinical and functional outcomes, including Boston  
182 Carpal Tunnel Questionnaire (BCTQ) in patients diagnosed with CTS.

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**METHODS**

**Study design**

This study is a three-arm, prospective, multicenter, randomized controlled trial that will recruit participants from 4 municipal tertiary hospitals with a diagnosis of mild to moderate CTS. The multi-centres are Shanghai Sixth People’s Hospital, Shanghai Tenth People’s Hospital, Shanghai East Hospital, and Pudong New Area People’s Hospital of Shanghai, respectively. This manuscript is written according to the SPIRIT guidelines.<sup>30</sup>

**Participant and public involvement**

There was no participant involvement in this study. Participants were not invited to make comments or suggestions on the protocol, were not consulted about the selection of patient-relevant evaluation outcomes, or were invited to participate in writing or editing the manuscript to improve readability or accuracy. The final findings will be disseminated to the public through mass media. Our published papers and conference presentations also acknowledge all participants as a whole.

**Participant recruitment**

**Figure 1** shows the participant flow chart throughout the study. Participants will be recruited over a 5-month period from outpatient clinics of 4 principals in each sub-centre. In addition, recruitment can also be through other doctors and healthcare professionals. Interested participants can contact the research assistant, who will provide more information about the study purpose and protocol, and conduct an initial eligibility screening by phone.

**Medical evaluation and enrolment procedure**

Eligible participants will be invited to participate in a physical examination to confirm CTS diagnosis and assess eligibility to participate in the program.

208 Inclusion criteria

- 209 ■ Age  $\geq 18$  years old;
- 210 ■ Clinical diagnosis on the basis of clinical symptoms, history and physical
- 211 examination, using criteria developed from a consensus survey by the UK Primary
- 212 Care Rheumatology Society;<sup>31</sup>
- 213 ■ Mild to moderate CTS,<sup>9</sup> with symptoms longer than 6 weeks duration; participants
- 214 with bilateral CTS will be designated their study hand based on the most severe
- 215 symptoms;
- 216 + Mild: intermittent paraesthesia in the distribution of the median nerve
- 217 + Moderate: constant paraesthesia, and reversible numbness or pain of
- 218 idiopathic nature
- 219 + Severe: constant pain, numbness or sensory loss in the wrist and hand
- 220 (specifically palm, index, or middle finger, or thumb), or thenar muscle
- 221 atrophy
- 222 ■ Able to read and write in simplified Chinese (Mainland), understand and complete
- 223 the questionnaire, and should provide informed consent.

224 Exclusion criteria

- 225 ■ CTS secondary to wrist deformity, trauma, mass, pregnancy, hypothyroidism, or
- 226 inflammatory arthropathy;
- 227 ■ Treatment by night splint, therapeutic ultrasound or injection within the past 6
- 228 months, or previous carpal tunnel surgery;
- 229 ■ Previous surgery on the affected wrist (or study wrist if bilateral CTS);
- 230 ■ Unable to tolerate the study interventions;
- 231 ■ Trauma to the affected upper limb requiring operation or immobilization within
- 232 the past 12 months;

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- 233 ■ Current illness including, poorly controlled diabetes mellitus or thyroid disease,
- 234 vibration-induced neuropathy, osteoarthritis or inflammatory joint disease,
- 235 suspected complex neurological and musculoskeletal conditions;
- 236 ■ Known drugs or alcohol abuse;
- 237 ■ Allergy to any of the splint materials;
- 238 ■ Contraindications to therapeutic ultrasound, including dermatological conditions,
- 239 abnormal sensation in the affected arm, indwelling electrical pumps/pacemakers,
- 240 epilepsy, pregnancy or breastfeeding.
- 241 Following the medical evaluation, a research assistant will meet with the eligible
- 242 participants and obtain their written informed consent. Demographic variables such as
- 243 age, sex, body mass index, affected wrist (whether bilateral), dominant arm, lifestyle
- 244 (smoking and alcohol use), and medical history of all participants will be collected
- 245 prior to treatment (baseline). Participants will also be asked relevant questions about
- 246 symptoms duration and previous treatments (rehabilitation exercises, injections or
- 247 others). Others like occupation, employment characteristics (full-time or part-time
- 248 work, manual or non-manual labor), employment status (whether on sickness
- 249 absence), and professional activity characteristics (repetitive movements for >4
- 250 hours/day; wrist flexion and extension for >2 hours/day and use of computer
- 251 keyboard/ mouse [how many hours/day]) will be also collected.

252 **Randomization and blinding**

253 Participants will be randomized in three intervention groups (either therapeutic

254 ultrasound or night splint or therapeutic ultrasound + night splint arm) in a ratio of

255 1:1:1, using a computer-generated randomized sequence with varying unknown block

256 sizes (either 3 or 6) for all study centres, without stratification. A research assistant

257 who are not involved in clinical care and participant evaluations will prepare

sequentially numbered, opaque, sealed envelopes based on a random list, and ensure that the allocation data will not be accessed or influenced by anyone. When appropriate, the assistant will open envelopes and ensure coordination of therapeutic interventions.

The outcome assessor and statistician will be blinded to group allocation and not involved in treatment procedures.

### **Intervention**

At the beginning, all participants will participate in an about 30-minute group educational presentation by a research assistant on the same day as the baseline assessment. This presentation will cover the pathophysiology, treatment options, posture and activity modification principles of CTS. The above information will also be provided to participants in the form of education booklets, to encourage them to review at home. Habits changes include limited wrist movement and a reduction in strenuous work activities, and the use of ergonomically friendly work tools helps reduce median nerve pressure.<sup>32,33</sup>

Participants in the [therapeutic ultrasound group] will receive pulsed therapeutic ultrasound (model 1:4, Shanghai, China) for 6 weeks at a frequency of 1 MHz and intensity of 1.0 W/cm<sup>2</sup> for 15 minutes per session, in daily 5 times a week for the first 2 weeks and twice a week for another 4 weeks, to the area over the carpal tunnel, referred to a published trial [BMJ. 1998;316:731-735].

Participants allocated to the [night splint group] will receive a splint to wear at night for 6 weeks, referred to a published trial [Lancet. 2018;392:1423-1433]. The splint holds the wrist in a neutral position or slightly extended 20° from the neutral position to avoid wrist movement, which can increase pressure on the carpal tunnel.<sup>34</sup> The choose of each splint will be based on the size of individual participant's hands

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283 and arms. Participants will be shown how to fit and remove the wrist splint according  
284 to a standardized trial protocol. Oral guidance from the clinician on how and when to  
285 use splints will encourage and reinforce compliance, which will be also supported by  
286 written information, detailed care, and splint fitting and use. Participants will be  
287 instructed to perform gentle range-of-motion exercises when removing the splint to  
288 prevent stiffness.

289 Participants randomized to the [therapeutic ultrasound + night splint group] will  
290 receive both therapeutic ultrasound for 6 weeks as in the [therapeutic ultrasound  
291 group] and night splint for 6 weeks as in the [night splint group].

292 For participants with bilateral CTS, the non-study hand will be treated according  
293 to normal clinical protocols in use at the research site.

294 We discouraged additional treatments to that assigned (that is, not per protocol)  
295 during the intervention period, but we allowed the use of simple analgesics as needed.  
296 Participants reported all not per protocol treatments, such as drugs, in a diary.

297 **Data management**

298 Data will be collected during the participants' visits to the hospital at baseline, 6  
299 weeks, 3 months, 6 months, and one-year after random assignment (**Table 1**).  
300 Reminder emails and phone calls from the research assistants will be programmed to  
301 maximize participant compliance in subsequent completion. A registered participant  
302 will withdraw from the study if (1) the participant withdraws his/her consent, and (2)  
303 exclusion criteria is found after registration. The cause and date of suspension will be  
304 recorded. Consent to use data that has been collected before the participant's  
305 withdrawal will be included in the consent form.

306 **Primary outcome measure**



The primary outcome measure will be the difference in Symptom Severity Scale of the Boston Carpal Tunnel Questionnaire (BCTQ-SSS) at 6-week. The BCTQ is a disease-specific questionnaire referring to a typical 24-hour period in the past two weeks,<sup>35</sup> and has been shown to be highly reproducible, internally consistent, valid and responsive to clinical change in CTS.<sup>36</sup> It consists of two different subscales: Symptom Severity Scale (11 items, about symptom severity) and Functional Status Scale (8 items, about the degrees of difficulty on daily activities), both rated on a five-point scale, with final scores for each subscale result in mean scores between 1 and 5. The overall score is calculated as the mean of all 19 items. Higher scores represent more severe symptoms and functional impairment. We use a validated Chinese version<sup>37</sup> of the BCTQ in this study.

### **Secondary outcome**

Secondary outcome measures will be the differences in Functional Status Scale of the Boston Carpal Tunnel Questionnaire (BCTQ-FSS), sleep questionnaire for interrupted sleep<sup>38</sup>, EuroQol-5D (EQ-5D)<sup>39</sup> for life quality and health status, Hospital Anxiety and Depression Scale (HADS)<sup>40</sup> for anxiety and depression status, Work Limitations Questionnaire (WLQ)-25<sup>41</sup> for functional limitations at work, Global Rating of Change (GROC) for treatment success and recurrence rate, physical function examination as well as various electrophysiology and ultrasound parameters.

#### **■ Interrupted sleep**

The sleep questionnaire, which will be used to assess sleep quality, consists of four questions asking participants how many times they have experienced it in the last month.<sup>38</sup> Each question has six response categories and are coded in 0-5 order: not at all, 1-3, 4-7, 8-14, 15-21 and 22-31 days. All questions have equal weights and add up. Higher scores are associated with more disrupted sleep.

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332 ■ Life quality and health status

333 EQ-5D has been widely validated and used to measure generic health-related  
334 quality of life (HRQoL) due to its simplicity.<sup>39</sup> It consists of a five-dimensional  
335 description system (mobility, self-care, usual activities, pain/discomfort and  
336 anxiety/depression) and a VAS that scales from 0 to 1, where 1 represents perfect  
337 health. All dimensions are divided into three levels (no problem, some problem and  
338 extreme problem). We used a validated Chinese version<sup>42,43</sup> of EQ-5D, which has  
339 been recommended by Guidelines for Pharmacoeconomic Evaluations 2011 for a  
340 measure for HRQoL and health utility.<sup>44</sup>

341 ■ Anxiety and depression status

342 HADS will be used to identify and quantify two of the most common  
343 psychological disorders - anxiety and depression.<sup>40</sup> There is evidence of increased  
344 anxiety and depression in LET patients.<sup>45</sup> The HADS is a 14-item scale independent  
345 of physical symptoms and consists of two 7-item subscales measuring depression and  
346 anxiety, respectively. A 4-point scale (0 for absence of symptoms, and 3 for  
347 maximum symptomatology) is used. Each subscale has an overall score ranging from  
348 0 to 21, with a higher score indicating a higher degree of impairment. HADS has two  
349 cut offs for categorization: 0-7, “non-case”; 8-10, “possible or doubtful case”; 11-21,  
350 “probable or definite case”.<sup>46</sup>

351 ■ Functional limitations at work

352 To gather information that is complementary to the pain and disability scales,  
353 functional limitations at work will be measured using WLQ-25. It contains 25 items,  
354 arranged under four sub-scales, covering four dimensions of job demands, namely  
355 time demands, physical demands, mental/interpersonal demands, and output  
356 demands.<sup>41</sup> A five-level ordinal response scale ranging from 0 (all of the time) to 4

(none of the time) with an additional sixth option (does not apply to my job) is used.

The overall score ranges from 0 to 100, with an increase of 13 points (out of 100) for clinically important differences.<sup>47</sup>

#### ■ Treatment success and recurrence rate

Participants' treatment impressions of changes in their condition (ranging from “completely recovered”, “much improved”, “somewhat improved”, “same”, “worse” to “much worse”) will be recorded on a six-level Likert scale. The success rate will be calculated by dichotomizing the response. Participants who report “completely recovered” or “much improved” in their overall condition since the study beginning will be considered successful, while other responses will be considered failures.<sup>48,49</sup> Recurrence will be defined primarily as when a participant rates a success at 6 weeks and a failure at 3 months, 6 months or one-year on GROC.<sup>48,49</sup>

#### ■ Physical function examination

The physical examinations will include measurement of 2-point discrimination (performed on the radial and ulnar aspects of each digit), grip strength with a dynamometer (CAMRY, City of Industry, CA, USA), and pinch strength with the pinch gauge (three trials for each hand). The affected side will be measured first and then the unaffected side. The measurement readings will be not revealed to the subjects until the completion of the test. The mean of three consecutive trials, separated by a 20s pause, will be calculated. Results will be presented as a ratio of values of the symptomatic side/ asymptomatic side $\times 100$ .<sup>50</sup>

The 2-point discrimination test starts at a distance of 4 mm and increases continuously by 2 mm as necessary. Grip strength and 3-point pinching force (3 tests per hand) as measured with baseline dynamometer and pinch gauge (Chattanooga Group, Hixson, Tennessee, USA) will be recorded.

■ Electrophysiological Study

Median nerve distal motor latency (DML), compound muscle action potential (CMAP), sensory nerve conduction velocity (SNCV) and sensory nerve action potential (SNAP) amplitudes will be recorded.<sup>48,49</sup> DML and CMAP will be measured by placing surface electrodes on the abductor pollicis brevis muscle, and stimulation applied 8 cm proximal to the active recording electrode. SNAP and SNCV will be obtained using ring electrodes placed on the proximal and distal interphalangeal joints of the index finger. Sensory conduction will be studied by antidromically stimulation at 14 cm proximal to the active electrode. Motor study will be performed by supramaximal stimulation while the amplitude will be measured an average of 10 times for the sensory study. All measurements will be made 3 times, and the values obtained will be averaged for analysis.

■ Ultrasound parameters

The cross-sectional area (CSA) will be measured using an electronic caliper at the scaphoid-pisiform level.<sup>51,52</sup> The measurements will be made 3 times, and the values obtained will be averaged for analysis.

**Adverse events**

All adverse events, defined as any negative or unwanted reactions to intervention, will be recorded through the symptoms reported by the patients, and observations by a researcher at every visit. Therapeutic ultrasound may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. Night splint may cause skin allergy, wrist stiffness, et al. The participants will be instructed to do gentle range-of-motion exercises when removing the splint to prevent stiffness and reinforced adherence by verbal instruction.

## 407 Sample size calculation

408 Sample size and power calculation are based on the primary outcome of BCTQ-  
409 SSS score at 6-week. All sample size calculations assume two-sided analysis with a  
410 power of 90% ( $1-\beta=0.90$ ) at a significant level of  $\alpha=0.05$ . Based on a published RCT  
411 trial ([Lancet. 2018;392:1423-1433], the authors compared corticosteroid injection  
412 and night splint for CTS, and participants in the night splint group had a standard  
413 deviation [SD] of 0.76 points for BCTQ-SSS at their 6-week followup, ["6-week" was  
414 the primary endpoint in this study]),<sup>9</sup> a SD of 0.76-point on BCTQ-SSS score will be  
415 used. To detect a minimum clinically significant difference of 0.8-point<sup>53</sup> (superiority  
416 margin) between therapeutic ultrasound + night splint and night splint groups  
417 (assuming a true difference of 1.19-point<sup>9,54</sup>), a total of 48 participants in each group  
418 is required. Allowing for an up to 10% drop out rate, we aim to enroll at least 54  
419 participants in each group to complete the study.

## 420 Analysis plan

421 Baseline characteristics of the three treatment groups will be summarized using  
422 appropriate descriptive statistics. Both the primary and secondary analyses will be  
423 blind analyses of treatment assignments and will be performed using the intention-to-  
424 treat (ITT)<sup>55</sup> method, with all randomized participants retaining their original assigned  
425 group. Multiple imputation by chained equations will be used to address missing data  
426 caused by lost access and non-response if these missing data are judged to be random.

427 The primary comparisons for BCTQ-SSS scores will be made using linear  
428 regression. In secondary analyses, repeated measures mixed model<sup>56</sup> will also be used  
429 to examine the associations between treatments and repeated outcome measures, with  
430 terms of treatment, time, trial center and corresponding baseline values as covariates  
431 (age, gender, body mass index, et al.). Bonferroni method will be used to adjust for

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432 multiplicity.<sup>57,58</sup> Linear regression will be used for numerical outcomes, and  
433 logistic/ordinal regression for any categorical outcomes.

434 **Quality assurance/monitoring/management**

435 In order to standardize the procedures of staff training and learning, such as  
436 participants recruitment, outcome measures, data import, security, management and  
437 analysis, a Manual of Operations and Procedures and a case report form will be  
438 developed as per protocol, which also include the monitoring plans to assure  
439 participant protection and data integrity, thus facilitating consistency in protocol  
440 implementation and data collection. The investigators, physicians, research assistants,  
441 outcome assessors and statisticians are different people and should be trained in good  
442 clinical practice. Trained project managers will visit each centre for monitoring to  
443 ensure data quality and compliance with the trial protocol.

444 All data obtained will be stored electronically and strictly in a database with  
445 secure and restricted access. Encryption will be used for data transmission, with  
446 removal for any information that can identify individuals. Data will only be de-  
447 identified for analysis at the completion of this study.

448 **Study duration**

449 Recruitment of the trial will begin in the November of 2021 and one-year follow-  
450 up for all participants is anticipated to be completed by June 2023. See **Table 1** for  
451 time points and recruitment progress.

452 **Ethics and dissemination**

453 This study has been approved by the Ethics Committee of Shanghai Sixth  
454 People's Hospital (lead Clinical Center, approval No. 2021-152), Ethics Committee of  
455 Shanghai East Hospital (EC.D(BG).016.03.1-2021-095), Ethics Committee of  
456 Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-194/01), and Ethics Committee

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3 457 of Pudong New Area People's Hospital (IRBY2021-006). The potential risks of this  
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6 458 clinical trial are considered minimal and are addressed in the protocol and consent  
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8 459 form. A written consent (**Supplemental file 1**) will be obtained by clinical  
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10 460 practitioners from each participant. The trial was registered on [www.chictr.org](http://www.chictr.org)  
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12 461 website (registration number ChiCTR2100050701). Data will be published in peer-  
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15 462 reviewed journals and presented at conferences, both nationally and internationally.  
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For peer review only

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**DISCUSSION**

CTS is a highly prevalent compression neuropathy, which results in significant paraesthesia and numbness in the median nerve distribution, especially nocturnal symptoms causing sleep disturbance, causing great socioeconomic burden. Up till now, there is still no consensus on the optimal management, and nonoperative treatment is generally accepted as the first-line intervention for mild and moderate CTS. Multiple methods have been studied and reviewed in the recent decades, however, the exact efficacy still remains controversial.

In an RCT published in BMJ for mild to moderate CTS, active therapeutic ultrasound (1 MHz, 1.0 W/cm<sup>2</sup>) was applied to the area over the carpal tunnel in the experimental group, and indistinguishable sham US treatment was applied in the control group.<sup>23</sup> At 6 months' follow up, satisfactory improvement or complete remission of symptoms was observed in 74% receiving active treatment, which is significantly higher than those receiving sham treatment (20%). As for electroneurography, DML and SNCV improved significantly with active treatment while remained unchanged with sham treatment. Hand grip and finger pinch strength in physical examination also improved significantly with active treatment. All results suggested satisfying effects from therapeutic ultrasound for CTS.

Therapeutic ultrasound can also be used as part of a multi-intervention approach. Some studies have compared night splint alone to night splint combined with therapeutic ultrasound in treatment of CTS, while the effects were different, and the grades of study design and data were low. Dincer U et al.<sup>26</sup> found that the improvements in the combined group were statistically significantly better (p=0.043) than those in night splint alone group in BCTQ-SSS, as well as BCTQ-FSS (p<0.001), and VAS for pain (p<0.001). Similar results were also reported by Baysal



O et al.<sup>59</sup>; while Jothi KP et al.<sup>27</sup>, Sim SE et al.<sup>28</sup> and Armagan O et al.<sup>29</sup> found therapeutic ultrasound may add no benefit to splinting in CTS.

In this study, to the best of our knowledge, it is the first to compared the efficacy between therapeutic ultrasound [therapeutic ultrasound group] and night splint [night splint group] in CTS treatment. What's more, the additional effects of therapeutic ultrasound [therapeutic ultrasound + night splint group] in a multi-intervention approach will be compared with night splint alone [night splint group]. In clinic, therapeutic ultrasound is less invasive, less expensive, safer and more portable than other nonoperative therapy like drug injections for compression neuropathy and, if proved to be effective, could be offered to selected patients as part of non-operative therapy.

There are some on-going clinical trials on CTS treatment recent years,<sup>60-63</sup> and our prospective randomized study proposes to complement and add to this relevant and much needed scientific effort.

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- 684 **Figure Legends**
- 685 **Figure 1** Participant flow chart
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**Table 1** Study evaluation procedures and timeline

Study procedure	Medical evaluation	Enrolment visit	6 weeks	3 months	6 months	One year
Determine eligibility	✓	✓				
Obtain signed consent		✓				
Obtain medical and demographic data		✓				
Give instructions for Pain medication diary		✓				
Outcome measures						
Boston Carpal Tunnel Questionnaire		✓	✓	✓	✓	✓
Interrupted sleep questionnaire		✓	✓	✓	✓	✓
EuroQol-5D		✓	✓	✓	✓	✓
Hospital Anxiety and Depression Scale		✓	✓	✓	✓	✓
Work Limitations Questionnaire-25		✓	✓	✓	✓	✓
Treatment success rate			✓	✓	✓	✓
Treatment recurrence rate				✓	✓	✓
Physical examination		✓	✓	✓	✓	✓
Electrophysiological and ultrasound parameters		✓	✓	✓	✓	✓

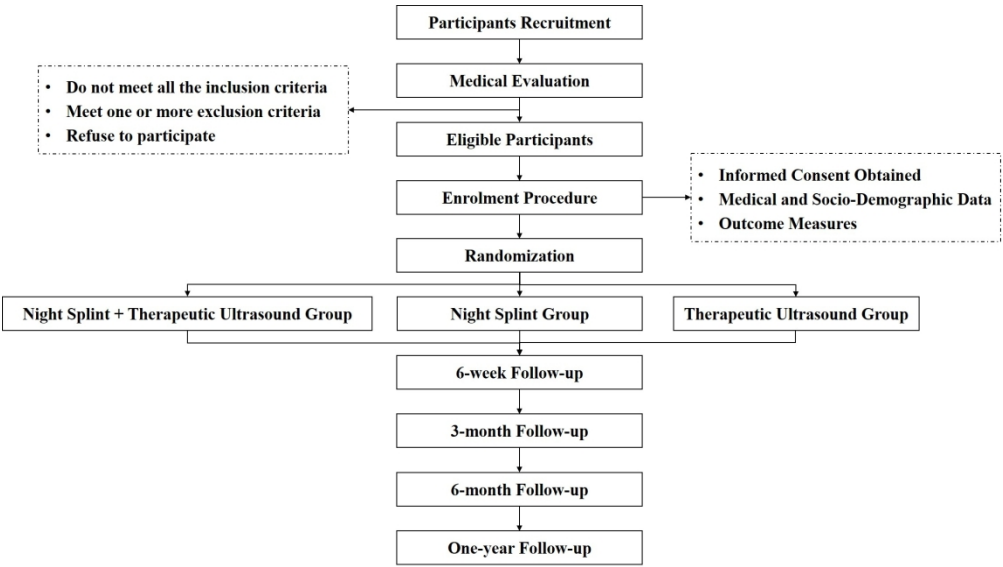


Figure 1 Participant flow chart

377x212mm (150 x 150 DPI)

# INFORMED CONSENT FORM

(English Version)

## Participant Information Page

**Study Title** : Effectiveness of ultrasound therapy for the treatment of carpal tunnel syndrome  
**Principal Investigator** : Cunyi Fan  
**Sponsor** : Shanghai Sixth People's Hospital

Dear participant:

You have been diagnosed with carpal tunnel syndrome, and will be invited to participate in the study named "Effectiveness of ultrasound therapy for the treatment of carpal tunnel syndrome". The study is conducted by the researchers themselves. Please read this informed consent carefully and make the decision whether to participate in this study or not. Participation in this study is entirely your choice. As a participant, you must give your written consent prior to joining the clinical study. When your doctor or researcher discusses informed consent with you, you can ask him or her to explain to you what you don't understand. We encourage you to discuss this thoroughly with your family and friends before making any decision to participate in this study. You have the right to refuse to participate in the study or withdraw from the study at any time without being penalized or losing your rights. If you are participating in another study, please inform your study doctor or investigator. The background, purpose, process and other important information of this study are as follows:

### 1. BACKGROUND

Carpal tunnel syndrome (CTS), the most common compression neuropathy, results from median nerve entrapment in the carpal tunnel, accounting for about 90% of all such disorders. The clinically confirmed CTS prevalence was 9.6% in the general population of China, with a yearly incidence rate of 2.76%, and women is more susceptible than men. CTS has significant impact on daily life and ability to work, and causes great burden on social economy, with an annual associated cost estimated at \$13 billion. Classically, CTS causes discomfort, paraesthesia and numbness in the median nerve distribution; and nocturnal symptoms are often clinically significant causing sleep disturbance. Patients can

be diagnosed by clinical history and physical examination; while electrophysiological methods will be additional for insufficient diagnosis by clinical findings and severe cases that need surgical management.

In general, the severity of CTS can be classified into mild, moderate and severe. Non-surgical interventions are suggested to be the first choice to treat mild and moderate CTS. To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. A consensus of multidisciplinary treatment guideline from the European HANDGUIDE Study suggests that “education” should be included as the first-line management approach, which has the advantages of low cost, high efficacy and non-invasiveness. In addition, “night splint (NS)” and “corticosteroid injection (CI)” are also recommended in guidelines of American Academy of Orthopaedic Surgeons (AAOS) and American Physical Therapy Association (APTA). One recent RCT published in Lancet compares both two methods, and finds that CI has superior clinical effectiveness at 6 weeks than NS, but no differences at 6 months; while CI may bring adverse events like thinning, lightening or darkening of the skin at the injection site, hot flushes and even more pain. Systematic reviews have also shown that the effects of other conservative treatments like acupuncture, exercise and mobilization interventions, laser, extracorporeal shockwave therapy and platelet-rich plasma injection still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. In the intensity range of 0.5-2.0 W/cm<sup>2</sup>, US may have the potential to induce a variety of biophysical effects in tissues. US experiments on stimulation of nerve conduction and regeneration, and discoveries of its anti-inflammatory effects all support that US may promote recovery of nerve compression. An RCT published in BMJ showed more pronounced subjective symptoms and electroneurographic variables for US treatment than sham control in patients with mild to moderate CTS. However, to our best of knowledge, no study has compared the efficacy between NS and US in CTS treatment yet. Additionally, some studies have also reported the efficacy of US to be used as part of a multi-intervention approach, but with low grade of study design and data. Therefore, the role of US in CTS treatment still needs to be further explored by high-quality study.

**2. STUDY PURPOSE**

The purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for CTS, that is, NS+US (combined) versus NS versus US, on clinical and functional outcomes, including Boston Carpal Tunnel

Questionnaire (BCTQ).

### 3. STUDY PROCESS

#### (1) How many people will participate in the study?

About 162 people will participate in the study at 4 municipal tertiary hospitals: Shanghai Sixth People's Hospital (leader unit), Shanghai East Hospital (participating unit), Shanghai Tenth People's Hospital (participating unit) and Pudong New Area People's Hospital of Shanghai (participating unit).

#### (2) What are the study procedures?

Before you are enrolled in the study, your medical history will be asked, and you will be screened for carpal tunnel syndrome by using criteria developed from a consensus survey by the UK Primary Care Rheumatology Society.

After determining that you are eligible to participate in the study based on inclusion and exclusion criteria, you will be collected and randomly assigned to treatment:

##### *A. Characteristic features collection*

You will be asked for your age, sex, body mass index, affected wrist (whether bilateral), dominant arm, lifestyle (smoking and alcohol use), and medical history. As well as relevant questions about symptoms duration and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-time work, manual or non-manual labor), employment status (whether on sickness absence), professional activity characteristics, and sports activities will be also collected.

##### *B. Clinical features collection*

You will complete the following questionnaires, including Boston Carpal Tunnel Questionnaire (BCTQ) for wrist function and symptom, sleep questionnaire for interrupted sleep, EuroQol-5D (EQ-5D) for life quality and health status, Hospital Anxiety and Depression Scale (HADS) for anxiety and depression status, Work Limitations Questionnaire (WLQ)-25 for functional limitations at work, Global Rating of Change (GROC) for treatment success and recurrence rate, as well as physical function examination and various electrophysiology and ultrasound parameters.

##### *C. Treatment by group*

At the beginning, all participants will participate in an about 30-minute group educational presentation by a research assistant on the same day as the baseline assessment. This presentation will cover the pathophysiology, treatment options, posture and activity

modification principles of CTS. The above information will also be provided to participants in the form of education booklets, to encourage them to review at home. Habits changes include limited wrist movement and a reduction in strenuous work activities, and the use of ergonomically friendly work tools helps reduce median nerve pressure.

You will be randomly assigned to one of three groups, [US group] vs. [NS group] vs. [US+NS group]:

(a) If you are assigned in the [US group], you will receive pulsed therapeutic ultrasound (model 1:4, Shanghai, China) for 6 weeks at a frequency of 1 MHz and intensity of 1.0 W/cm<sup>2</sup> for 15 minutes per session, in daily 5 times a week for the first 2 weeks and twice a week for another 4 weeks, to the area over the carpal tunnel, referred to a published trial [BMJ. 1998;316:731-735].

(b) If you are allocated to the [NS group], you will receive a splint to wear at night for 6 weeks, referred to a published trial [Lancet. 2018;392:1423-1433]. The splint holds the wrist in a neutral position or slightly extended 20° from the neutral position to avoid wrist movement, which can increase pressure on the carpal tunnel. The choose of each splint will be based on the size of each of your hands and arms. You will be shown how to fit and remove the wrist splint according to a standardized trial protocol. Oral guidance from the clinician on how and when to use splints will encourage and reinforce compliance, which will be also supported by written information, detailed care, and splint fitting and use. You will be instructed to perform gentle range-of-motion exercises when removing the splint to prevent stiffness.

(c) If you are randomized to the [US+NS group], you will receive both US for 6 weeks as in the [US group] and NS for 6 weeks as in the [NS group].

We discourage additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allowed the use of simple analgesics as needed. You will report all not per protocol treatments, such as drugs, in a diary.

*D. Follow-up features collection*

Follow-up data will be collected during your visits to the hospital at 6 weeks, 3 and 6 months, and one year after random assignment.

**(3) How long will the study last?**

This study will continue for 1 year from the time you receive treatment, and we will collect follow-up information from you at 6 weeks, 3 months, 6 months, and one year at your regular outpatient review.

You may drop out of the study at any time without losing any benefits to which you are entitled. However, if you decide to withdraw during the study, you are encouraged to



talk to your doctor first. If you experience a serious adverse event, or if your study doctor feels it is not in your best interest to continue in the study, he or she may decide to withdraw you from the study. The sponsor or regulatory agency may also terminate during the study period. However, your withdrawal will not affect your normal medical treatment and rights.

If you withdraw from the study for any reason, you may be asked about your participation in the study. You may also be asked for a medical examination and follow-up questionnaire if your doctor deems it necessary.

#### **(4) Information and biological specimens collected during the study**

Biological specimens are not involved in this study, and the information collected is basic characteristics features, preoperative and follow-up clinical features (see the study procedures for details).

All data obtained will be kept strict and stored electronically on a database with secured and restricted access. An encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

### **4. RISKS AND BENEFITS**

#### **(1) What are the risks of participating in this study?**

The risks you may incur by participating in this study are as follows. You should discuss these risks with your study doctor or, if you prefer, with your regular care provider.

US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. The occurrence of these reactions depends on the dose of treatment, the extent of the lesion, and the individual patient, and usually does not require special treatment. Severe adverse reactions can be treated locally, or prolong the interval of treatment, reduce the intensity of treatment. If the treatment does not improve or abnormal conditions occur, the treatment should be stopped and immediately go to the hospital.

NS treatment may cause skin allergy, wrist stiffness, et al. You will be instructed to do gentle range-of-motion exercises when removing the splint to prevent stiffness and reinforced adherence by verbal instruction.

If you experience any discomfort, new changes, or any unexpected conditions during the study period, whether or not related to the study, you should inform your doctor in a timely manner, and he/she will judge and administer appropriate medical treatment.

During the study period, you need to visit the hospital on time and do some

examinations, which will take up some of your time and may cause trouble or inconvenience to you.

**(2) What are the benefits of participating in the study?**

If you agree to participate in this study, you may receive direct medical benefits, such as accelerated relief of symptoms of CTS. You can also have a deeper understanding of diseases and so on. In addition, we hope that the information gained from your participation in this study will benefit you or other patients with similar conditions in the future.

**5. ALTERNATIVE TREATMENT OPTIONS**

In addition to participating in this study, you may receive the other treatments provided by your doctor: corticosteroid injection, acupuncture, exercise and mobilization interventions, laser, extracorporeal shockwave therapy and platelet-rich plasma injection, and surgery, etc.

Please discuss these and other possible options with your doctor.

In general, the severity of CTS can be classified into mild, moderate and severe. Non-surgical interventions are suggested to be the first choice to treat mild and moderate CTS. To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. A consensus of multidisciplinary treatment guideline from the European HANDGUIDE Study suggests that “education” should be included as the first-line management approach, which has the advantages of low cost, high efficacy and non-invasiveness. In addition, “night splint (NS)” and “corticosteroid injection (CI)” are also recommended in guidelines of American Academy of Orthopaedic Surgeons (AAOS) and American Physical Therapy Association (APTA). One recent RCT published in Lancet compares both two methods, and finds that CI has superior clinical effectiveness at 6 weeks than NS, but no differences at 6 months; while CI may bring adverse events like thinning, lightening or darkening of the skin at the injection site, hot flushes and even more pain. Systematic reviews have also shown that the effects of other conservative treatments like acupuncture, exercise and mobilization interventions, laser, extracorporeal shockwave therapy and platelet-rich plasma injection still remain controversial or provide little to no benefit.

**6. USE OF RESEACH RESULTS AND CONFIDENTIALITY OF PERSONAL INFORMATION**

Results conducted through this program may be published in medical journals with the understanding and assistance of you and other participants, but we will keep your study records confidential as required by law.

The personal information of study participants will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws.

If necessary, government administrative departments, hospital ethics committees and other relevant researchers can access your data according to regulations.

## **7. RESEARCH EXPENSES AND RELATED COPENSAATION**

### **(1) Cost of drugs/instruments used in the study and related examinations**

There are no potential additional costs for this study. Routine outpatient fees include registration, examination for CTS, oral non-steroidal anti-inflammatory drugs, etc. The expenses related to US and NS will be borne by our research group and funding. In addition, you will be solely responsible for the expenses incurred by you for any treatment other than this study, as well as for the routine treatment and examination required for any concurrent disease.

### **(2) Compensation for participation in the study**

There are no additional compensation costs for this study.

### **(3) Compensation/compensation after damage**

For participants who suffer damage related to this study, the sponsor Shanghai Sixth People's Hospital will bear the treatment cost and corresponding economic compensation in accordance with Chinese laws and regulations.

## **8. RIGHTS OF PARTICIPANTS AND RELEVANT MATTERS NEEDING ATTENTION**

### **(1) Your rights**

Your participation in the study is voluntary throughout the entire process.

If you decide not to participate in this study, it will not affect other treatments you should receive.

If you decide to participate, you will be asked to sign this written informed consent. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your medical treatment and rights will not be affected.

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**(2) Matters needing attention**

As a subject, you are required to provide true information about your medical history and current medical condition;

Inform the study doctor of any discomfort observed during the study;

Do not take any restricted drugs, food, etc. as advised by your doctor;

Tell the study doctor if you have recently participated in or are currently participating in other studies.

During the intervention, we discouraged additional therapy (i.e., not according to the grouping protocol), but we permitted the use of analgesics when needed (only acetaminophen and NSAIDs).

For medications taken, the name, dose, frequency and duration will be recorded at all follow-up visits.

**9. RELEVANT CONTACT INFORMATION**

If there is any significant new information during the study that may affect your willingness to continue to participate, your doctor will inform you promptly. If you are interested in your own study data, or you would like to know the findings after this study, you may ask any questions about this study at any time and receive answers accordingly, Please contact doctor Shuai Chen at \*\*\*\*\*.

## Participant Signature Page

### Informed Consent Statement:

I have been informed of the purpose, background, process, risks and benefits of this study. I have plenty of time and opportunity to ask questions, and I am satisfied with the answers.

I am also told who to contact when I have questions, want to report difficulties, concerns, suggestions for research, or want further information, or to help with research.

I have read this informed consent and agree to participate in this study.

I understand that I may choose not to participate in the study or withdraw from the study at any time during the study without any reason.

I already know that if I get worse, or if I have a serious adverse event, or if my study doctor decides it's not in my best interest to continue, he or she will decide to withdraw me from the study. The funder or regulatory agency may terminate during the study without my consent. If this happens, the doctor will inform me and the study doctor will discuss other options with me.

I will be provided with a copy of the informed consent which contains my signature and that of the investigator.

Participant Signature: \_\_\_\_\_

Date: \_\_\_\_\_

(NOTE: If participant has no capacity/limited capacity, legal representative signature and date will be required)

Legal Representative's Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Investigator Signature: \_\_\_\_\_

Date: \_\_\_\_\_

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

			Page
Reporting Item			Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered,	4/6

		name of intended registry	
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	4/6
Protocol version	<a href="#">#3</a>	Date and version identifier	5
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	2
Roles and responsibilities: sponsor contact information	<a href="#">#5b</a>	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2

## Introduction

1	Background and	<a href="#">#6a</a>	Description of research question and justification for	8-9
2				
3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
6				
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	8-9
12				
13	rationale: choice of			
14				
15	comparators			
16				
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18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	10
19				
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21				
22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	10
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
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32	Methods:			
33				
34	Participants,			
35				
36	interventions, and			
37				
38	outcomes			
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41				
42	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	10
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
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52	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	11-12
53			applicable, eligibility criteria for study centres and	
54			individuals who will perform the interventions (eg,	
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		surgeons, psychotherapists)	
Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-14
description			
Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	13-14
modifications			
Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
adherence			
Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
concomitant care			
Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-19
Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	20-21

1	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study	19
2			objectives and how it was determined, including clinical and	
3			statistical assumptions supporting any sample size	
4			calculations	
5				
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11	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to	10-11
12			reach target sample size	
13				
14				
15				
16	<b>Methods: Assignment</b>			
17	<b>of interventions (for</b>			
18	<b>controlled trials)</b>			
19				
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24	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	12-13
25	generation		computer-generated random numbers), and list of any	
26			factors for stratification. To reduce predictability of a	
27			random sequence, details of any planned restriction (eg,	
28			blocking) should be provided in a separate document that is	
29			unavailable to those who enrol participants or assign	
30			interventions	
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41	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,	12-13
42	concealment		central telephone; sequentially numbered, opaque, sealed	
43	mechanism		envelopes), describing any steps to conceal the sequence	
44			until interventions are assigned	
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51	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	12-13
52	implementation		participants, and who will assign participants to	
53			interventions	
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Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12-13
Blinding (masking): emergency unblinding	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12-13
<b>Methods: Data collection, management, and analysis</b>			
Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14, 19- 21
Data collection plan: retention	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14, 19- 21
Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	14, 19- 21

1		Reference to where details of data management	
2		procedures can be found, if not in the protocol	
3			
4			
5			
6	Statistics: outcomes	<a href="#">#20a</a> Statistical methods for analysing primary and secondary	19-20
7		outcomes. Reference to where other details of the	
8		statistical analysis plan can be found, if not in the protocol	
9			
10			
11			
12			
13	Statistics: additional	<a href="#">#20b</a> Methods for any additional analyses (eg, subgroup and	19-20
14	analyses	adjusted analyses)	
15			
16			
17			
18	Statistics: analysis	<a href="#">#20c</a> Definition of analysis population relating to protocol non-	19-20
19	population and	adherence (eg, as randomised analysis), and any statistical	
20	missing data	methods to handle missing data (eg, multiple imputation)	
21			
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23			
24			
25			
26	<b>Methods: Monitoring</b>		
27			
28			
29	Data monitoring:	<a href="#">#21a</a> Composition of data monitoring committee (DMC);	14, 19-
30	formal committee	summary of its role and reporting structure; statement of	21
31		whether it is independent from the sponsor and competing	
32		interests; and reference to where further details about its	
33		charter can be found, if not in the protocol. Alternatively, an	
34		explanation of why a DMC is not needed	
35			
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44	Data monitoring:	<a href="#">#21b</a> Description of any interim analyses and stopping	14, 19-
45	interim analysis	guidelines, including who will have access to these interim	21
46		results and make the final decision to terminate the trial	
47			
48			
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51	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing	19
52		solicited and spontaneously reported adverse events and	
53		other unintended effects of trial interventions or trial	
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		conduct	
Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
<b>Ethics and dissemination</b>			
Research ethics approval	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21
Consent or assent: ancillary studies	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	21

1	interests		investigators for the overall trial and each study site	
2				
3				
4	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	14, 19-
5				
6			and disclosure of contractual agreements that limit such	21
7				
8			access for investigators	
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11	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	19-21
12				
13	trial care		compensation to those who suffer harm from trial	
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15			participation	
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19	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	19-21
20				
21	trial results		results to participants, healthcare professionals, the public,	
22				
23			and other relevant groups (eg, via publication, reporting in	
24				
25			results databases, or other data sharing arrangements),	
26				
27			including any publication restrictions	
28				
29				
30				
31	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	19-21
32				
33	authorship		professional writers	
34				
35				
36	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	19-21
37				
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41				
42	Appendices			
43				
44				
45	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given	21
46				
47	materials		to participants and authorised surrogates	
48				
49				
50	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	/
51				
52			biological specimens for genetic or molecular analysis in	
53				
54			the current trial and for future use in ancillary studies, if	
55				
56			applicable	
57				
58				
59				
60				

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