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Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

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51	
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53	The authors, their immediate families, and any research foundation with which
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The Ethics Committee of the 4 clinical centers have approved this study. The Ethics Committee approval number of the leading clinical center (Shanghai Sixth People's Hospital) is 2021-153. The research registry number is ChiCTR2100050547 at http://www.chictr.org.cn. Data will be analyzed anonymously; all patients will approve the results of this study by oral consent. The oral consent approval will be documented in the patients' files. All clinical investigations will be conducted in accordance with the guidelines of the Declaration of Helsinki.

83 ABSTRACT

84 Introduction

Lateral elbow tendinopathy (LET) is a highly prevalent disease among middleaged population, with no consensus on optimal management. Nonoperative treatment is generally accepted as the first-line intervention. Ultrasound (US) therapy has been widely reported to be treatment beneficial in various orthopedics diseases including tendinopathy. The purpose of this study is to investigate the effectiveness of US for LET treatment.

91 Methods and analysis

This protocol entails a three-arm, prospective, multicenter, randomised controlled trial. 72 eligible participants with clinically confirmed LET will be assigned to either (1) US, (2) Corticosteroid Injections or (3) control group. All participants will receive an Exercise-based Therapy as fundamental intervention. Primary outcome is Patient-Rated Tennis Elbow Evaluation. Secondary outcomes included Visual Analogue Scale for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 for functional limitations at work, EuroQol-5D for general health, Hospital Anxiety and Depression Scale for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction. Adverse events will be recorded. Intention-to-treat analyses will be used.

103 Ethics and dissemination

Ethics Committees of all clinical centers have approved this study. The leading center is Shanghai Sixth People's Hospital, whose approval number is 2021-153. New versions with appropriate amendments will be submitted to the committee for further Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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108 local, national and international conferences.

109 Trial registration number

110 ChiCTR2100050547.

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112	STRENGTHS AND LIMITATIONS OF THIS STUDY
113	• Exercise-based Therapy as fundamental intervention for all participants with lateral
114	elbow tendinopathy (LET).
115	• The first randomised controlled trial (RCT) to compared the efficacy between
116	ultrasound therapy and corticosteroid injections in LET treatment.
117	• Multicenter RCT with blinded outcome assessor and statistician.
118	• Use of several patient-reported outcome measures as well as objective parameters.
119	• Participants and treating surgeons not blinded.
120	

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121 INTRODUCTION

First described by Runge,¹ lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution.² LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults.³ Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis".⁴ A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.^{5,6}

Though LET usually is a self-limiting condition, but complaints may last up to 2 years or longer,⁷ therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration.⁸ Surgery is only considered for patients with persistent pain and disability after a course of wellperformed conservative therapy, with a proportion as low as 3% in the whole LET population;² therefore, nonoperative treatment is suggested as first-line treatment.⁹

To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first-line intervention.¹⁰ EBT was also supported by high quality clinical trials¹¹⁻¹³ and systematic reviews^{14,15}, regarding as the most cost-effective treatment for LET.¹⁶

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The survey also showed, though the recurrence rate may be high and prognosis may be worsened in the long term,¹¹⁻¹³ the long mainstay treatment traditionally - corticosteroid injection (CI), due to its use for quick pain relief and physical functioning improvement, was still the most recommended first-line intervention apart from EBT and second-line intervention (27%).¹⁰ In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection,¹⁷ platelet-rich plasma injection,¹⁸ extracorporeal shock-wave therapy¹⁹ and acupuncture²⁰ still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators.²¹ US has been widely reported to be treatment beneficial in fracture nonunions,^{22,23} osteoarthritis,^{24,25} chronic muscle pain,^{26,27} soft tissue injury,²⁸ etc. As for tendinopathy, US is also reported to be a potential noninvasive treatment modality for frozen shoulder,^{29,30} rotator cuff.³¹ achilles^{32,33} and patellar³⁴ tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data,³⁵ and most of them focused on the comparison between US and extracorporeal shockwave therapy³⁶⁻⁴⁰. Therefore, the role of US in LET treatment still needs to be further explored by high-quality study. Additionally, to our best of knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

Therefore, the purpose of the current three-arm, prospective, randomized,
multicenter trial is to investigate the effectiveness of US in treatment for LET, that is,
US versus CI versus control, with a fundamental intervention of EBT, on clinical and
functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE) in
patients diagnosed with LET.

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171 METHODS

172 Study design

The design of this study is a three-arm, prospective, multicenter, randomised controlled trial, that will enroll participants with a diagnosis of chronic symptomatic LET 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.⁴¹

178 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.

193 Medical evaluation and enrolment procedure

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

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2		
3 ⊿	196	Inclusion criteria
5	107	
6	197	• Age ≥ 18 years old;
7 8 9	198	■ Unilateral lateral elbow pain longer than 6 weeks duration;
10 11	199	■ Pain over the lateral humeral epicondyle with pain severity of greater than 30 mm
12 13	200	on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following:
14 15 16	201	gripping, palpation, resisted wrist or middle finger extension, or stretching of
10 17 18	202	forearm extensor muscles with reduced pain-free grip; ^{11,42}
19 20	203	• Able to read and write in simplified Chinese (Mainland), understand and complete
21 22 22	204	the questionnaire, and should provide informed consent.
23 24 25	205	Exclusion criteria
26 27	206	• Concomitant musculoskeletal pain conditions reported by participants to be their
28 29	207	predominant complaint within the past 6 months;
30 31 32	208	• History of symptoms suggesting radicular, neurological, inflammatory or systemic
33 34	209	arthritic conditions;
35 36	210	Treatment by physiotherapy, electrophysical therapy, or injection within the past 6
37 38 20	211	months, or previous tennis elbow surgery;
40 41	212	Contraindications to US, including dermatological conditions, abnormal sensation
42 43	213	in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy
44 45 46	214	or breastfeeding, et al.;
40 47 48	215	Contraindications to CI, including hypertension, gastrointestinal ulcers, diabetes,
49 50	216	mental illness, et al.
51 52	217	Following the medical evaluation, a research assistant will meet with the eligible
53 54 55	218	participants and obtain written informed consent. Demographic variables will be
55 56 57	219	reported before treatment (baseline) of all participants regarding age, sex, body mass
58 59 60	220	index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous

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> medical history. Participants will also be asked relevant questions about duration of symptoms 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), and professional activity characteristics (repetitive movements for >4hours/day; wrist flexion for >2hours/day; elbow flexion and extension for >2hours/day; use of computer keyboard/ mouse [how many hours/day] and use of vibrating instruments for >2hours/day) will be also collected.

229 Randomization and blinding

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

238 The outcome assessor and statistician will be blinded to group allocation and not239 involved in treatment procedures.

240 Intervention

At the beginning, all participants will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. Participants will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment Page 13 of 45

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in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all participants will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles.¹⁰ The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs,^{11,13,43,44} mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm.

Pain-free gripping exercise with exercise putty, which allows practice of various
 different gripping actions.

260 2) Forearm extensor muscle exercise using a free-standing dumbbell. Note that the 261 forearm is fully stabilized by the bench and upper body in sound postural alignment. 262 Duration per repetition lasts about 6-10 s.

263 3) Dumbbell weight exercise for the forearm flexor muscle with 6-10 s per repetition.
264 The postural is the same as 2).

4) Exercises for forearm supinator and pronator muscles using an imbalanced adjustable dumbbell weight with 6-10 s per repetition, from end range of supination to pronation with the participant maintaining full active control of the weight. The elbow bent to 90° with the arm stabilizing besides the trunk. Progressions in load imposed on the muscles can be achieved by increasing the weight or by increasing the distance between weight and hand.

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271 5) Radial and ulnar deviation exercises are performed with similar equipment and272 guidelines in 4).

Education on recognition and correction of the poor posture from the pelvis to neck.
Once the spine and trunk are aligned more optimally then the upper limb position
should be addressed.

Participants in the [US group] will receive continuous mode US (Shanghai, China)
at a frequency of 1 MHz and intensity of 1.0 W/cm² for 10 minutes in 5 days per week
for 3 weeks on the maximum pain region of lateral elbow.

Participants allocated to the [CI group] will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

Participants randomized to the [Control group] will neither receive US therapy nor
corticosteroid injection. They will only receive the fundamental intervention, EBT
program.

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

295 Data management

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

304 Primary outcome measure

The primary outcome measure will be the difference in Patient-rated Tennis Elbow Evaluation (PRTEE). The PRTEE, formerly known as the Patient-Rated Forearm Evaluation Questionnaire, is a well validated composite scale measuring pain (5 items, with 0=no pain and 10=worst imaginable) and physical function (6 items for specific activities and 4 items for usual activities, with 0=no difficulty and 10=unable to do),⁴⁵ ranging from 0 to 100, with higher scores represent worse possible pain and more loss of function. The pain (intraclass correlation coefficients, ICC=0.89), physical function (ICC=0.83) and the total (ICC=0.89) scores all demonstrate excellent reliability.⁴⁶ A variation of 11/100 points or 37% of baseline scores are reported for clinical significance defined as "much better" or "completely recovered".⁴⁷ We use a validated Hong Kong Chinese version⁴⁸ of the PRTEE translated into simplified Chinese (Mainland) because the culture and language are the same.

317 Secondary outcome

318 Secondary outcome measures will be the differences in Visual Analogue Scale
319 (VAS)⁴⁹ for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand
320 (Quick-DASH)⁵⁰ for upper limb disability, pain free/maximum grip strength, Work

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Limitations Questionnaire-25 (WLQ-25)⁵¹ for functional limitations at work, EuroQol5D (EQ-5D)⁵² for life quality and health status, The Hospital Anxiety and Depression
Scale (HADS)⁵³ for anxiety and depression status, Global Rating of Change (GROC)
for treatment success and recurrence rate, and Mahomed scale⁵⁴ for participants'
satisfaction.

326 🔳 Pain

The VAS will be used for pain evaluation, which consists of a 100-mm horizontal numbered line anchored at one end (0) with the words "no pain" and at the other end (100) with the words "worst pain imaginable", and whose score is determined by the distance between the left end of the line and the participant's mark in mm.⁴⁹ VAS is considered to be the most sensitive of all pain scoring scales and has been specifically validated in the LET population with high reliability (r=0.89) and a moderate correlation with pain-free grip strength (r=0.47).⁵⁵ Participants are asked to score their pain on this line during rest (at time of measure), provocation and maximum grip strength. The provocation test is conducted on the outpatient clinic by resisted dorsiflexion of the wrist during full elbow extension. Clinically relevant improvement will be defined when a 50% decrease in VAS is observed before and after the treatment.⁵⁶ The consumption of rescue medication taken by each patient will be also recorded at each follow-up visit.

■ Upper limb disability

The well-validated simplified Chinese (Mainland) version of Quick-DASH⁵⁷ will be used for elbow function evaluation, which consists of eleven questions scored on a 5-point scale similar to the DASH.⁵⁰ 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.⁵⁸

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■ Grip strength

Pain free/maximum grip strength will be measured using a dynamometer (CAMRY, City of Industry, CA, USA). The participants will be asked to take a shoulder-width stance and allow their arms to hang loose, holding their arm adducted along the body and the elbow in full extension. The pain-free grip strength will be measured, followed by the measurement of the maximum grip strength, and 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 pain-free grip strength will be measured up to the point when the subject slowly squeezes the dynamometer until the occurrence of pain. The maximum grip strength will be measured at the maximum grip level. 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×100.59

• 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.⁵¹ 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.⁶⁰

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.⁵² It contains a five-dimension descriptive

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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 version⁶¹ of the EQ-5D, which has been recommended by
China Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQol
and health utility.⁶²

Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders - anxiety and depression.⁵³ There is evidence of increased levels of anxiety and depression in people with LET.⁶³ 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. HADS has two cut offs for categorization: 0-7, "non-case"; 8-10, "possible or doubtful case"; 11-21, "probable or definite case".⁶⁴

387 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.^{11,13} 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.^{11,13}

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Participants' satisfaction

397 Similarly, participants' level of satisfaction on the evolution of their condition will
398 be determined on a validated 4-point Likert scale ranging from "very satisfied",
399 "somewhat satisfied", "somewhat dissatisfied" to "very dissatisfied".⁶⁵

400 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. CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection.

411 Sample size calculation

Sample size and power calculation are based on the primary outcome of PRTEE score. All sample size calculations assume two-sided analysis with a power of 90% (1- β =0.90) at a significant level of α =0.05. Based on previous trial, a standard deviation (SD) of 5.1-point on PRTEE score will be used.⁶⁶ To detect a minimum clinically significant difference of 11.0-point⁴⁷ (superiority margin) between US and control groups (assuming a true difference of 15.6-point^{38,66}), a total of 22 participants in each group is required. Allowing for an up to 10% drop out rate, we aim to enroll at least 24 participants in each group to complete the study.

420 Analysis plan

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> 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)⁶⁷ 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 PRTEE scores will be made using linear regression. In secondary analyses, repeated measures mixed model⁶⁸ 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.

433 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

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for any information able to identify individuals. Data will be only deidentified foranalysis at the completion of this study.

447 Study duration

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

451 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 2021-153) 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 website (registration number ChiCTR2100050547). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

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DISCUSSION

LET is a highly prevalent degenerative condition, which results in significant pain and limited function in the affected upper limb and causes 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. Multiple methods have been studied and reviewed in the recent decades, however, the exact efficacy still remains controversial and the evidence is very low.

Both Yalvaç B³⁸ and Özmen T³⁶ have shown significant improvements in terms of pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a blank control group, which would make it confuse and unclear whether the efficacy come from US itself or passing time, as LET is a self-limited disease. In this study, under the fundamental intervention of EBT program, the effects of US [US group] will be compared with blank [control group]. In additional, to the best of our knowledge, this study is the first to compared the efficacy between US [US group] and CI [CI group] in LET treatment. In clinic, US is less invasive, less expensive, safer and more portable than other nonoperative therapy like drug injections for tendinopathy and, if proved to be effective, could be offered to selected patients as part of non-operative therapy.

In view of recent literature, CI should be discouraged in the treatment of LET.^{17,69} However, in order to satisfy the patient's need to relieve pain, CI are still commonly used in clinic. Therefore, a change in the paradigm of LET treatment is necessary. This change will come about through proposed evidence-based treatment guidelines. There are some on-going clinical trials on LET treatment recent years,^{42,70,71} and our prospective RCT proposes to complement and add to this relevant and much needed scientific effort.

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1		
2 3 4	487	REFERENCES
5 6 7	488	1. Knobloch K, Gohritz A. Dr Runge: a German pioneer in sclerosing therapy in
, 8 9	489	epicondylitis in 1873. Br J Sports Med. 2010.
10 11	490	2. Sanders TL Jr, Maradit Kremers H, Bryan AJ, et al. The epidemiology and health
12 13 14	491	care burden of tennis elbow: a population-based study. Am J Sports Med.
15 16	492	2015;43(5):1066-71.
17 18	493	3. Walker-Bone K, Palmer KT, Reading I, et al. Occupation and epicondylitis: a
19 20 21	494	population-based study. Rheumatology (Oxford). 2012;51(2):305-10.
22 23	495	4. Khan KM, Cook JL, Kannus P, et al. Time to abandon the "tendinitis" myth. BMJ.
24 25	496	2002;324(7338):626-7.
20 27 28	497	5. Haahr JP, Andersen JH. Physical and psychosocial risk factors for lateral
29 30	498	epicondylitis: a population based case-referent study. Occup Environ Med.
31 32	499	2003;60(5):322-9.
33 34 25	500	6. Herquelot E, Guéguen A, Roquelaure Y, et al. Work-related risk factors for
36 37	501	incidence of lateral epicondylitis in a large working population. Scand J Work
38 39	502	Environ Health. 2013;39(6):578-88.
40 41	503	7. Hudak PL, Cole DC, Haines AT. Understanding prognosis to improve rehabilitation:
42 43 44	504	the example of lateral elbow pain. Arch Phys Med Rehabil. 1996;77(6):586-93.
45 46	505	8. Ahmad Z, Siddiqui N, Malik SS, et al. Lateral epicondylitis: a review of pathology
47 48	506	and management. Bone Joint J. 2013;95-B(9):1158-64.
49 50 51	507	9. Vaquero-Picado A, Barco R, Antuña SA. Lateral epicondylitis of the elbow.
52 53	508	EFORT Open Rev. 2017;1(11):391-7.
54 55	509	10. Bateman M, Titchener AG, Clark DI, et al. Management of tennis elbow: a survey
56 57 58 59	510	of UK clinical practice. Shoulder Elbow. 2019;11(3):233-8.

Page 24 of 45

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

511 11. Coombes BK, Bisset L, Brooks P, et al. Effect of corticosteroid injection,
512 physiotherapy, or both on clinical outcomes in patients with unilateral lateral
513 epicondylalgia: a randomized controlled trial. JAMA. 2013;309(5):461-9.

- 514 12. Smidt N, van der Windt DA, Assendelft WJ, et al. Corticosteroid injections,
 515 physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised
 516 controlled trial. Lancet. 2002;359(9307):657-62.
- 517 13. Bisset L, Beller E, Jull G, et al. Mobilisation with movement and exercise,
 518 corticosteroid injection, or wait and see for tennis elbow: randomised trial. BMJ.
 519 2006;333(7575):939.
- 520 14. Karanasios S, Korakakis V, Whiteley R, et al. Exercise interventions in lateral
 521 elbow tendinopathy have better outcomes than passive interventions, but the effects
 522 are small: a systematic review and meta-analysis of 2123 subjects in 30 trials. Br J
 523 Sports Med. 2021;55(9):477-85.
 - 524 15. Hoogvliet P, Randsdorp MS, Dingemanse R, et al. Does effectiveness of exercise
 525 therapy and mobilisation techniques offer guidance for the treatment of lateral and
 526 medial epicondylitis? A systematic review. Br J Sports Med. 2013;47(17):1112-9.
- 527 16. Coombes BK, Connelly L, Bisset L, et al. Economic evaluation favours
 528 physiotherapy but not corticosteroid injection as a first-line intervention for chronic
 529 lateral epicondylalgia: evidence from a randomised clinical trial. Br J Sports Med.
 530 2016;50(22):1400-5.
 - 531 17. Dong W, Goost H, Lin XB, et al. Injection therapies for lateral epicondylalgia: a
 532 systematic review and Bayesian network meta-analysis. Br J Sports Med.
 533 2016;50(15):900-8.

BMJ Open

534	18. de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections
535	for chronic lateral epicondylar tendinopathy: a systematic review. Br J Sports Med.
536	2014;48(12):952-6.
537	19. Yoon SY, Kim YW, Shin IS, et al. Does the Type of Extracorporeal Shock Therapy
538	Influence Treatment Effectiveness in Lateral Epicondylitis? A Systematic Review
539	and Meta-analysis. Clin Orthop Relat Res. 2020;478(10):2324-39.
540	20. Chang WD, Lai PT, Tsou YA. Analgesic effect of manual acupuncture and laser
541	acupuncture for lateral epicondylalgia: a systematic review and meta-analysis. Am
542	J Chin Med. 2014;42(6):1301-14.
543	21. Watson T. Ultrasound in contemporary physiotherapy practice. Ultrasonics.
544	2008;48(4):321-9.
545	22. Leighton R, Watson JT, Giannoudis P, et al. Healing of fracture nonunions treated
546	with low-intensity pulsed ultrasound (LIPUS): A systematic review and meta-
547	analysis. Injury. 2017;48(7):1339-47.
548	23. Korstjens CM, Rutten S, Nolte PA, et al. Low-intensity pulsed ultrasound increases
549	blood vessel size during fracture healing in patients with a delayed-union of the
550	osteotomized fibula. Histol Histopathol. 2018;33(7):737-46.
551	24. Rutjes AW, Nüesch E, Sterchi R, et al. Therapeutic ultrasound for osteoarthritis of
552	the knee or hip. Cochrane Database Syst Rev. 2010;(1):CD003132.
553	25. Alfredo PP, Junior WS, Casarotto RA. Efficacy of continuous and pulsed
554	therapeutic ultrasound combined with exercises for knee osteoarthritis: a
555	randomized controlled trial. Clin Rehabil. 2020;34(4):480-90.
556	26. Ebadi S, Henschke N, Forogh B, et al. Therapeutic ultrasound for chronic low back
557	pain. Cochrane Database Syst Rev. 2020;7(7):CD009169.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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45 46
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60

1 2

558 27. Altan L, Kasapoğlu Aksoy M, Kösegil Öztürk E. Efficacy of diclofenac &
559 thiocolchioside gel phonophoresis comparison with ultrasound therapy on acute
560 low back pain; a prospective, double-blind, randomized clinical study. Ultrasonics.
561 2019;91:201-5.

- 28. Lai WC, Iglesias BC, Mark BJ, et al. Low-Intensity Pulsed Ultrasound Augments
 Tendon, Ligament, and Bone-Soft Tissue Healing in Preclinical Animal Models: A
 Systematic Review. Arthroscopy. 2021;37(7):2318-33.e3.
- 565 29. Ebenbichler GR, Erdogmus CB, Resch KL, et al. Ultrasound therapy for calcific
 566 tendinitis of the shoulder. N Engl J Med. 1999;340(20):1533-8.
- 30. Pieber K, Grim-Stieger M, Kainberger F, et al. Long-Term Course of Shoulders
 After Ultrasound Therapy for Calcific Tendinitis: Results of the 10-Year FollowUp of a Randomized Controlled Trial. Am J Phys Med Rehabil. 2018;97(9):651-8.
 31. Desmeules F, Boudreault J, Roy JS, et al. The efficacy of therapeutic ultrasound for
 rotator cuff tendinopathy: A systematic review and meta-analysis. Phys Ther Sport.
 2015;16(3):276-84.

573 32. Chester R, Costa ML, Shepstone L, et al. Eccentric calf muscle training compared 574 with therapeutic ultrasound for chronic Achilles tendon pain--a pilot study. Man 575 Ther. 2008;13(6):484-91.

- 576 33. Draper DO, Edvalson CG, Knight KL, et al. Temperature increases in the human
 577 achilles tendon during ultrasound treatments with commercial ultrasound gel and
 578 full-thickness and half-thickness gel pads. J Athl Train. 2010;45(4):333-7.
- 579 34. Stasinopoulos D, Stasinopoulos I. Comparison of effects of exercise programme,
 580 pulsed ultrasound and transverse friction in the treatment of chronic patellar
 581 tendinopathy. Clin Rehabil. 2004;18(4):347-52.

Page 27 of 45

BMJ Open

35. Dingemanse R, Randsdorp M, Koes BW, et al. Evidence for the effectiveness of
electrophysical modalities for treatment of medial and lateral epicondylitis: a
systematic review. Br J Sports Med. 2014;48(12):957-65.
36. Özmen T, Koparal SS, Karataş Ö, et al. Comparison of the clinical and sonographic

- 586 effects of ultrasound therapy, extracorporeal shock wave therapy, and Kinesio
 587 taping in lateral epicondylitis. Turk J Med Sci. 2021;51(1):76-83.
- 588 37. Dedes V, Tzirogiannis K, Polikandrioti M, et al. Comparison of radial
 589 extracorporeal shockwave therapy with ultrasound therapy in patients with lateral
 590 epicondylitis. J Med Ultrason (2001). 2020;47(2):319-25.
- 38. Yalvaç B, Mesci N, Geler Külcü D, et al. Comparison of ultrasound and
 extracorporeal shock wave therapy in lateral epicondylosis. Acta Orthop Traumatol
 Turc. 2018;52(5):357-62.
- 39. Kubot A, Grzegorzewski A, Synder M, et al. Radial Extracorporeal Shockwave
 Therapy and Ultrasound Therapy in the Treatment of Tennis Elbow Syndrome.
 Ortop Traumatol Rehabil. 2017;19(5):415-26.
 - 40. Lizis P. Analgesic effect of extracorporeal shock wave therapy versus ultrasound
 therapy in chronic tennis elbow. J Phys Ther Sci. 2015;27(8):2563-7.
- 41. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and
 elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
 - 42. Lungu E, Grondin P, Tétreault P, et al. Ultrasound-guided tendon fenestration
 versus open-release surgery for the treatment of chronic lateral epicondylosis of the
 elbow: protocol for a prospective, randomised, single blinded study. BMJ Open.
 2018;8(6):e021373.
 - 605 43. Coombes BK, Bisset L, Connelly LB, et al. Optimising corticosteroid injection for
 606 lateral epicondylalgia with the addition of physiotherapy: a protocol for a

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

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44
44
45
40
47
48
49
50
51
52
52
55
54
55
56
57
58
59
60

607 randomised control trial with placebo comparison. BMC Musculoskelet Disord
608 2009;10:76.
609 44. Vicenzino B. Lateral epicondylalgia: a musculoskeletal physiotherapy perspective
610 Man Ther. 2003;8(2):66-79.
611 45. Rompe JD, Overend TJ, MacDermid JC. Validation of the Patient-rated Tenni
Elbow Evaluation Questionnaire. J Hand Ther. 2007;20(1):3-10; quiz 11.
613 46. Giray E, Karali-Bingul D, Akyuz G. The Effectiveness of Kinesiotaping, Shar
614 Taping or Exercises Only in Lateral Epicondylitis Treatment: A Randomize
615 Controlled Study. PM R. 2019;11(7):681-93.
616 47. Poltawski L, Watson T. Measuring clinically important change with the Patient
617 rated Tennis Elbow Evaluation. Hand Therapy 2011;16:52-7.
618 48. Leung HB, Yen CH, Tse PY. Reliability of Hong Kong Chinese version of th
619 Patient-rated Forearm Evaluation Questionnaire for lateral epicondylitis. Hon
620 Kong Med J. 2004;10(3):172-7.
621 49. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and
622 change scores: a reanalysis of two clinical trials of postoperative pain. J Pair
623 2003;4(7):407-14.
624 50. Beaton DE, Wright JG, Katz JN. Development of the QuickDASH: comparison o
three item-reduction approaches. J Bone Joint Surg Am. 2005;87(5):1038-46.
626 51. Lerner D, Amick BC 3rd, Rogers WH, et al. The Work Limitations Questionnaire
627 Med Care. 2001;39(1):72-85.
628 52. EuroQol Group. EuroQola new facility for the measurement of health-related
629 quality of life. Health Policy. 1990;16(3):199-208.
630 53. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiat
631 Scand. 1983;67(6):361-70.
2

Page 29 of 45

BMJ Open

632	54. Mahomed N, Gandhi R, Daltroy L, et al. The sel
633	scale for primary hip and knee arthroplasty. Arth
634	55. Stratford PW, Levy DR, Gauldie S, et al. Exte
635	validation of selected outcome measures. Physiot
636	56. Shin KM, Kim JH, Lee S, et al. Acupuncture for la
637	study protocol for a randomized, practitioner-a
638	clinical trial. Trials. 2013;14:174.
639	57. Cao S, Zhou R, Zhou H, et al. Reliability and vali
640	of Quick Disabilities of the Arm, Shoulder, and H
641	cross-cultural adaptation and validation. Clin Rh
642	58. Franchignoni F, Vercelli S, Giordano A, et
643	difference of the disabilities of the arm, shou
644	(DASH) and its shortened version (QuickDAS
645	2014;44(1):30-9.
646	59. Smidt N, van der Windt DA, Assendelft WJ, et a
647	the assessment of severity of complaints, grip str
648	in patients with lateral epicondylitis. Arch Phys N
649	60. Roy JS, MacDermid JC, Amick BC 3rd, et al
650	presenteeism scales in chronic work-related upper
651	2011;91(2):254-66.
652	61. Wu C, Gong Y, Wu J, et al. Chinese Version o
653	Applicability in a Chinese General Population. P
654	62. Sun S, Chen J, Johannesson M, et al. Population
655	results, by age, sex and socio-economic status, f
656	Survey 2008. Qual Life Res. 2011;20(3):309-20.

632	54. Mahomed N, Gandhi R, Daltroy L, et al. The self-administered patient satisfactio
633	scale for primary hip and knee arthroplasty. Arthritis. 2011;2011:591253.
634	55. Stratford PW, Levy DR, Gauldie S, et al. Extensor carpi radialis tendonitis: A
635	validation of selected outcome measures. Physiotherapy Canada 1987;39(4):250-5
636	56. Shin KM, Kim JH, Lee S, et al. Acupuncture for lateral epicondylitis (tennis elbow)
637	study protocol for a randomized, practitioner-assessor blinded, controlled pilo
638	clinical trial. Trials. 2013;14:174.
639	57. Cao S, Zhou R, Zhou H, et al. Reliability and validity of Simplified Chinese versio
640	of Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire
641	cross-cultural adaptation and validation. Clin Rheumatol. 2019;38(11):3281-7.
642	58. Franchignoni F, Vercelli S, Giordano A, et al. Minimal clinically importar
643	difference of the disabilities of the arm, shoulder and hand outcome measur
644	(DASH) and its shortened version (QuickDASH). J Orthop Sports Phys The
645	2014;44(1):30-9.
646	59. Smidt N, van der Windt DA, Assendelft WJ, et al. Interobserver reproducibility c
647	the assessment of severity of complaints, grip strength, and pressure pain threshol
648	in patients with lateral epicondylitis. Arch Phys Med Rehabil. 2002;83(8):1145-50
649	60. Roy JS, MacDermid JC, Amick BC 3rd, et al. Validity and responsiveness of
650	presenteeism scales in chronic work-related upper-extremity disorders. Phys The
651	2011;91(2):254-66.
652	61. Wu C, Gong Y, Wu J, et al. Chinese Version of the EQ-5D Preference Weights
653	Applicability in a Chinese General Population. PLoS One 2016;11(10):e0164334
654	62. Sun S, Chen J, Johannesson M, et al. Population health status in China: EQ-51
655	results, by age, sex and socio-economic status, from the National Health Service

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

657 63. Alizadehkhaiyat O, Fisher AC, Kemp GJ, et al. Pain, functional disability, and
658 psychologic status in tennis elbow. Clin J Pain. 2007;23(6):482-9.

659 64. Pallant JF, Bailey CM. Assessment of the structure of the Hospital Anxiety and 660 Depression Scale in musculoskeletal patients. Health Qual Life Outcomes. 661 2005;3:82.

- 662 65. Razmjou H, Holtby R. Impact of rotator cuff tendon reparability on patient
 663 satisfaction. JSES Open Access. 2017;1(1):5-9.
- 664 66. Rabago D, Lee KS, Ryan M, et al. Hypertonic dextrose and morrhuate sodium
 665 injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single666 blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil.
 667 2013;92(7):587-96.
- 668 67. Sedgwick P. Intention to treat analysis versus per protocol analysis of trial data.
 669 BMJ. 2015;350:h681.
 - 670 68. Detry MA, Ma Y. Analyzing Repeated Measurements Using Mixed Models. JAMA.
 671 2016;315(4):407-8.
- 672 69. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid
 673 injections and other injections for management of tendinopathy: a systematic
 674 review of randomised controlled trials. Lancet. 2010;376(9754):1751-67.
- 675 70. Schwitzguebel AJ, Bogoev M, Nikolov V, et al. Tennis elbow, study protocol for a
 676 randomized clinical trial: needling with and without platelet-rich plasma after
 677 failure of up-to-date rehabilitation. J Orthop Surg Res. 2020;15(1):462.
- 678 71. Keijsers R, Kuijer P, Koenraadt KLM, et al. Effectiveness of standardized
 679 ultrasound guided percutaneous treatment of lateral epicondylitis with application
 680 of autologous blood, dextrose or perforation only on pain: a study protocol for a

BMJ Open

681	multi-center blinded randomized controlled trial with a 1 year follow up BMC
001	Marcala laslat Disard 2010-20(1)-251
682	Musculoskelet Disord. 2019;20(1):351.
683	

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685 Figure 1 Participant flow chart

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3 4 5	Table	• 1 Study evaluation procedures ar	nd timeline		
6 7	Study procedure	Medical evaluation	Enrolment visit 53 weel	ks 6 weeks	3 months
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3 1			Reporting Item	Number	
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3)	information			ogies.	
) <u>}</u>	Title	<u>#1</u>	Descriptive title identifying the study design, population,	1	
3 1 5			interventions, and, if applicable, trial acronym		
5 7 8	Trial registration	<u>#2a</u>	Trial identifier and registry name. If not yet registered,	4/6	
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		name of intended registry	
Trial registration: dat	ta <u>#2b</u>	All items from the World Health Organization Trial	4/6
set		Registration Data Set	
Protocol version	<u>#3</u>	Date and version identifier	5
Funding	<u>#4</u>	Sources and types of financial, material, and other support	3
Roles and	<u>#5a</u>	Names, affiliations, and roles of protocol contributors	2
responsibilities:			
contributorship			
Roles and	<u>#5b</u>	Name and contact information for the trial sponsor	2
responsibilities:			
sponsor contact			
information			
Roles and	<u>#5c</u>	Role of study sponsor and funders, if any, in study design;	2
responsibilities:		collection, management, analysis, and interpretation of	
sponsor and funder		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	
Roles and	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating	2
responsibilities:		centre, steering committee, endpoint adjudication	
committees		committee, data management team, and other individuals	
		or groups overseeing the trial, if applicable (see Item 21a	
		for data monitoring committee)	
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1 2	Background and	<u>#6a</u>	Description of research question and justification for	8
3 4	rationale		undertaking the trial, including summary of relevant studies	
5 6 7			(published and unpublished) examining benefits and harms	
7 8 9			for each intervention	
10 11 12	Background and	<u>#6b</u>	Explanation for choice of comparators	8
15 14 15	rationale: choice of			
15 16 17 18	comparators			
19 20 21	Objectives	<u>#7</u>	Specific objectives or hypotheses	9
22 23	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel	9
24 25			group, crossover, factorial, single group), allocation ratio,	
26 27			and framework (eg, superiority, equivalence, non-inferiority,	
28 29 30			exploratory)	
32 32	Methods:			
33 34 35	Participants,			
30 37 29	interventions, and			
39 40 41	outcomes			
41 42 43	Study setting	<u>#9</u>	Description of study settings (eg, community clinic,	10
44 45			academic hospital) and list of countries where data will be	
46 47			collected. Reference to where list of study sites can be	
48 49 50			obtained	
51 52	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If	11
53 54			applicable, eligibility criteria for study centres and	
22 56				
57			individuals who will perform the interventions (eg,	

1 2			surgeons, psychotherapists)	
3 4	Interventions:	<u>#11a</u>	Interventions for each group with sufficient detail to allow	12-14
5 6 7	description		replication, including how and when they will be	
, 8 9 10			administered	
11 12	Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated	12-14
13 14	modifications		interventions for a given trial participant (eg, drug dose	
15 16 17			change in response to harms, participant request, or	
18 19 20			improving / worsening disease)	
21 22	Interventions:	<u>#11c</u>	Strategies to improve adherence to intervention protocols,	12-14
23 24	adherance		and any procedures for monitoring adherence (eg, drug	
25 26 27 28			tablet return; laboratory tests)	
29 30	Interventions:	<u>#11d</u>	Relevant concomitant care and interventions that are	12-14
31 32 33	concomitant care		permitted or prohibited during the trial	
34 35	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the	15-19
36 37			specific measurement variable (eg, systolic blood	
38 39 40			pressure), analysis metric (eg, change from baseline, final	
40 41 42			value, time to event), method of aggregation (eg, median,	
43 44			proportion), and time point for each outcome. Explanation	
45 46			of the clinical relevance of chosen efficacy and harm	
47 48 49			outcomes is strongly recommended	
50 51 52	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any	21
53 54			run-ins and washouts), assessments, and visits for	
55 56			participants. A schematic diagram is highly recommended	
57 58			(see Figure)	
60		For peer rev	iew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3 4 5 6 7 8 9	Sample size	<u>#14</u>	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	BMJ Open: first published as 1
10 11 12 13 14 15	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to reach target sample size	10-11	Protected by co
16 17	Methods: Assignmen	ıt			ו-2021- pyrigh
18 19 20	of interventions (for				-05726(1t, inclu
20 21 22 23	controlled trials)				6 on 17 Ja Jaing for
24 25	Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg,	12	anuary Ensei uses re
26 27	generation		computer-generated random numbers), and list of any		2022. gneme elated
28 29 30			factors for stratification. To reduce predictability of a		Downl ent Sul to text
30 31 32			random sequence, details of any planned restriction (eg,		oaded perieur
33 34			blocking) should be provided in a separate document that is		r (ABE ata mi
35 36			unavailable to those who enrol participants or assign		ning, /
37 38 30			interventions		v train
39 40 41	Allocation	#16b	Mechanism of implementing the allocation sequence (eq	12	ing, ar
42 43		<u>"100</u>	central telephone: sequentially numbered, onaque, sealed	12	nd sim
44 45	mochanism		onvolonos), describing any stops to conceal the sequence		on Jun ilar tec
46 47	mechanism		until interventions are assigned		e 12, 2 ;hnolo
48 49 50					2025 at gies.
50 51 52	Allocation:	<u>#16c</u>	Who will generate the allocation sequence, who will enrol	12	t Agen
53 54	implementation		participants, and who will assign participants to		ce Bib
55 56			interventions		liogra
57 58 59 60		For peer rev	riew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		phique de l

1 2	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg,	12
3 4			trial participants, care providers, outcome assessors, data	
5 6 7			analysts), and how	
8 9 10	Blinding (masking):	<u>#17b</u>	If blinded, circumstances under which unblinding is	12
11 12	emergency		permissible, and procedure for revealing a participant's	
13 14 15	unblinding		allocated intervention during the trial	
16 17	Methods: Data			
18 19 20	collection,			
20 21 22	management, and			
23 24 25	analysis			
26 27	Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline,	15, 20-
28 29 30			and other trial data, including any related processes to	21
31 32			promote data quality (eg, duplicate measurements, training	
33 34			of assessors) and a description of study instruments (eg,	
35 36			questionnaires, laboratory tests) along with their reliability	
37 38 39			and validity, if known. Reference to where data collection	
40 41			forms can be found, if not in the protocol	
42 43 44	Data collection plan:	<u>#18b</u>	Plans to promote participant retention and complete follow-	15, 20-
45 46	retention		up, including list of any outcome data to be collected for	21
47 48			participants who discontinue or deviate from intervention	
49 50 51			protocols	
52 53	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage,	15, 20-
54 55 56			including any related processes to promote data quality	21
57 58			(eg, double data entry; range checks for data values).	
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		BMJ Open	Page	42 of -
		Reference to where details of data management		
		procedures can be found, if not in the protocol		
Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and secondary	19-20	
		outcomes. Reference to where other details of the		
		statistical analysis plan can be found, if not in the protocol		Protec
Statistics: additional	<u>#20b</u>	Methods for any additional analyses (eg, subgroup and	19-20	ted by
analyses		adjusted analyses)		copyrig
Statistics: analysis	<u>#20c</u>	Definition of analysis population relating to protocol non-	19-20	lht, inclu
oopulation and		adherence (eg, as randomised analysis), and any statistical		uding f
nissing data		methods to handle missing data (eg, multiple imputation)		Ense or uses
Methods: Monitoring				eigneme related t
Data monitoring:	<u>#21a</u>	Composition of data monitoring committee (DMC);	15, 20-	nt Supe to text a
ormal committee		summary of its role and reporting structure; statement of	21	rieur (nd dat
		whether it is independent from the sponsor and competing		ABES) a minir
		interests; and reference to where further details about its		ıg, Al t
		charter can be found, if not in the protocol. Alternatively, an		raining
		explanation of why a DMC is not needed		y, and si
Data monitoring:	<u>#21b</u>	Description of any interim analyses and stopping	15, 20-	imilar te
nterim analysis		guidelines, including who will have access to these interim	21	echnol
		results and make the final decision to terminate the trial		ogies.
Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing	19	ú
		solicited and spontaneously reported adverse events and		
		other unintended effects of trial interventions or trial		
	For peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		-

1 2			conduct	
- 3 4	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any,	19
5 6 7			and whether the process will be independent from	
7 8 9			investigators and the sponsor	
10 11 12	Ethics and			
13 14 15	dissemination			
16 17	Research ethics	<u>#24</u>	Plans for seeking research ethics committee / institutional	21
18 19 20	approval		review board (REC / IRB) approval	
21 22 23	Protocol	<u>#25</u>	Plans for communicating important protocol modifications	21
24 25	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
26 27			relevant parties (eg, investigators, REC / IRBs, trial	
28 29 20			participants, trial registries, journals, regulators)	
30 31 32	Consent or assent	#26a	Who will obtain informed consent or assent from potential	21
33 34			trial participants or authorised surrogates, and how (see	
35 36 37			Item 32)	
38 39				
40 41	Consent or assent:	<u>#26b</u>	Additional consent provisions for collection and use of	21
42 43	ancillary studies		participant data and biological specimens in ancillary	
44 45			studies, if applicable	
46 47 48	Confidentiality	<u>#27</u>	How personal information about potential and enrolled	21
49 50			participants will be collected, shared, and maintained in	
51 52			order to protect confidentiality before, during, and after the	
53 54 55			trial	
56 57 58	Declaration of	<u>#28</u>	Financial and other competing interests for principal	21
59 60		For peer rev	iew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	interests		investigators for the overall trial and each study site		BMJ Ope
- 3 4	Data access	<u>#29</u>	Statement of who will have access to the final trial dataset,	15, 20-	n: tirst
5 6 7			and disclosure of contractual agreements that limit such	21	publis
7 8 9			access for investigators		hed as
10 11 12	Ancillary and post	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for	20-21	10.1136 Protec
13 14	trial care		compensation to those who suffer harm from trial		/bmjo ted by
15 16			participation		r copyri
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19 20	Dissemination policy:	<u>#31a</u>	Plans for investigators and sponsor to communicate trial	20-21	7266 Incluc
21 22	trial results		results to participants, healthcare professionals, the public,		on 1/ ding f
23 24			and other relevant groups (eg, via publication, reporting in		Janua Ens or uses
25 26			results databases, or other data sharing arrangements),		ry zuz seigne s relat
27 28 29			including any publication restrictions		ment Su ed to tex
30 31 32	Dissemination policy:	<u>#31b</u>	Authorship eligibility guidelines and any intended use of	20-21	loaded Iperieur t and d
33 34 35	authorship		professional writers		r (ABES) ata minii
36 37	Dissemination policy:	<u>#31c</u>	Plans, if any, for granting public access to the full protocol,	20-21	ng, Al ti
38 39 40	reproducible research		participant-level dataset, and statistical code		open.p raining
41 42 43	Appendices				, and sim
44 45 46	Informed consent	<u>#32</u>	Model consent form and other related documentation given	/	on June ilar tech
47 48	materials		to participants and authorised surrogates		nologie
49 50 51	Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of	/	5 at Age s.
52 53			biological specimens for genetic or molecular analysis in		ence E
54 55 56			the current trial and for future use in ancillary studies, if		sibliogi
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Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

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Primary Subject Heading :	Sports and exercise medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Elbow & shoulder < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, SPORTS MEDICINE

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1 2 2

TITLE PAGE 1 2 Title Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy 3 (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, 4 randomised controlled trial 5 6 7 **Running Title** study protocol of UCICLET trial for lateral elbow tendinopathy 8 9 Keywords 10 Lateral elbow tendinopathy, randomised controlled trial, ultrasound therapy, 11 thera 12 corticosteroid injections, exercise-based therapy, Patient-Rated Tennis Elbow 13 Evaluation 14 Word count 15 3999 words 16 17 18 Authors and information Ziyang Sun, MD^{a, b, 1}, Shuai Chen, MD^{a, b, 1}, Weixuan Liu, MD^{a, b, 1}, Guixin Sun, 19 20 MD, PhD ^c, JunJian Liu, MD, PhD ^d, Jian Wang, MD, PhD ^e, Wei Wang, MD ^{a, b}, Yuanyi Zheng, MD, PhD f,*, Cunyi Fan, MD, PhD a, b,* 21 22 a Department of Orthopedics, Shanghai Jiao Tong University Affiliated Sixth 23 People's Hospital, Shanghai, 200233, P. R. China b Shanghai Engineering Research Center for Orthopaedic Material Innovation and 24

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41	
42	Author Contributions
43	SZY and CS are the primary investigators.
44	SZY, CS, LWX, ZYY, FCY participated in the development of the study design.
45	SZY, CS, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the study
46	conduct.
47	SZY, CS and LWX drafted the manuscript under FCY's supervision.
48	FCY contributed to applying for and gaining funding.
49	All authors contributed to the content and critical revision and approved the final
50	draft of the manuscript.

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51	
52	Conflict of interests
53	The authors, their immediate families, and any research foundation with which
54	they are affiliated have not received any financial payments or other benefits from any
55	commercial entity related to the subject of this article.
56	The authors declare no competing financial interests.
57	
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61	Center and Professional Technology Service Platform project of 2020 "Science and
62	Technology Innovation Action Plan" of Shanghai (20DZ2254100); Municipal Hospital
63	Clinical Skills and Innovation Capacity of Three-year Action Plan Program of Shanghai
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66	Technology Innovation Action Plan" (20S31900300, 21S31902300); Clinical Research
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Innovation Studio of Shanghai Jiao Tong University School of Medicine.

ETHICS

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (LL-2021-KYHZ-003), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The research registry number is ChiCTR2100050547 at http://www.chictr.org.cn. Data will be analyzed anonymously; all patients will approve the results of this study by written consent. The written consent approval will be documented in the patients' files. All clinical investigations will be conducted in accordance with the guidelines of the Declaration of Helsinki.

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86 ABSTRACT

87 Introduction

Lateral elbow tendinopathy (LET) is a highly prevalent disease among middleaged population, with no consensus on optimal management. Nonoperative treatment is generally accepted as the first-line intervention. Ultrasound (US) therapy has been widely reported to be a treatment that was beneficial for various orthopedics diseases including tendinopathy. The purpose of this study is to investigate the effectiveness of US for LET treatment.

94 Methods and analysis

This protocol entails a three-arm, prospective, multicenter, randomised controlled trial. 72 eligible participants with clinically confirmed LET will be assigned to either (1) US, (2) Corticosteroid Injections or (3) control group. All participants will receive an Exercise-based Therapy as fundamental intervention. Primary outcome is Patient-Rated Tennis Elbow Evaluation. Secondary outcomes include Visual Analogue Scale for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 for functional limitations at work, EuroQol-5D for general health, Hospital Anxiety and Depression Scale for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction. Adverse events will be recorded. Intention-to-treat analyses will be used.

106 Ethics and dissemination

Ethics Committees of all clinical centers have approved this study. The leading
center is Shanghai Sixth People's Hospital, whose approval number is 2021-153. New
versions with appropriate amendments will be submitted to the committee for further

2 3 4	110	approval. Study results will be published in peer-reviewed journals and presented at
5 6	111	local, national and international conferences.
7 8	112	Trial registration number
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STRENGTHS AND LIMITATIONS OF THIS STUDY

Exercise-based Therapy as fundamental intervention for all participants.

The first randomised controlled trial (RCT) to compare the efficacy between ultrasound therapy and corticosteroid injections in lateral elbow tendinopathy treatment.

- Multicenter RCT with blinded outcome assessor and statistician.
- Use of several patient-reported outcome measures as well as objective parameters.
- rating surg. Participants and treating surgeons not blinded.

1. INTRODUCTION

First described by Runge,¹ lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution.² LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults.³ Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis".⁴ A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.^{5,6}

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer,⁷ therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration.⁸ Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin.9 Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery,¹⁰ has a satisfied long-term (90 months) outcomes reported by Ang BFH.¹¹ However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population;² therefore, nonoperative treatment is suggested as first-

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line treatment.¹² Generally, nonsurgical methods include injections (like corticosteroid,
platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy,
extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or
oral naproxen, etc.^{13,14}

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention.¹⁵ EBT was also supported by high quality clinical trials¹⁶⁻¹⁸ and systematic reviews^{19,20}, regarding as the most cost-effective treatment for LET.²¹ The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT,¹⁵ due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term.¹⁶⁻¹⁸ In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hvaluronate injection,²² platelet-rich plasma injection,²³ ESWT²⁴ and acupuncture²⁵ still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators.²⁶ US has been widely reported to be treatment beneficial in fracture nonunions,^{27,28} osteoarthritis,^{29,30} chronic muscle pain,^{31,32} soft tissue injury,³³ etc. As for tendinopathy, US is also reported to be a potential noninvasive treatment modality for frozen shoulder,^{34,35} rotator cuff,³⁶ achilles^{37,38} and patellar³⁹ tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data,⁴⁰ and most of them focused on the comparison between US and ESWT⁴¹⁻⁴⁵. Both Yalvac B⁴³

and Özmen T⁴¹ have shown significant improvements in terms of pain, upper limb
function, strength and life quality from baseline after treatment with US. However, they
did not have a control group, which would make it unclear whether the efficacy come
from US itself or passing time, as LET is a self-limited disease. Therefore, the role of
US in LET treatment still needs to be further explored by high-quality study.
Additionally, to our best of knowledge, no study has compared the efficacy between
US and CI in LET treatment yet.

Therefore, the purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE). In view of recent literatures, CI should be discouraged in LET;^{22,46} however, it's still common in clinic due to the ability of satisfying patient's need of quick pain relief.¹⁵ Thus, a change in the paradigm of LET treatment is necessary. This change will come about through proposed evidence-based treatment guidelines. There are some on-going clinical trials on LET treatment in recent years,⁴⁷⁻⁴⁹ and our prospective RCT proposes to complement and add to this relevant and much needed scientific effort.

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2. METHODS

2.1. Study design

The design of this study is a three-arm, prospective, multicenter, randomised controlled trial, that will enroll participants with a diagnosis of chronic symptomatic LET from 4 municipal tertiary hospitals (Shanghai Sixth People's Hospital, Shanghai East Hospital, Shanghai Tenth People's Hospital, and Pudong New Area People's Hospital of Shanghai). This manuscript is written according to the SPIRIT guidelines.⁵⁰

2.2. 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.

205 2.3. 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. Those interested will contact the research assistant who will provide further information about the study objectives and procedures and will perform an initial eligibility screening interview by telephone.

2.4. Medical evaluation and enrolment procedure

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

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1 2		
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	216	• Age ≥ 18 years old;
	217	■ Unilateral lateral elbow pain longer than 6 weeks duration;
	218	■ Pain over the lateral humeral epicondyle with pain severity of greater than 30 mm
	219	on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following:
	220	gripping, palpation, resisted wrist or middle finger extension, or stretching of
	221	forearm extensor muscles with reduced pain-free grip; ^{16,49}
	222	• Able to read and write in simplified Chinese (Mainland), understand and complete
19 20	223	the questionnaire, and should provide informed consent.
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45	224	Exclusion criteria
	225	• Concomitant musculoskeletal pain conditions reported by participants to be their
	226	predominant complaint within the past 6 months;
	227	 History of symptoms suggesting radicular, neurological, inflammatory or systemic
	228	arthritic conditions;
	229	Treatment by physiotherapy, electrophysical therapy, or injection within the past 6
	230	months, or previous tennis elbow surgery;
	231	Contraindications to US, including dermatological conditions, abnormal sensation
	232	in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy
	233	or breastfeeding, et al.;
	234	Contraindications to CI, including hypertension, gastrointestinal ulcers, diabetes,
46 47	235	mental illness, et al.
48 49 50	236	Following the medical evaluation, a research assistant will meet with the eligible
51 52	237	participants and obtain written informed consent. Demographic variables will be
53 54	238	reported before treatment (baseline) of all participants regarding age, sex, body mass
55 56	239	index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous
58 59 60	240	medical history. Participants will also be asked relevant questions about duration of

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> symptoms 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 (repetitive movements for >4hours/day; wrist flexion for >2hours/day; elbow flexion and extension for >2hours/day; use of computer keyboard/ mouse [how many hours/day] and use of vibrating instruments for >2hours/day), and sports activities (how many hours/week, activity type, team or individual sports)⁵¹ will be also collected.

2.5. Randomization and blinding

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

258 The outcome assessor and statistician will be blinded to group allocation and not259 involved in treatment procedures.

2.6. Intervention

At the beginning, all participants will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. Participants will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment Page 15 of 57

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in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all participants will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles.¹⁵ The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs,^{16,18,52,53} mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm. Pain-free gripping exercise with exercise putty, which allows practice of various 1)

278 1) Pain-free gripping exercise with exercise putty, which allows practice of vario
 279 different gripping actions.

280 2) Forearm extensor muscle exercise using a free-standing dumbbell. Note that the 281 forearm is fully stabilized by the bench and upper body in sound postural alignment. 282 Duration per repetition lasts about 6-10 s.

283 3) Dumbbell weight exercise for the forearm flexor muscle with 6-10 s per repetition.
284 The postural is the same as 2).

4) Exercises for forearm supinator and pronator muscles using an imbalanced adjustable dumbbell weight with 6-10 s per repetition, from end range of supination to pronation with the participant maintaining full active control of the weight. The elbow bent to 90° with the arm stabilizing besides the trunk. Progressions in load imposed on the muscles can be achieved by increasing the weight or by increasing the distance between weight and hand.

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291 5) Radial and ulnar deviation exercises are performed with similar equipment and292 guidelines in 4).

Education on recognition and correction of the poor posture from the pelvis to neck.
Once the spine and trunk are aligned more optimally then the upper limb position
should be addressed.

Participants in the [US group] will receive continuous mode US (Shanghai, China)
at a frequency of 1 MHz and intensity of 1.0 W/cm² for 10 minutes in 5 days per week
for 3 weeks on the maximum pain region of lateral elbow.

Participants allocated to the [CI group] will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

309 Participants randomized to the [Control group] will neither receive US therapy nor
310 corticosteroid injection. They will only receive the fundamental intervention, EBT
311 program.

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

315 2.7. Data management

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

2.8. Outcome measures

325 Primary outcome

The primary outcome measure will be the difference in Patient-rated Tennis Elbow Evaluation (PRTEE). The PRTEE, formerly known as the Patient-Rated Forearm Evaluation Questionnaire, is a well validated composite scale measuring pain (5 items, with 0=no pain and 10=worst imaginable) and physical function (6 items for specific activities and 4 items for usual activities, with 0=no difficulty and 10=unable to do).⁵⁴ ranging from 0 to 100, with higher scores represent worse possible pain and more loss of function. The pain (intraclass correlation coefficients, ICC=0.89), physical function (ICC=0.83) and the total (ICC=0.89) scores all demonstrate excellent reliability.⁵⁵ A variation of 11/100 points or 37% of baseline scores are reported for clinical significance defined as "much better" or "completely recovered".⁵⁶ We use a validated Hong Kong Chinese version⁵⁷ of the PRTEE translated into simplified Chinese (Mainland) because the culture and language are the same.

338 Secondary outcome

339 Secondary outcome measures will be the differences in Visual Analogue Scale
340 (VAS)⁵⁸ for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand

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(Quick-DASH)⁵⁹ for upper limb disability, pain free/maximum grip strength, Work
Limitations Questionnaire-25 (WLQ-25)⁶⁰ for functional limitations at work, EuroQol5D (EQ-5D)⁶¹ for life quality and health status, The Hospital Anxiety and Depression
Scale (HADS)⁶² for anxiety and depression status, Global Rating of Change (GROC)
for treatment success and recurrence rate, and Mahomed scale⁶³ for participants'
satisfaction.

347 🔳 Pain

The VAS will be used for pain evaluation, which consists of a 100-mm horizontal numbered line anchored at one end (0) with the words "no pain" and at the other end (100) with the words "worst pain imaginable", and whose score is determined by the distance between the left end of the line and the participant's mark in mm.⁵⁸ VAS is considered to be the most sensitive of all pain scoring scales and has been specifically validated in the LET population with high reliability (r=0.89) and a moderate correlation with pain-free grip strength (r=0.47).⁶⁴ Participants are asked to score their pain on this line during rest (at time of measure), provocation and maximum grip strength. The provocation test is conducted on the outpatient clinic by resisted dorsiflexion of the wrist during full elbow extension. Clinically relevant improvement will be defined when a 50% decrease in VAS is observed before and after the treatment.⁶⁵ The consumption of rescue medication taken by each patient will be also recorded at each follow-up visit.

361 ■ Upper limb disability

The well-validated simplified Chinese (Mainland) version of Quick-DASH⁶⁶ will be used for elbow function evaluation, which consists of eleven questions scored on a 5-point scale similar to the DASH.⁵⁹ Total and individual module scores will be calculated out of 100, with a higher score indicating a worse status. A minimal clinically

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366 important difference of 15.91 points has been reported.⁶⁷

Grip strength

Pain free/maximum grip strength will be measured using a dynamometer (CAMRY, City of Industry, CA, USA). The participants will be asked to take a shoulder-width stance and allow their arms to hang loose, holding their arm adducted along the body and the elbow in full extension. The pain-free grip strength will be measured, followed by the measurement of the maximum grip strength, and 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 pain-free grip strength will be measured up to the point when the subject slowly squeezes the dynamometer until the occurrence of pain. The maximum grip strength will be measured at the maximum grip level. 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×100.68

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.⁶⁰ 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.⁶⁹

389 ■ Life quality and health status

The EQ-5D is one of the widely validated generic health-related quality of life

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(HRQol) measures known as its simplicity.⁶¹ 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 version⁷⁰ of the EQ-5D, which has been recommended by
China Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQol
and health utility.⁷¹

• Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders - anxiety and depression.⁶² There is evidence of increased levels of anxiety and depression in people with LET.⁷² 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. HADS has two cut offs for categorization: 0-7, "non-case"; 8-10, "possible or doubtful case"; 11-21, "probable or definite case".⁷³

408 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.^{16,18} Recurrence will primarily be defined as occurring when a participant rates a success at

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416 3 weeks and a failure at 2 or 6 months or one year on GROC.^{16,18}

What's more, additional treatments after failure of management in this study (that
is, not per protocol), if any, including subsequent interventions and even surgery, will
be also recorded.

420 • Participants' satisfaction

421 Similarly, participants' level of satisfaction on the evolution of their condition will
422 be determined on a validated 4-point Likert scale ranging from "very satisfied",
423 "somewhat satisfied", "somewhat dissatisfied" to "very dissatisfied".⁷⁴

2.9. 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. CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection.

2.10. Sample size calculation

Sample size and power calculation are based on the primary outcome of PRTEE 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 5.1-point on PRTEE score will be used.⁷⁵ To detect a minimum clinically significant difference of 11.0-point⁵⁶ (superiority margin) between US and control Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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groups (assuming a true difference of 15.6-point^{43,75}), a total of 22 participants in each
group is required. Allowing for an up to 10% drop out rate, we aim to enroll at least 24
participants in each group to complete the study.

444 2.11. 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)⁷⁶ 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 PRTEE scores will be made using linear regression. In secondary analyses, repeated measures mixed model⁷⁷ 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.

2.12. 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 Page 23 of 57

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465 project manager will visit each center for monitoring to ensure data quality and466 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.

2.13. Study duration

472 Recruitment of the trial will begin in the November of 2021 and one-year follow473 up for all participants is anticipated to be completed by March 2023. See Table 1 for
474 time points and recruitment progress.

2.14

2.14. Ethics and dissemination

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (LL-2021-KYHZ-003), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The potential risks of this clinical trial are considered to be minimal and are addressed in the protocol and consent forms. A written consent (Supplementary 1) will be obtained by clinical practitioners from each participant. The trial was registered on www.chictr.org website (registration number ChiCTR2100050547). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

2.15. Limitation

488 This study will have one limitation. Participants and treating surgeons are489 inevitable not blinded, which may produce bias. However, we will strictly control the

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490 outcome assessors and statisticians to be blinded to group allocation and not involved

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491 in treatment procedures to reduce the bias.
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	492	3.	REFERENCES
	493	1.	Knobloch K, Gohritz A. Dr Runge: a German pioneer in sclerosing therapy in
	494		epicondylitis in 1873. Br J Sports Med. 2010.
)	495	2.	Sanders TL Jr, Maradit Kremers H, Bryan AJ, et al. The epidemiology and health
<u>2</u> 3	496		care burden of tennis elbow: a population-based study. Am J Sports Med.
+ 5	497		2015;43(5):1066-71.
) 7 }	498	3.	Walker-Bone K, Palmer KT, Reading I, et al. Occupation and epicondylitis: a
)	499		population-based study. Rheumatology (Oxford). 2012;51(2):305-10.
<u>)</u>	500	4.	Khan KM, Cook JL, Kannus P, et al. Time to abandon the "tendinitis" myth. BMJ.
3 	501		2002;324(7338):626-7.
, , ,	502	5.	Haahr JP, Andersen JH. Physical and psychosocial risk factors for lateral
3	503		epicondylitis: a population based case-referent study. Occup Environ Med.
))	504		2003;60(5):322-9.
- 3 1	505	6.	Herquelot E, Guéguen A, Roquelaure Y, et al. Work-related risk factors for
5	506		incidence of lateral epicondylitis in a large working population. Scand J Work
7 3	507		Environ Health. 2013;39(6):578-88.
)	508	7.	Hudak PL, Cole DC, Haines AT. Understanding prognosis to improve rehabilitation:
<u>2</u> 3	509		the example of lateral elbow pain. Arch Phys Med Rehabil. 1996;77(6):586-93.
+ 5	510	8.	Ahmad Z, Siddiqui N, Malik SS, et al. Lateral epicondylitis: a review of pathology
) 7 }	511		and management. Bone Joint J. 2013;95-B(9):1158-64.
)	512	9.	Pierce TP, Issa K, Gilbert BT, et al. A Systematic Review of Tennis Elbow Surgery:
<u>)</u>	513		Open Versus Arthroscopic Versus Percutaneous Release of the Common Extensor
5 	514		Origin. Arthroscopy. 2017;33(6):1260-1268.e2.
5			

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Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

515 10. Vajapey S, Ghenbot S, Baria MR, et al. Utility of Percutaneous Ultrasonic
516 Tenotomy for Tendinopathies: A Systematic Review. Sports Health.
517 2021;13(3):258-264.

- 518 11. Ang BFH, Mohan PC, Png MA, et al. Ultrasonic Percutaneous Tenotomy for
 519 Recalcitrant Lateral Elbow Tendinopathy: Clinical and Sonographic Results at 90
 520 Months. Am J Sports Med. 2021;49(7):1854-1860.
- 521 12. Vaquero-Picado A, Barco R, Antuña SA. Lateral epicondylitis of the elbow.
 522 EFORT Open Rev. 2017;1(11):391-7.
- 523 13. Lian J, Mohamadi A, Chan JJ, et al. Comparative Efficacy and Safety of
 524 Nonsurgical Treatment Options for Enthesopathy of the Extensor Carpi Radialis
 525 Brevis: A Systematic Review and Meta-analysis of Randomized Placebo526 Controlled Trials. Am J Sports Med. 2019;47(12):3019-3029.
- 527 14. Sayegh ET, Strauch RJ. Does nonsurgical treatment improve longitudinal outcomes
 528 of lateral epicondylitis over no treatment? A meta-analysis. Clin Orthop Relat Res.
 529 2015:473(3):1093-1107.
 - 530 15. Bateman M, Titchener AG, Clark DI, et al. Management of tennis elbow: a survey
 531 of UK clinical practice. Shoulder Elbow. 2019;11(3):233-8.
 - 532 16. Coombes BK, Bisset L, Brooks P, et al. Effect of corticosteroid injection,
 533 physiotherapy, or both on clinical outcomes in patients with unilateral lateral
 534 epicondylalgia: a randomized controlled trial. JAMA. 2013;309(5):461-9.
 - 535 17. Smidt N, van der Windt DA, Assendelft WJ, et al. Corticosteroid injections,
 536 physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised
 537 controlled trial. Lancet. 2002;359(9307):657-62.

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55	
54	
55	
56	
57	
50	
20	
59	
60	

538 18. Bisset L, Beller E, Jull G, et al. Mobilisation with movement and exercise,
539 corticosteroid injection, or wait and see for tennis elbow: randomised trial. BMJ.
540 2006;333(7575):939.

541 19. Karanasios S, Korakakis V, Whiteley R, et al. Exercise interventions in lateral
542 elbow tendinopathy have better outcomes than passive interventions, but the effects
543 are small: a systematic review and meta-analysis of 2123 subjects in 30 trials. Br J
544 Sports Med. 2021;55(9):477-85.

545 20. Hoogvliet P, Randsdorp MS, Dingemanse R, et al. Does effectiveness of exercise
546 therapy and mobilisation techniques offer guidance for the treatment of lateral and
547 medial epicondylitis? A systematic review. Br J Sports Med. 2013;47(17):1112-9.

548 21. Coombes BK, Connelly L, Bisset L, et al. Economic evaluation favours
549 physiotherapy but not corticosteroid injection as a first-line intervention for chronic
550 lateral epicondylalgia: evidence from a randomised clinical trial. Br J Sports Med.
551 2016;50(22):1400-5.

552 22. Dong W, Goost H, Lin XB, et al. Injection therapies for lateral epicondylalgia: a 553 systematic review and Bayesian network meta-analysis. Br J Sports Med. 554 2016;50(15):900-8.

555 23. de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections
556 for chronic lateral epicondylar tendinopathy: a systematic review. Br J Sports Med.
557 2014;48(12):952-6.

558 24. Yoon SY, Kim YW, Shin IS, et al. Does the Type of Extracorporeal Shock Therapy
559 Influence Treatment Effectiveness in Lateral Epicondylitis? A Systematic Review
560 and Meta-analysis. Clin Orthop Relat Res. 2020;478(10):2324-39.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

561 25. Chang WD, Lai PT, Tsou YA. Analgesic effect of manual acupuncture and laser
562 acupuncture for lateral epicondylalgia: a systematic review and meta-analysis. Am
563 J Chin Med. 2014;42(6):1301-14.

- 564 26. Watson T. Ultrasound in contemporary physiotherapy practice. Ultrasonics.
 565 2008;48(4):321-9.
- 566 27. Leighton R, Watson JT, Giannoudis P, et al. Healing of fracture nonunions treated
 567 with low-intensity pulsed ultrasound (LIPUS): A systematic review and meta568 analysis. Injury. 2017;48(7):1339-47.
- 569 28. Korstjens CM, Rutten S, Nolte PA, et al. Low-intensity pulsed ultrasound increases
 570 blood vessel size during fracture healing in patients with a delayed-union of the
 571 osteotomized fibula. Histol Histopathol. 2018;33(7):737-46.
- 572 29. Rutjes AW, Nüesch E, Sterchi R, et al. Therapeutic ultrasound for osteoarthritis of
 573 the knee or hip. Cochrane Database Syst Rev. 2010;(1):CD003132.
- 574 30. Alfredo PP, Junior WS, Casarotto RA. Efficacy of continuous and pulsed
 575 therapeutic ultrasound combined with exercises for knee osteoarthritis: a
 576 randomized controlled trial. Clin Rehabil. 2020;34(4):480-90.
- 577 31. Ebadi S, Henschke N, Forogh B, et al. Therapeutic ultrasound for chronic low back
 578 pain. Cochrane Database Syst Rev. 2020;7(7):CD009169.
 - 32. Altan L, Kasapoğlu Aksoy M, Kösegil Öztürk E. Efficacy of diclofenac &
 thiocolchioside gel phonophoresis comparison with ultrasound therapy on acute
 low back pain; a prospective, double-blind, randomized clinical study. Ultrasonics.
 2019;91:201-5.
 - 33. Lai WC, Iglesias BC, Mark BJ, et al. Low-Intensity Pulsed Ultrasound Augments
 Tendon, Ligament, and Bone-Soft Tissue Healing in Preclinical Animal Models: A
 Systematic Review. Arthroscopy. 2021;37(7):2318-33.e3.

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BMJ Open

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586	34. Ebenbichler GR, Erdogmus CB, Resch KL, et al. Ultrasound therapy for calcific
587	tendinitis of the shoulder. N Engl J Med. 1999;340(20):1533-8.
588	35. Pieber K, Grim-Stieger M, Kainberger F, et al. Long-Term Course of Shoulders
589	After Ultrasound Therapy for Calcific Tendinitis: Results of the 10-Year Follow-
590	Up of a Randomized Controlled Trial. Am J Phys Med Rehabil. 2018;97(9):651-8.
591	36. Desmeules F, Boudreault J, Roy JS, et al. The efficacy of therapeutic ultrasound for
592	rotator cuff tendinopathy: A systematic review and meta-analysis. Phys Ther Sport.
593	2015;16(3):276-84.
594	37. Chester R, Costa ML, Shepstone L, et al. Eccentric calf muscle training compared
595	with therapeutic ultrasound for chronic Achilles tendon paina pilot study. Man
596	Ther. 2008;13(6):484-91.
597	38. Draper DO, Edvalson CG, Knight KL, et al. Temperature increases in the human
598	achilles tendon during ultrasound treatments with commercial ultrasound gel and
599	full-thickness and half-thickness gel pads. J Athl Train. 2010;45(4):333-7.
600	39. Stasinopoulos D, Stasinopoulos I. Comparison of effects of exercise programme,
601	pulsed ultrasound and transverse friction in the treatment of chronic patellar
602	tendinopathy. Clin Rehabil. 2004;18(4):347-52.
603	40. Dingemanse R, Randsdorp M, Koes BW, et al. Evidence for the effectiveness of
604	electrophysical modalities for treatment of medial and lateral epicondylitis: a
605	systematic review. Br J Sports Med. 2014;48(12):957-65.
606	41. Özmen T, Koparal SS, Karataş Ö, et al. Comparison of the clinical and sonographic
607	effects of ultrasound therapy, extracorporeal shock wave therapy, and Kinesio
608	taping in lateral epicondylitis. Turk J Med Sci. 2021;51(1):76-83.
	28

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

42. Dedes V, Tzirogiannis K, Polikandrioti M, et al. Comparison of radial
extracorporeal shockwave therapy with ultrasound therapy in patients with lateral
epicondylitis. J Med Ultrason (2001). 2020;47(2):319-25.

- 43. Yalvaç B, Mesci N, Geler Külcü D, et al. Comparison of ultrasound and
 extracorporeal shock wave therapy in lateral epicondylosis. Acta Orthop Traumatol
 Turc. 2018;52(5):357-62.
- 615 44. Kubot A, Grzegorzewski A, Synder M, et al. Radial Extracorporeal Shockwave
 616 Therapy and Ultrasound Therapy in the Treatment of Tennis Elbow Syndrome.
 617 Ortop Traumatol Rehabil. 2017;19(5):415-26.
- 618 45. Lizis P. Analgesic effect of extracorporeal shock wave therapy versus ultrasound
 619 therapy in chronic tennis elbow. J Phys Ther Sci. 2015;27(8):2563-7.
- 620 46. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid
 621 injections and other injections for management of tendinopathy: a systematic
 622 review of randomised controlled trials. Lancet. 2010;376(9754):1751-67.
- 623 47. Schwitzguebel AJ, Bogoev M, Nikolov V, et al. Tennis elbow, study protocol for a
 624 randomized clinical trial: needling with and without platelet-rich plasma after
 625 failure of up-to-date rehabilitation. J Orthop Surg Res. 2020;15(1):462.
- 48. Keijsers R, Kuijer P, Koenraadt KLM, et al. Effectiveness of standardized
 ultrasound guided percutaneous treatment of lateral epicondylitis with application
 of autologous blood, dextrose or perforation only on pain: a study protocol for a
 multi-center, blinded, randomized controlled trial with a 1 year follow up. BMC
 Musculoskelet Disord. 2019;20(1):351.
 - 49. Lungu E, Grondin P, Tétreault P, et al. Ultrasound-guided tendon fenestration
 versus open-release surgery for the treatment of chronic lateral epicondylosis of the

Page 31 of 57

BMJ Open

633	elbow: protocol for a prospective, randomised, single blinded study. BMJ Open.
634	2018·8(6)·e021373
625	50 Chan AW Tatzlaff IM Gatzsaha PC at al SPIPIT 2013 avalanation and
035	50. Chan Aw, Tetzian Jw, Obizsche PC, et al. SPIKIT 2015 explanation and
636	elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
637	51. Usuelli FG, Di Silvestri CA, D'Ambrosi R, et al. Return to sport activities after
638	medial displacement calcaneal osteotomy and flexor digitorum longus transfer.
639	Knee Surg Sports Traumatol Arthrosc. 2018;26(3):892-896.
640	52. Coombes BK, Bisset L, Connelly LB, et al. Optimising corticosteroid injection for
641	lateral epicondylalgia with the addition of physiotherapy: a protocol for a
642	randomised control trial with placebo comparison. BMC Musculoskelet Disord.
643	2009;10:76.
644	53. Vicenzino B. Lateral epicondylalgia: a musculoskeletal physiotherapy perspective.
645	Man Ther. 2003;8(2):66-79.
646	54. Rompe JD, Overend TJ, MacDermid JC. Validation of the Patient-rated Tennis
647	Elbow Evaluation Questionnaire. J Hand Ther. 2007;20(1):3-10; quiz 11.
648	55. Giray E, Karali-Bingul D, Akyuz G. The Effectiveness of Kinesiotaping, Sham
649	Taping or Exercises Only in Lateral Epicondylitis Treatment: A Randomized
650	Controlled Study. PM R. 2019;11(7):681-93.
651	56. Poltawski L, Watson T. Measuring clinically important change with the Patient-
652	rated Tennis Elbow Evaluation. Hand Therapy 2011;16:52-7.
653	57. Leung HB, Yen CH, Tse PY. Reliability of Hong Kong Chinese version of the
654	Patient-rated Forearm Evaluation Questionnaire for lateral epicondylitis. Hong
655	Kong Med J. 2004;10(3):172-7.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

58. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and
change scores: a reanalysis of two clinical trials of postoperative pain. J Pain.
2003;4(7):407-14.

- 659 59. Beaton DE, Wright JG, Katz JN. Development of the QuickDASH: comparison of
 660 three item-reduction approaches. J Bone Joint Surg Am. 2005;87(5):1038-46.
- 661 60. Lerner D, Amick BC 3rd, Rogers WH, et al. The Work Limitations Questionnaire.
 662 Med Care. 2001;39(1):72-85.
- 663 61. EuroQol Group. EuroQol--a new facility for the measurement of health-related664 quality of life. Health Policy. 1990;16(3):199-208.
- 665 62. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr
 666 Scand. 1983;67(6):361-70.
- 667 63. Mahomed N, Gandhi R, Daltroy L, et al. The self-administered patient satisfaction
 668 scale for primary hip and knee arthroplasty. Arthritis. 2011;2011:591253.
- 669 64. Stratford PW, Levy DR, Gauldie S, et al. Extensor carpi radialis tendonitis: A
- 670 validation of selected outcome measures. Physiotherapy Canada 1987;39(4):250-5.
- 671 65. Shin KM, Kim JH, Lee S, et al. Acupuncture for lateral epicondylitis (tennis elbow):
- 672 study protocol for a randomized, practitioner-assessor blinded, controlled pilot673 clinical trial. Trials. 2013;14:174.
- 674 66. Cao S, Zhou R, Zhou H, et al. Reliability and validity of Simplified Chinese version
 675 of Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire:
 676 cross-cultural adaptation and validation. Clin Rheumatol. 2019;38(11):3281-7.
- 677 67. Franchignoni F, Vercelli S, Giordano A, et al. Minimal clinically important
 678 difference of the disabilities of the arm, shoulder and hand outcome measure
 679 (DASH) and its shortened version (QuickDASH). J Orthop Sports Phys Ther.
 680 2014;44(1):30-9.

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BMJ Open

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681 68. Smidt N, van der Windt DA, Assendelft WJ, et al. Interobserver reproducibility of the assessment of severity of complaints, grip strength, and pressure pain threshold 682 in patients with lateral epicondylitis. Arch Phys Med Rehabil. 2002;83(8):1145-50. 683 69. Roy JS, MacDermid JC, Amick BC 3rd, et al. Validity and responsiveness of 684 presenteeism scales in chronic work-related upper-extremity disorders. Phys Ther. 685 2011;91(2):254-66. 686 687 70. Wu C, Gong Y, Wu J, et al. Chinese Version of the EQ-5D Preference Weights: Applicability in a Chinese General Population. PLoS One 2016;11(10):e0164334. 688 689 71. Sun S, Chen J, Johannesson M, et al. Population health status in China: EQ-5D results, by age, sex and socio-economic status, from the National Health Services 690 Survey 2008. Qual Life Res. 2011;20(3):309-20. 691 72. Alizadehkhaiyat O, Fisher AC, Kemp GJ, et al. Pain, functional disability, and 692 693 psychologic status in tennis elbow. Clin J Pain. 2007;23(6):482-9. 73. Pallant JF, Bailey CM. Assessment of the structure of the Hospital Anxiety and 694 695 Depression Scale in musculoskeletal patients. Health Qual Life Outcomes. 2005;3:82. 696 74. Razmjou H, Holtby R. Impact of rotator cuff tendon reparability on patient 697 satisfaction. JSES Open Access. 2017;1(1):5-9. 698 699 75. Rabago D, Lee KS, Ryan M, et al. Hypertonic dextrose and morrhuate sodium 700 injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a singleblind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil. 701 702 2013;92(7):587-96. 703 76. Sedgwick P. Intention to treat analysis versus per protocol analysis of trial data. 704 BMJ. 2015;350:h681.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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705 77. Detry MA, Ma Y. Analyzing Repeated Measurements Using Mixed Models. JAMA.

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706 2016;315(4):407-8.

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Table 1	Study	evaluation	procedures	and	timel	line
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	Table 1 Stud	ly evaluation procedures a	and timeline	ז-2021 pyrigh			
Study procedure		Medical evaluation	Enrolment visit	3 weeks	2 months	6 months	One year
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INFORMED CONSENT FORM

(English Version)

Participant Information Page

Study Title	:	Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy
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 lateral elbow tendinopathy". 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

First described by Runge, lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution. LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults. Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis". A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of

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pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer, therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration. Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied longterm (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention. EBT was also supported by high quality clinical trials and systematic reviews, regarding as the most cost-effective treatment for LET. The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT, due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators. US has been widely reported to be treatment beneficial in fracture nonunions, osteoarthritis, chronic muscle pain, soft tissue injury, etc. As for tendinopathy, US is also reported to be a potential

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noninvasive treatment modality for frozen shoulder, rotator cuff, achilles and patellar tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data, and most of them focused on the comparison between US and ESWT. Both Yalvaç B and Özmen T have shown significant improvements in terms of pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a control group, which would make it unclear whether the efficacy come from US itself or passing time, as LET is a self-limited disease.

Therefore, the role of US in LET treatment still needs to be further explored by highquality study. Additionally, to our best of knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

2. STUDY PURPOSE

The purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE).

3. STUDY PROCESS

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

About 72 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 lateral elbow tendinopathy with a lateral elbow irritation test.

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, dominant arm, lifestyle (smoking and drinking), and previous medical history. As well as relevant questions about duration of symptoms 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 Patient-Rated Tennis Elbow Evaluation (PRTEE) for elbow function and symptom, Visual Analogue Scale (VAS) for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH) for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 (WLQ-25) for functional limitations at work, EuroQol-5D (EQ-5D) for general health, Hospital Anxiety and Depression Scale (HADS) for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction.

C. Treatment by group

At the beginning, all of you will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. You will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all of you will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles. The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs, mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm.

You will be randomly assigned to one of three groups, [US group] vs. [CI group] vs. [Control 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^2 for 10 minutes in 5 days per week for 3 weeks on the maximum pain region of lateral elbow.

(b) If you are allocated to the [CI group], you will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/ mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral

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epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

(c) If you are randomized to the [Control group], you will neither receive US therapy nor corticosteroid injection. They will only receive the fundamental intervention, EBT program.

We discourage additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allowed the use of simple analysics 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 3 weeks, 2 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 3 weeks, 2 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

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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.

CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. The occurrence of these reactions depends on the individual patient, and usually does not require special treatment. In addition, during the injection, there may be a slight tingling sensation due to tissue and nerve damage in the skin. If the patient is physically sensitive, the pain may be more intense. Someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection. The drugs in the CI contain hormones, therefore, if are injected repeatedly and for a long time, it will cause damage to the tissues in the skin, so local calcification and skin stiffness occur. If the drug penetrates the bones, it can cause osteoporosis. After the injection, if the patient's physical condition decreases, and the wound is not kept clean, it may lead to bacterial invasion of the wound, so the wound healing speed will be slow, and there will develop infection and inflammation. These adverse reactions can be avoided by reducing the number of CIs and standardizing injection procedures.

EBT is exercise, and theoretically there are no complications.

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

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Protocol Date: 2021.06.15.	
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 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 LET. 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, EBT, autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT, acupuncture, and surgery, etc.

Please discuss these and other possible options with your doctor.

Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied long-term (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention. EBT was also supported by high quality clinical trials and systematic reviews, regarding as the most cost-effective treatment for LET. The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT, due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be

worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture 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 COPENSATION

(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 LET, oral non-steroidal anti-inflammatory drugs, etc. There is no cost involved in EBT. The expenses related to US and CI injection 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

(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 Ziyang Sun at *********

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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: _____ FE: If participant (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 SPIR	IT guidelin	es.				
Instructions to	authors		Protecte			
Complete this chec	klist by en	tering the page numbers from your manuscript where readers	s will find by			
each of the items lis	sted below		opyrig			
Your article may no	ot currently	address all the items on the checklist. Please modify your te	ext to			
include the missing	informatic	n. If you are certain that an item does not apply, please write	e "n/a" and g			
provide a short exp	lanation.		Ens r uses			
Upload your comple	eted check	list as an extra file when you submit to a journal.	related to			
In your methods se	ction, say	that you used the SPIRITreporting guidelines, and cite them	as: as:			
Chan A-W, Tetzlaff	JM, Gøtzs	sche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjart	sson A, and 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						
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		Reporting Item	Number			
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information			gies.			
Title	<u>#1</u>	Descriptive title identifying the study design, population,	1			
		interventions, and, if applicable, trial acronym				
Trial registration	<u>#2a</u>	Trial identifier and registry name. If not yet registered,	4/6			
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		BMJ Open	Page 50 of
		name of intended registry	
Trial registration: data	<u>#2b</u>	All items from the World Health Organization Trial	4/6
set		Registration Data Set	
Protocol version	<u>#3</u>	Date and version identifier	5 P
Funding	<u>#4</u>	Sources and types of financial, material, and other support	otected t
Roles and	<u>#5a</u>	Names, affiliations, and roles of protocol contributors	2 сору
responsibilities:			right, i
contributorship			ncludin
Roles and	<u>#5b</u>	Name and contact information for the trial sponsor	g for us
responsibilities:			inseig ies rela
sponsor contact			ated to
information			t Superi text an
Roles and	<u>#5c</u>	Role of study sponsor and funders, if any, in study design;	d data n 2/3 1
responsibilities:		collection, management, analysis, and interpretation of	nining,
sponsor and funder		data; writing of the report; and the decision to submit the	Al trai
		report for publication, including whether they will have	ining, a
		ultimate authority over any of these activities	and simi
Roles and	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating	2/3 tech
responsibilities:		centre, steering committee, endpoint adjudication	nolog
committees		committee, data management team, and other individuals	ies.
		or groups overseeing the trial, if applicable (see Item 21a	
		for data monitoring committee)	
Introduction			
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1 2	Background and	<u>#6a</u>	Description of research question and justification for	8-10
3 4 5	rationale		undertaking the trial, including summary of relevant studies	
5 6 7			(published and unpublished) examining benefits and harms	
, 8 9			for each intervention	
10				
11 12	Background and	<u>#6b</u>	Explanation for choice of comparators	8-10
13 14	rationale: choice of			
15 16	comparators			
17 18				
19 20	Objectives	<u>#7</u>	Specific objectives or hypotheses	10
21 22 23	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel	10
24 25			group, crossover, factorial, single group), allocation ratio,	
26 27			and framework (eg, superiority, equivalence, non-inferiority,	
28 29 20			exploratory)	
30 31				
32 33	Methods:			
34 35	Participants,			
36 37	interventions, and			
38 39 40	outcomes			
41 42	Study setting	<u>#9</u>	Description of study settings (eg, community clinic,	11
43 44 45			academic hospital) and list of countries where data will be	
46 47			collected. Reference to where list of study sites can be	
48 49			obtained	
50 51				
52 53	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If	11-12
54 55			applicable, eligibility criteria for study centres and	
56 57			individuals who will perform the interventions (eg,	
58 59 60		For peer rev	/iew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

		BMJ Open	Page	52 of 57
		surgeons, psychotherapists)		BMJ Oper
Interventions:	<u>#11a</u>	Interventions for each group with sufficient detail to allow	13-15	ı: first
description		replication, including how and when they will be		publisl
		administered		ned as
Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated	13-15	10.1136/k Protecte
modifications		interventions for a given trial participant (eg, drug dose		omjope ∌d by c
		change in response to harms, participant request, or		∘opyrig
		improving / worsening disease)		I-057266 ht, inclu
Interventions:	<u>#11c</u>	Strategies to improve adherence to intervention protocols,	13-15	on 17 ding fo
adherance		and any procedures for monitoring adherence (eg, drug		Janua Ens or uses
		tablet return; laboratory tests)		ry 2022 seigner s relate
Interventions:	<u>#11d</u>	Relevant concomitant care and interventions that are	13-15	2. Dowr nent Su d to tey
concomitant care		permitted or prohibited during the trial		nloaded fi uperieur (ct and dat
Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the	16-20	rom <mark>ht</mark> ABES) ta mini
		specific measurement variable (eg, systolic blood		ng, Al t
		pressure), analysis metric (eg, change from baseline, final		jopen. trainin
		value, time to event), method of aggregation (eg, median,		bmj.co g, and
		proportion), and time point for each outcome. Explanation		m∕ on simila
		of the clinical relevance of chosen efficacy and harm		June 1 . techn
		outcomes is strongly recommended		2, 2025 ologies
Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any	22	at Ager s.
		run-ins and washouts), assessments, and visits for		nce Bik
		participants. A schematic diagram is highly recommended		oliogra
		(see Figure)		phique
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	Interventions: description Interventions: modifications Interventions: adherance Interventions: concomitant care Outcomes	Interventions: #11a description #11b nodifications #11b nodifications #11c adherance #11c outcomes #112	BWU Open surgeons, psychotherapists) Interventions: #11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Interventions: #11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) Interventions: #11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) Interventions: #11d Relevant concomitant care and interventions that are permitted or prohibited during the trial Outcomes #12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Participant timeline #13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	BMU Open Page Interventions: #11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 13-15 Interventions: #11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) 13-15 Interventions: #11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) 13-15 Interventions: #11c Relevant concomitant care and interventions that are permitted or prohibited during the trial 13-15 Outcomes #112 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 22 Participant timeline #113 Time schedule of enrolment, interventions (including any participarts. A schematic diagram is highly recommended isee Figure) 21

1 2	Sample size	<u>#14</u>	Estimated number of participants needed to achieve study	20-21
3 4			objectives and how it was determined, including clinical and	
5 6 7			statistical assumptions supporting any sample size	
7 8 9			calculations	
10 11	-			
12 13	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to	11
14 15			reach target sample size	
16 17	Methods: Assignment			
18 19	of interventions (for			
20 21	controlled trials)			
22 23				
24 25	Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg,	13
26 27	generation		computer-generated random numbers), and list of any	
28 29 20			factors for stratification. To reduce predictability of a	
30 31 32			random sequence, details of any planned restriction (eg,	
32 33 34			blocking) should be provided in a separate document that is	
35 36			unavailable to those who enrol participants or assign	
37 38			interventions	
39 40				
41 42	Allocation	<u>#16b</u>	Mechanism of implementing the allocation sequence (eg,	13
43 44	concealment		central telephone; sequentially numbered, opaque, sealed	
45 46	mechanism		envelopes), describing any steps to conceal the sequence	
47 48			until interventions are assigned	
49 50	Allesstien	#40-		40
51 52	Allocation:	<u>#16C</u>	who will generate the allocation sequence, who will enrol	13
53 54	implementation		participants, and who will assign participants to	
55 56			interventions	
57 58				
60	Fc	or peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg,	13
3 4			trial participants, care providers, outcome assessors, data	
5 6 7			analysts), and how	
8 9 10	Blinding (masking):	<u>#17b</u>	If blinded, circumstances under which unblinding is	13
11 12	emergency		permissible, and procedure for revealing a participant's	
13 14 15	unblinding		allocated intervention during the trial	
16 17	Methods: Data			
18 19 20	collection,			
21 22	management, and			
23 24 25	analysis			
26 27	Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline,	15-16,
28 29 20			and other trial data, including any related processes to	21-22
30 31 32			promote data quality (eg, duplicate measurements, training	
33 34			of assessors) and a description of study instruments (eg,	
35 36			questionnaires, laboratory tests) along with their reliability	
37 38			and validity, if known. Reference to where data collection	
39 40 41 42			forms can be found, if not in the protocol	
42 43 44	Data collection plan:	<u>#18b</u>	Plans to promote participant retention and complete follow-	15-16,
45 46	retention		up, including list of any outcome data to be collected for	21-22
47 48			participants who discontinue or deviate from intervention	
49 50 51			protocols	
52 53 54	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage,	15-16,
55 56			including any related processes to promote data quality	21-22
57 58			(eg, double data entry; range checks for data values).	
59 60	F	or peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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		Reference to where details of data management	
		procedures can be found, if not in the protocol	
Statistics: outcomes	s <u>#20a</u>	Statistical methods for analysing primary and secondary	21
		outcomes. Reference to where other details of the	
		statistical analysis plan can be found, if not in the protocol	
Statistics: additiona	l <u>#20b</u>	Methods for any additional analyses (eg, subgroup and	21
analyses		adjusted analyses)	
Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	21
	<u> </u>	adherence (og as randomised analysis) and any statistical	21
missing data		methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring	g		
Data monitoring:	<u>#21a</u>	Composition of data monitoring committee (DMC);	15-16,
formal committee		summary of its role and reporting structure; statement of	21-22
		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	
Data monitoring:	<u>#21b</u>	Description of any interim analyses and stopping	15-16,
interim analysis		guidelines, including who will have access to these interim	21-22
		results and make the final decision to terminate the trial	
Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing	20
		solicited and spontaneously reported adverse events and	
		other unintended effects of trial interventions or trial	
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1 2			conduct	
3	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any,	21
5 6 7			and whether the process will be independent from	
7 8 9			investigators and the sponsor	
10 11 12	Ethics and			
12 13 14	dissemination			
15 16 17	Research ethics	<u>#24</u>	Plans for seeking research ethics committee / institutional	22
18 19 20	approval		review board (REC / IRB) approval	
21 22	Protocol	<u>#25</u>	Plans for communicating important protocol modifications	22
23 24 25	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
26 27			relevant parties (eg, investigators, REC / IRBs, trial	
28 29 30			participants, trial registries, journals, regulators)	
31 32	Consent or assent	<u>#26a</u>	Who will obtain informed consent or assent from potential	22
35 34 35			trial participants or authorised surrogates, and how (see	
36 37 38			Item 32)	
39 40	Consent or assent:	<u>#26b</u>	Additional consent provisions for collection and use of	22
41 42 43	ancillary studies		participant data and biological specimens in ancillary	
44 45			studies, if applicable	
46 47 48	Confidentiality	<u>#27</u>	How personal information about potential and enrolled	22
49 50			participants will be collected, shared, and maintained in	
51 52 53			order to protect confidentiality before, during, and after the	
54 55			trial	
56 57 58	Declaration of	<u>#28</u>	Financial and other competing interests for principal	22
59 60		For peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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2	interests		investigators for the overall trial and each study site	
; ;	Data access	<u>#29</u>	Statement of who will have access to the final trial dataset,	20-22
)) ,			and disclosure of contractual agreements that limit such	
3			access for investigators	
0 1 2	Ancillary and post	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for	21-22
3 4	trial care		compensation to those who suffer harm from trial	
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, 8 9	Dissemination policy:	#312	Plans for investigators and sponsor to communicate trial	21-22
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3 4			and other relevant groups (eg, via publication, reporting in	
5 6			results databases, or other data sharing arrangements),	
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3 4	authorship		professional writers	
5 6 7	Dissemination policy:	<u>#31c</u>	Plans, if any, for granting public access to the full protocol,	21-22
8 9	reproducible research		participant-level dataset, and statistical code	
0 1 2 3	Appendices			
4 5	Informed consent	<u>#32</u>	Model consent form and other related documentation given	22
6 7 8	materials		to participants and authorised surrogates	
9 0 1	Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of	/
2 3			biological specimens for genetic or molecular analysis in	
4 5			the current trial and for future use in ancillary studies, if	
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Efficacy of ultrasound therapy for the treatment of lateral elbow tendinopathy (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

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1	TITLE PAGE
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44	SZY, CS, LWX, ZYY, FCY participated in the development of the study design.
45	SZY, CS, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the study
46	conduct.
47	SZY, CS and LWX drafted the manuscript under FCY's supervision.
48	FCY contributed to applying for and gaining funding.
49	All authors contributed to the content and critical revision and approved the final
50	draft of the manuscript.

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52 **Conflict of interests**

53 The authors, their immediate families, and any research foundation with which 54 they are affiliated have not received any financial payments or other benefits from any 55 commercial entity related to the subject of this article.

The authors declare no competing financial interests.

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51

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69

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ETHICS

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (EC.D(BG).016.03.1-2021-096), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The research registry number is ChiCTR2100050547 at http://www.chictr.org.cn. Data will be analyzed anonymously; all patients will approve the results of this study by written consent. The written consent approval will be documented in the patients' files. All clinical investigations will be conducted in accordance with the guidelines of the Declaration of Helsinki.

86 ABSTRACT

87 Introduction

Lateral elbow tendinopathy (LET) is a highly prevalent disease among the middleaged population, with no consensus on optimal management. Nonoperative treatment is generally accepted as the first-line intervention. Ultrasound (US) therapy has been reported to be beneficial for various orthopedics diseases, including tendinopathy. The purpose of this study is to investigate the efficacy of US for LET treatment.

93 Methods and analysis

This protocol entails a three-arm, prospective, multicenter, randomised controlled trial. Seventy-two eligible participants with clinically confirmed LET will be assigned to either (1) US, (2) Corticosteroid Injections or (3) control group. All participants will receive Exercise-based Therapy as a fundamental intervention. The primary outcome is Patient-Rated Tennis Elbow Evaluation. The secondary outcomes include Visual Analogue Scale for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 for functional limitations at work, EuroQol-5D for general health, Hospital Anxiety and Depression Scale for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction. Adverse events will be recorded. Intention-to-treat analyses will be used.

105 Ethics and dissemination

Ethics Committees of all clinical centers have approved this study. The leading center is Shanghai Sixth People's Hospital, whose approval number is 2021-153. New versions with appropriate amendments will be submitted to the committee for further approval. Study results will be published in peer-reviewed journals and presented at local, national and international conferences.

1 2		
3 4	111	Trial registration number
5 6	112	ChiCTR2100050547.
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STRENGTHS AND LIMITATIONS OF THIS STUDY

Exercise-based Therapy as a fundamental intervention for all participants.

The first randomised controlled trial (RCT) to compare the efficacy between ultrasound therapy and corticosteroid injections in lateral elbow tendinopathy treatment.

- Multicenter RCT with blinded outcome assessor and statistician.
- Use of several patient-reported outcome measures as well as objective parameters.
- eating surge Participants and treating surgeons not blinded.

1. INTRODUCTION

First described by Runge,¹ lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution.² LET causes a great burden on the social economy, with an annual sickness absence rate as high as 5% in the working-aged adults.³ Though previously considered as a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis".⁴ A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. The patient most often complains of pain at or around the bony surface of the upper half of the lateral epicondyle and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.^{5,6}

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer,⁷ therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration.⁸ Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin.9 Among these, Ultrasonic Percutaneous Tenotomy, a recently developed method, appealing to many researchers for its good durability of pain relief and functional recovery,¹⁰ has satisfactory long-term (90 months) outcomes reported by Ang BFH.¹¹ However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population;² therefore, nonoperative treatment is suggested as first-

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line treatment.¹² Generally, nonsurgical methods include injections (like corticosteroid,
platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy,
extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or
oral naproxen, etc.^{13,14}

So far, despite the wide range of treatments, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% of experts recommended Exercise-based Therapy (EBT) as the first choice of intervention.¹⁵ EBT was also supported by high-quality clinical trials¹⁶⁻¹⁸ and systematic reviews^{19,20}, regarded as the most cost-effective treatment for LET.²¹ The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT,¹⁵ due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term.¹⁶⁻¹⁸ In addition, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hvaluronate injection,²² platelet-rich plasma injection,²³ ESWT²⁴ and acupuncture²⁵ remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators.²⁶ US has been widely reported to be treatment beneficial in fracture nonunions,^{27,28} osteoarthritis,^{29,30} chronic muscle pain,^{31,32} soft tissue injury,³³ etc. As for tendinopathy, US is also a potential noninvasive treatment modality for frozen shoulder,^{34,35} rotator cuff,³⁶ achilles^{37,38} and patellar³⁹ tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data,⁴⁰ and most of them focused on the comparison between US and ESWT⁴¹⁻⁴⁵. Both Yalvaç B⁴³ and Özmen

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T⁴¹ have shown significant improvements in pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a control group, which would make it unclear whether the efficacy comes from US itself or the passing time, as LET is a self-limited disease. Therefore, the role of US in LET treatment still needs to be further explored by high-quality studies. Additionally, to our best knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

Therefore, the purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the efficacy of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE). In view of recent literatures, CI should be discouraged in LET;^{22,46} however, it's still common in clinics due to the ability to satisfy patient's need for quick pain relief.¹⁵ Thus, a change in the paradigm of LET treatment is necessary. This change will come about through proposed evidence-based treatment guidelines. There have been some ongoing clinical trials on LET treatment in recent years,47-49 and our prospective RCT proposes to complement and add to this relevant and much needed scientific effort.

2. METHODS

2.1. Study design

The design of this study is a three-arm, prospective, multicenter, randomised controlled trial that will enroll participants with a diagnosis of chronic symptomatic LET from 4 municipal tertiary hospitals (Shanghai Sixth People's Hospital, Shanghai East Hospital, Shanghai Tenth People's Hospital, and Pudong New Area People's Hospital of Shanghai). This manuscript is written according to the SPIRIT guidelines.⁵⁰

2.2. Participant and public involvement

This study was done without participant involvement. Participants were not invited to comment on the design and were 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 the public via mass media. Participants as a whole will be acknowledged at the end of our publications and presentations.

204 2.3. 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. Those interested will contact the research assistant who will provide further information about the study objectives and procedures and will perform an initial eligibility screening interview by telephone.

2.4. Medical evaluation and enrolment procedure

Participants potentially eligible will be invited to attend a medical examination to
confirm the LET diagnosis and assess eligibility to participate in the research project.
Inclusion criteria

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2		
3 4	215	• Age ≥ 18 years old;
5 6	216	■ Unilateral lateral elbow pain longer than 6 weeks duration;
7 8 9	217	■ Pain over the lateral humeral epicondyle with pain severity of greater than 30 mm
10 11	218	on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following:
12 13	219	gripping, palpation, resisted wrist or middle finger extension, or stretching of
14 15 16	220	forearm extensor muscles with reduced pain-free grip; ^{16,49}
17 18	221	• Able to read and write in simplified Chinese (Mainland), understand and complete
19 20	222	the questionnaire, and provide informed consent.
21 22 23	223	Exclusion criteria
24 25	224	• Concomitant musculoskeletal pain conditions reported by participants to be their
26 27	225	predominant complaint within the past 6 months;
28 29 30	226	• History of symptoms suggesting radicular, neurological, inflammatory or systemic
31 32	227	arthritic conditions;
33 34	228	Treatment by physiotherapy, electrophysical therapy, or injection within the past 6
35 36 27	229	months, or previous tennis elbow surgery;
37 38 39	230	Contraindications to US, including dermatological conditions, abnormal sensation
40 41	231	in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy
42 43	232	or breastfeeding, et al.;
44 45 46	233	Contraindications to CI, including hypertension, gastrointestinal ulcers, diabetes,
47 48	234	mental illness, et al.
49 50	235	Following the medical evaluation, a research assistant will meet with the eligible
51 52	236	participants and obtain written informed consent. Demographic variables will be
53 54 55	237	reported before treatment (baseline) of all participants regarding age, sex, body mass
56 57	238	index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous
58 59 60	239	medical history. Participants will also be asked relevant questions about the duration of

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> symptoms 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 (repetitive movements for >4hours/day; wrist flexion for >2hours/day; elbow flexion and extension for >2hours/day; use of computer keyboard/ mouse [how many hours/day] and use of vibrating instruments for >2hours/day), and sports activities (how many hours/week, activity type, team or individual sports)⁵¹ will also be collected.

2.5. Randomization and blinding

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

257 The outcome assessor and statistician will be blinded to group allocation and not258 involved in treatment procedures.

2.6. Intervention

At the beginning, all participants will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. Participants will be told that the absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical

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impairment in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all participants will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles.¹⁵ The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs, ^{16,18,52,53} mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. Thirty minutes per day, including basic tasks (pain-free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises performed for the upper limb be done with sound alignment of the spine, trunk, and proximal arm. 1) Pain-free gripping exercise with exercise putty, which allows practice of various gripping actions.

279 2) Forearm extensor muscle exercise using a free-standing dumbbell. Note that the 280 forearm is fully stabilized by the bench and upper body in sound postural alignment. 281 Duration per repetition lasts about 6-10 s.

282 3) Dumbbell weight exercise for the forearm flexor muscle with 6-10 s per repetition.
283 The postural is the same as 2).

4) Exercises for forearm supinator and pronator muscles using an imbalanced
adjustable dumbbell weight with 6-10 s per repetition, from end range of supination
to pronation with the participant maintaining full active control of the weight. The
elbow bent to 90° with the arm stabilizing beside the trunk. Progressions in load
imposed on the muscles can be achieved by increasing the weight or the distance
between weight and hand.

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290 5) Radial and ulnar deviation exercises are performed with similar equipment and291 guidelines in 4).

Education on recognition and correction of the poor posture from the pelvis to neck.
Once the spine and trunk are aligned more optimally, the upper limb position
should be addressed.

Participants in the [US group] will receive continuous mode US (Shanghai, China)
at a frequency of 1 MHz and intensity of 1.0 W/cm² for 10 minutes in 5 days per week
for 3 weeks on the maximum pain region of the lateral elbow.

Participants allocated to the [CI group] will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral epicondyle. Participants will be advised to wait for 20 min following injection and inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by a gradual return to normal activities. Participants will be instructed to avoid an aggressive return to activities even if substantial relief is obtained to minimize the potential recurrence of their symptoms.

308 Participants randomized to the [Control group] will neither receive US therapy nor
309 corticosteroid injection. They will only receive the fundamental intervention, EBT
310 program.

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

314 2.7. Data management

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

2.8. Outcome measures

324 Primary outcome

The primary outcome measure will be the difference in Patient-rated Tennis Elbow Evaluation (PRTEE). The PRTEE, formerly known as the Patient-Rated Forearm Evaluation Questionnaire, is a well-validated composite scale measuring pain (5 items, with 0=no pain and 10=worst imaginable) and physical function (6 items for specific activities and 4 items for usual activities, with 0=no difficulty and 10=unable to do).⁵⁴ ranging from 0 to 100, with higher scores represent worse possible pain and more loss of function. The pain (intraclass correlation coefficients, ICC=0.89), physical function (ICC=0.83) and the total (ICC=0.89) scores all demonstrate excellent reliability.⁵⁵ A variation of 11/100 points or 37% of baseline scores are reported for clinical significance defined as "much better" or "completely recovered".⁵⁶ We use a validated Hong Kong Chinese version⁵⁷ of the PRTEE translated into simplified Chinese (Mainland) because the culture and language are the same.

337 Secondary outcome

338 Secondary outcome measures will be the differences in Visual Analogue Scale
339 (VAS)⁵⁸ for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand

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(Quick-DASH)⁵⁹ for upper limb disability, pain free/maximum grip strength, Work
Limitations Questionnaire-25 (WLQ-25)⁶⁰ for functional limitations at work, EuroQol5D (EQ-5D)⁶¹ for life quality and health status, The Hospital Anxiety and Depression
Scale (HADS)⁶² for anxiety and depression status, Global Rating of Change (GROC)
for treatment success and recurrence rate, and Mahomed scale⁶³ for participants'
satisfaction.

346 🔳 Pain

The VAS will be used for pain evaluation, which consists of a 100-mm horizontal numbered line anchored at one end (0) with the words "no pain" and at the other end (100) with the words "worst pain imaginable". The score is determined by the distance between the left end of the line and the participant's mark in mm.⁵⁸ VAS is considered to be the most sensitive of all pain scoring scales and has been specifically validated in the LET population with high reliability (r=0.89) and a moderate correlation with painfree grip strength (r=0.47).⁶⁴ Participants are asked to score their pain on this line during rest (at time of measure), provocation and maximum grip strength. The provocation test is conducted on the outpatient clinic by resisted wrist dorsiflexion during full elbow extension. Clinically relevant improvement will be defined when a 50% decrease in VAS is observed before and after the treatment.⁶⁵ The consumption of rescue medication taken by each patient will be also recorded at each follow-up visit.

359 ■ Upper limb disability

The well-validated simplified Chinese (Mainland) version of Quick-DASH⁶⁶ will be used for elbow function evaluation, consisting of eleven questions scored on a 5point scale similar to the DASH.⁵⁹ 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.⁶⁷

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■ Grip strength

Pain free/maximum grip strength will be measured using a dynamometer (CAMRY, City of Industry, CA, USA). The participants will be asked to take a shoulder-width stance and allow their arms to hang loose, holding their arm adducted along the body and the elbow in full extension. The pain-free grip strength will be measured, followed by the maximum grip strength, and 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 pain-free grip strength will be measured up to the point when the subject slowly squeezes the dynamometer until the occurrence of pain. The maximum grip strength will be measured at the maximum grip level. 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×100.68

Functional limitations at work

In order to gather the 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: time demands, physical demands, mental/interpersonal demands, and output demands.⁶⁰ 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.⁶⁹

• Life quality and health status

388 The EQ-5D is a widely validated generic health-related quality of life (HRQol)
 389 measure known for its simplicity.⁶¹ It contains a five-dimension descriptive system

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(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 version⁷⁰ of the EQ-5D, which has been recommended by China
Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQol and
health utility.⁷¹

• Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders, anxiety and depression.⁶² There is evidence of increased levels of anxiety and depression in people with LET.⁷² 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 the absence of symptoms to 3 representing the maximum symptomatology) is used. The total scores for each subscale range from 0 to 21, with higher scores indicating higher levels of disorder. HADS has two cut-offs for categorization: 0-7, "non-case"; 8-10, "possible or doubtful case"; 11-21, "probable or definite case".⁷³

406 ■ Treatment success and recurrence rate

Participants' treatment impressions 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.^{16,18} Recurrence will primarily be defined as occurring when a participant rates a success at 3 weeks and a failure at 2 or 6 months or one year on GROC.^{16,18}

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Additional treatments will also be recorded after the failure of management in this
study (that is, not per protocol), if any, including subsequent interventions and even
surgery.

418 • Participants' satisfaction

Similarly, participants' level of satisfaction on the evolution of their condition will
be determined on a validated 4-point Likert scale ranging from "very satisfied",
"somewhat satisfied", "somewhat dissatisfied" to "very dissatisfied".⁷⁴

2.9. 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. CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection.

433 2.10. Sample size calculation

Sample size and power calculation are based on the primary outcome of the PRTEE score. All sample size calculations assume two-sided analysis with a power of 90% (1- β =0.90) at a significant level of α =0.05. A standard deviation (SD) of 5.1-point on the PRTEE score will be used based on the previous trial.⁷⁵ To detect a minimum clinically significant difference of 11.0-point⁵⁶ (superiority margin) between US and control groups (assuming a true difference of 15.6-point^{43,75}), a total of 22 participants Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

in each group is required. Allowing for an up to 10% dropout rate, we aim to enroll atleast 24 participants in each group to complete the study.

442 2.11. 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)⁷⁶ 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 PRTEE scores will be made using linear regression. In secondary analyses, repeated measures mixed model⁷⁷ 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.

2.12. 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 the trial protocol.

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

2.13. Study duration

Recruitment will begin in November 2021, and a one-year follow-up for all participants is anticipated to be completed by March 2023. See Table 1 for time points and recruitment progress.

2.14. Ethics and dissemination

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (EC.D(BG).016.03.1-2021-096), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The potential risks of this clinical trial are considered to be minimal and are addressed in the protocol and consent forms. A written consent (Supplementary 1) will be obtained by clinical practitioners from each participant. The trial was registered on www.chictr.org website (registration number ChiCTR2100050547). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

2.15. Limitation

This study will have one limitation. Participants and treating surgeons are inevitably not blinded, which may produce bias. However, we will strictly control the outcome assessors and statisticians to be blinded to group allocation and not involved in treatment procedures to reduce the bias.

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3. REFERENCES

- 491 1. Knobloch K, Gohritz A. Dr Runge: a German pioneer in sclerosing therapy in
 492 epicondylitis in 1873. Br J Sports Med. 2010.
- 2. Sanders TL Jr, Maradit Kremers H, Bryan AJ, et al. The epidemiology and health
 care burden of tennis elbow: a population-based study. Am J Sports Med.
 2015;43(5):1066-71.
- 496 3. Walker-Bone K, Palmer KT, Reading I, et al. Occupation and epicondylitis: a
 497 population-based study. Rheumatology (Oxford). 2012;51(2):305-10.
- 498 4. Khan KM, Cook JL, Kannus P, et al. Time to abandon the "tendinitis" myth. BMJ.
 499 2002;324(7338):626-7.
- 500 5. Haahr JP, Andersen JH. Physical and psychosocial risk factors for lateral
 501 epicondylitis: a population based case-referent study. Occup Environ Med.
 502 2003;60(5):322-9.
- 503 6. Herquelot E, Guéguen A, Roquelaure Y, et al. Work-related risk factors for
 504 incidence of lateral epicondylitis in a large working population. Scand J Work
 505 Environ Health. 2013;39(6):578-88.
- 506 7. Hudak PL, Cole DC, Haines AT. Understanding prognosis to improve rehabilitation:
 507 the example of lateral elbow pain. Arch Phys Med Rehabil. 1996;77(6):586-93.
 - 8. Ahmad Z, Siddiqui N, Malik SS, et al. Lateral epicondylitis: a review of pathology
 and management. Bone Joint J. 2013;95-B(9):1158-64.
- 510 9. Pierce TP, Issa K, Gilbert BT, et al. A Systematic Review of Tennis Elbow Surgery:
- 511 Open Versus Arthroscopic Versus Percutaneous Release of the Common Extensor
 - 512 Origin. Arthroscopy. 2017;33(6):1260-1268.e2.

Page 25 of 56

1

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50 57	
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58	
59	

60

513 10. Vajapey S, Ghenbot S, Baria MR, et al. Utility of Percutaneous Ultrasonic
514 Tenotomy for Tendinopathies: A Systematic Review. Sports Health.
515 2021;13(3):258-264.

- 516 11. Ang BFH, Mohan PC, Png MA, et al. Ultrasonic Percutaneous Tenotomy for
 517 Recalcitrant Lateral Elbow Tendinopathy: Clinical and Sonographic Results at 90
 518 Months. Am J Sports Med. 2021;49(7):1854-1860.
- 519 12. Vaquero-Picado A, Barco R, Antuña SA. Lateral epicondylitis of the elbow.
 520 EFORT Open Rev. 2017;1(11):391-7.
- 521 13. Lian J, Mohamadi A, Chan JJ, et al. Comparative Efficacy and Safety of
 522 Nonsurgical Treatment Options for Enthesopathy of the Extensor Carpi Radialis
 523 Brevis: A Systematic Review and Meta-analysis of Randomized Placebo524 Controlled Trials. Am J Sports Med. 2019;47(12):3019-3029.
- 525 14. Sayegh ET, Strauch RJ. Does nonsurgical treatment improve longitudinal outcomes
 526 of lateral epicondylitis over no treatment? A meta-analysis. Clin Orthop Relat Res.
 527 2015;473(3):1093-1107.
 - 528 15. Bateman M, Titchener AG, Clark DI, et al. Management of tennis elbow: a survey
 529 of UK clinical practice. Shoulder Elbow. 2019;11(3):233-8.
 - 530 16. Coombes BK, Bisset L, Brooks P, et al. Effect of corticosteroid injection,
 531 physiotherapy, or both on clinical outcomes in patients with unilateral lateral
 532 epicondylalgia: a randomized controlled trial. JAMA. 2013;309(5):461-9.
 - 533 17. Smidt N, van der Windt DA, Assendelft WJ, et al. Corticosteroid injections,
 534 physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised
 535 controlled trial. Lancet. 2002;359(9307):657-62.

BMJ Open

536 18. Bisset L, Beller E, Jull G, et al. Mobilisation with movement and exercise,
537 corticosteroid injection, or wait and see for tennis elbow: randomised trial. BMJ.
538 2006;333(7575):939.

539 19. Karanasios S, Korakakis V, Whiteley R, et al. Exercise interventions in lateral
540 elbow tendinopathy have better outcomes than passive interventions, but the effects
541 are small: a systematic review and meta-analysis of 2123 subjects in 30 trials. Br J
542 Sports Med. 2021;55(9):477-85.

543 20. Hoogvliet P, Randsdorp MS, Dingemanse R, et al. Does effectiveness of exercise
544 therapy and mobilisation techniques offer guidance for the treatment of lateral and
545 medial epicondylitis? A systematic review. Br J Sports Med. 2013;47(17):1112-9.

546 21. Coombes BK, Connelly L, Bisset L, et al. Economic evaluation favours
547 physiotherapy but not corticosteroid injection as a first-line intervention for chronic
548 lateral epicondylalgia: evidence from a randomised clinical trial. Br J Sports Med.
549 2016;50(22):1400-5.

550 22. Dong W, Goost H, Lin XB, et al. Injection therapies for lateral epicondylalgia: a
551 systematic review and Bayesian network meta-analysis. Br J Sports Med.
552 2016;50(15):900-8.

553 23. de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections
554 for chronic lateral epicondylar tendinopathy: a systematic review. Br J Sports Med.
555 2014;48(12):952-6.

556 24. Yoon SY, Kim YW, Shin IS, et al. Does the Type of Extracorporeal Shock Therapy
557 Influence Treatment Effectiveness in Lateral Epicondylitis? A Systematic Review
558 and Meta-analysis. Clin Orthop Relat Res. 2020;478(10):2324-39.

BMJ Open

2		
3 4	559	25. Chang WD, Lai PT, Tsou YA. Analgesic effect of manual acupuncture and laser
5	560	acununcture for lateral enicondulations a systematic review and meta-analysis. Am
6 7	500	acupulicule for lateral epicondylargia. a systematic review and meta-analysis. 74m
8 9	561	J Chin Med. 2014;42(6):1301-14.
10 11	562	26. Watson T. Ultrasound in contemporary physiotherapy practice. Ultrasonics.
12 13	563	2008;48(4):321-9.
14 15	564	27. Leighton R, Watson JT, Giannoudis P, et al. Healing of fracture nonunions treated
16 17 19	565	with low-intensity pulsed ultrasound (LIPUS): A systematic review and meta-
19 20	566	analysis. Injury. 2017;48(7):1339-47.
21	567	28 Karstians CM Button S. Nolta BA at al. Low intensity pulsed ultrasound increases
22 23	507	28. Korsijens Civi, Kutten S, None FA, et al. Low-intensity pulsed unitasound increases
24 25	568	blood vessel size during fracture healing in patients with a delayed-union of the
26 27	569	osteotomized fibula. Histol Histopathol. 2018;33(7):737-46.
28 29	570	29. Rutjes AW, Nüesch E, Sterchi R, et al. Therapeutic ultrasound for osteoarthritis of
30 31 32	571	the knee or hip. Cochrane Database Syst Rev. 2010;(1):CD003132.
32 33 34	572	30. Alfredo PP, Junior WS, Casarotto RA. Efficacy of continuous and pulsed
35 36	573	therapeutic ultrasound combined with exercises for knee osteoarthritis: a
37 38	574	randomized controlled trial. Clin Rehabil. 2020;34(4):480-90.
39 40 41	575	31. Ebadi S, Henschke N, Forogh B, et al. Therapeutic ultrasound for chronic low back
42 43	576	pain. Cochrane Database Syst Rev. 2020;7(7):CD009169.
44 45	577	32. Altan L, Kasapoğlu Aksoy M, Kösegil Öztürk E. Efficacy of diclofenac &
46 47 48	578	thiocolchioside gel phonophoresis comparison with ultrasound therapy on acute
49 50	579	low back pain; a prospective, double-blind, randomized clinical study. Ultrasonics.
51 52	580	2019;91:201-5.
53 54	581	33. Lai WC, Iglesias BC, Mark BJ, et al. Low-Intensity Pulsed Ultrasound Augments
55 56 57	582	Tendon, Ligament, and Bone-Soft Tissue Healing in Preclinical Animal Models: A
58 59 60	583	Systematic Review. Arthroscopy. 2021;37(7):2318-33.e3.

Page 28 of 56

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

34. Ebenbichler GR, Erdogmus CB, Resch KL, et al. Ultrasound therapy for calcific tendinitis of the shoulder. N Engl J Med. 1999;340(20):1533-8. 35. Pieber K, Grim-Stieger M, Kainberger F, et al. Long-Term Course of Shoulders After Ultrasound Therapy for Calcific Tendinitis: Results of the 10-Year Follow-Up of a Randomized Controlled Trial. Am J Phys Med Rehabil. 2018;97(9):651-8. 36. Desmeules F, Boudreault J, Roy JS, et al. The efficacy of therapeutic ultrasound for rotator cuff tendinopathy: A systematic review and meta-analysis. Phys Ther Sport. 2015;16(3):276-84. 37. Chester R, Costa ML, Shepstone L, et al. Eccentric calf muscle training compared with therapeutic ultrasound for chronic Achilles tendon pain--a pilot study. Man Ther. 2008;13(6):484-91. 38. Draper DO, Edvalson CG, Knight KL, et al. Temperature increases in the human achilles tendon during ultrasound treatments with commercial ultrasound gel and full-thickness and half-thickness gel pads. J Athl Train. 2010;45(4):333-7. 39. Stasinopoulos D, Stasinopoulos I. Comparison of effects of exercise programme, pulsed ultrasound and transverse friction in the treatment of chronic patellar tendinopathy. Clin Rehabil. 2004;18(4):347-52. 40. Dingemanse R, Randsdorp M, Koes BW, et al. Evidence for the effectiveness of electrophysical modalities for treatment of medial and lateral epicondylitis: a systematic review. Br J Sports Med. 2014;48(12):957-65. 41. Özmen T, Koparal SS, Karatas Ö, et al. Comparison of the clinical and sonographic effects of ultrasound therapy, extracorporeal shock wave therapy, and Kinesio taping in lateral epicondylitis. Turk J Med Sci. 2021;51(1):76-83.

Page 29 of 56

1

BMJ Open

607	42. Dedes V, Tzirogiannis K, Polikandrioti M, et al. Comparison of radial
608	extracorporeal shockwave therapy with ultrasound therapy in patients with lateral
609	epicondylitis. J Med Ultrason (2001). 2020;47(2):319-25.

610 43. Yalvaç B, Mesci N, Geler Külcü D, et al. Comparison of ultrasound and
611 extracorporeal shock wave therapy in lateral epicondylosis. Acta Orthop Traumatol
612 Turc. 2018;52(5):357-62.

- 613 44. Kubot A, Grzegorzewski A, Synder M, et al. Radial Extracorporeal Shockwave
 614 Therapy and Ultrasound Therapy in the Treatment of Tennis Elbow Syndrome.
 615 Ortop Traumatol Rehabil. 2017;19(5):415-26.
- 616 45. Lizis P. Analgesic effect of extracorporeal shock wave therapy versus ultrasound
 617 therapy in chronic tennis elbow. J Phys Ther Sci. 2015;27(8):2563-7.
- 618 46. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid
 619 injections and other injections for management of tendinopathy: a systematic
 620 review of randomised controlled trials. Lancet. 2010;376(9754):1751-67.
- 47. Schwitzguebel AJ, Bogoev M, Nikolov V, et al. Tennis elbow, study protocol for a
 randomized clinical trial: needling with and without platelet-rich plasma after
 failure of up-to-date rehabilitation. J Orthop Surg Res. 2020;15(1):462.
- 48. Keijsers R, Kuijer P, Koenraadt KLM, et al. Effectiveness of standardized
 ultrasound guided percutaneous treatment of lateral epicondylitis with application
 of autologous blood, dextrose or perforation only on pain: a study protocol for a
 multi-center, blinded, randomized controlled trial with a 1 year follow up. BMC
 Musculoskelet Disord. 2019;20(1):351.
 - 49. Lungu E, Grondin P, Tétreault P, et al. Ultrasound-guided tendon fenestration
 versus open-release surgery for the treatment of chronic lateral epicondylosis of the

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Page 30 of 56

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

elbow: protocol for a prospective, randomised, single blinded study. BMJ Open.
2018;8(6):e021373.
50. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and

- 633 50. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and
 634 elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
- 51. Usuelli FG, Di Silvestri CA, D'Ambrosi R, et al. Return to sport activities after
 medial displacement calcaneal osteotomy and flexor digitorum longus transfer.
 Knee Surg Sports Traumatol Arthrosc. 2018;26(3):892-896.
- 638 52. Coombes BK, Bisset L, Connelly LB, et al. Optimising corticosteroid injection for
 639 lateral epicondylalgia with the addition of physiotherapy: a protocol for a
 640 randomised control trial with placebo comparison. BMC Musculoskelet Disord.
 641 2009;10:76.
- 642 53. Vicenzino B. Lateral epicondylalgia: a musculoskeletal physiotherapy perspective.
 643 Man Ther. 2003;8(2):66-79.
- 644 54. Rompe JD, Overend TJ, MacDermid JC. Validation of the Patient-rated Tennis
 645 Elbow Evaluation Questionnaire. J Hand Ther. 2007;20(1):3-10; quiz 11.
- 646 55. Giray E, Karali-Bingul D, Akyuz G. The Effectiveness of Kinesiotaping, Sham
 647 Taping or Exercises Only in Lateral Epicondylitis Treatment: A Randomized
 648 Controlled Study. PM R. 2019;11(7):681-93.
 - 56. Poltawski L, Watson T. Measuring clinically important change with the Patientrated Tennis Elbow Evaluation. Hand Therapy 2011;16:52-7.
 - 57. Leung HB, Yen CH, Tse PY. Reliability of Hong Kong Chinese version of the
 Patient-rated Forearm Evaluation Questionnaire for lateral epicondylitis. Hong
 Kong Med J. 2004;10(3):172-7.

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2 3 4	654
5 6	655
7 8	656
9 10 11	657
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42 43	671
44 45	672
46 47 48	673
49 50	674
51 52	675
53 54	676
55 56 57	677
58 59	678

Page 31 of 56

58. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and
change scores: a reanalysis of two clinical trials of postoperative pain. J Pain.
2003;4(7):407-14.

BMJ Open

- 657 59. Beaton DE, Wright JG, Katz JN. Development of the QuickDASH: comparison of
 658 three item-reduction approaches. J Bone Joint Surg Am. 2005;87(5):1038-46.
- 659 60. Lerner D, Amick BC 3rd, Rogers WH, et al. The Work Limitations Questionnaire.
 660 Med Care. 2001;39(1):72-85.
- 661 61. EuroQol Group. EuroQol--a new facility for the measurement of health-related662 quality of life. Health Policy. 1990;16(3):199-208.
- 663 62. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr
 664 Scand. 1983;67(6):361-70.
- 665 63. Mahomed N, Gandhi R, Daltroy L, et al. The self-administered patient satisfaction
 666 scale for primary hip and knee arthroplasty. Arthritis. 2011;2011:591253.
- 667 64. Stratford PW, Levy DR, Gauldie S, et al. Extensor carpi radialis tendonitis: A
 668 validation of selected outcome measures. Physiotherapy Canada 1987;39(4):250-5.
- 669 65. Shin KM, Kim JH, Lee S, et al. Acupuncture for lateral epicondylitis (tennis elbow):
- 670 study protocol for a randomized, practitioner-assessor blinded, controlled pilot671 clinical trial. Trials. 2013;14:174.
- 672 66. Cao S, Zhou R, Zhou H, et al. Reliability and validity of Simplified Chinese version
 673 of Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire:
 674 cross-cultural adaptation and validation. Clin Rheumatol. 2019;38(11):3281-7.
- 675 67. Franchignoni F, Vercelli S, Giordano A, et al. Minimal clinically important
 676 difference of the disabilities of the arm, shoulder and hand outcome measure
 677 (DASH) and its shortened version (QuickDASH). J Orthop Sports Phys Ther.
 678 2014;44(1):30-9.

BMJ Open

679 68. Smidt N, van der Windt DA, Assendelft WJ, et al. Interobserver reproducibility of
680 the assessment of severity of complaints, grip strength, and pressure pain threshold
681 in patients with lateral epicondylitis. Arch Phys Med Rehabil. 2002;83(8):1145-50.
682 69. Roy JS, MacDermid JC, Amick BC 3rd, et al. Validity and responsiveness of
683 presenteeism scales in chronic work-related upper-extremity disorders. Phys Ther.
684 2011;91(2):254-66.

685 70. Wu C, Gong Y, Wu J, et al. Chinese Version of the EQ-5D Preference Weights:
686 Applicability in a Chinese General Population. PLoS One 2016;11(10):e0164334.

687 71. Sun S, Chen J, Johannesson M, et al. Population health status in China: EQ-5D
688 results, by age, sex and socio-economic status, from the National Health Services
689 Survey 2008. Qual Life Res. 2011;20(3):309-20.

- 690 72. Alizadehkhaiyat O, Fisher AC, Kemp GJ, et al. Pain, functional disability, and
 691 psychologic status in tennis elbow. Clin J Pain. 2007;23(6):482-9.
- 692 73. Pallant JF, Bailey CM. Assessment of the structure of the Hospital Anxiety and
 693 Depression Scale in musculoskeletal patients. Health Qual Life Outcomes.
 694 2005;3:82.
- 695 74. Razmjou H, Holtby R. Impact of rotator cuff tendon reparability on patient
 696 satisfaction. JSES Open Access. 2017;1(1):5-9.

697 75. Rabago D, Lee KS, Ryan M, et al. Hypertonic dextrose and morrhuate sodium
698 injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single699 blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil.
700 2013;92(7):587-96.

701 76. Sedgwick P. Intention to treat analysis versus per protocol analysis of trial data.
702 BMJ. 2015;350:h681.

2 3 4	703	77. Detry MA, Ma Y. Analyzing Repeated Measurements Using Mixed Models. JAMA.
- 5 6	704	2016;315(4):407-8.
$\begin{array}{c} 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 5\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 5\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 56\\ 57\\ 58\end{array}$	704	
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706 Figure Legends

707 Figure 1 Participant flow chart

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	Table 1 Study ev	valuation procedures a	nd timeline	-2021- pyrigh			
Study procedure		Medical evaluation	Enrolment visit	3 weeks	2 months	6 months	One year
Determine eligibility		\checkmark	\checkmark	266 or cludir			
Obtain signed consent			\checkmark	ו 17 Ja ng for			
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Give instructions for pain medication diary			\checkmark	2022. gnemo elated			
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Visual Analogue Scale for pain			\checkmark	d fron ur (AB √	\checkmark	\checkmark	\checkmark
Shortened version of the Disabilities of the	Arm, Shoulder and		al	۱ http: ES) . Jining	2	2	al
Hand questionnaire			v	//bmj	v	v	v
Pain free/maximum grip strength			\checkmark	open.l √	\checkmark	\checkmark	\checkmark
Work Limitations Questionnaire-25			\checkmark	bmj.cc √ and	\checkmark	\checkmark	\checkmark
EuroQol-5D			√ O	m/ on √	\checkmark	\checkmark	\checkmark
Hospital Anxiety and Depression Scale			\checkmark	June r techr	\checkmark	\checkmark	\checkmark
Treatment success rate				12, 202 hologie	\checkmark	\checkmark	\checkmark
Treatment recurrence rate				95 at A	\checkmark	\checkmark	\checkmark
Participants' satisfaction				gence √	\checkmark	\checkmark	\checkmark
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710	INDEX SECTION
711	1. INTRODUCTION
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713	2.1. Study design
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INFORMED CONSENT FORM

(English Version)

Participant Information Page

Study Title	:	Effectiveness of ultrasound therapy for the treatment of
		lateral elbow tendinopathy
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 <u>"Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy"</u>. 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

First described by Runge, lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution. LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults. Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis". A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of

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pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer, therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration. Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied longterm (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention. EBT was also supported by high quality clinical trials and systematic reviews, regarding as the most cost-effective treatment for LET. The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT, due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators. US has been widely reported to be treatment beneficial in fracture nonunions, osteoarthritis, chronic muscle pain, soft tissue injury, etc. As for tendinopathy, US is also reported to be a potential

noninvasive treatment modality for frozen shoulder, rotator cuff, achilles and patellar tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data, and most of them focused on the comparison between US and ESWT. Both Yalvaç B and Özmen T have shown significant improvements in terms of pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a control group, which would make it unclear whether the efficacy come from US itself or passing time, as LET is a self-limited disease.

Therefore, the role of US in LET treatment still needs to be further explored by highquality study. Additionally, to our best of knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

2. STUDY PURPOSE

The purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE).

3. STUDY PROCESS

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

About 72 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 lateral elbow tendinopathy with a lateral elbow irritation test.

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, dominant arm, lifestyle (smoking and drinking), and previous medical history. As well as relevant questions about duration of symptoms and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-

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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 Patient-Rated Tennis Elbow Evaluation (PRTEE) for elbow function and symptom, Visual Analogue Scale (VAS) for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH) for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 (WLQ-25) for functional limitations at work, EuroQol-5D (EQ-5D) for general health, Hospital Anxiety and Depression Scale (HADS) for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction.

C. Treatment by group

At the beginning, all of you will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. You will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all of you will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles. The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs, mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm.

You will be randomly assigned to one of three groups, [US group] vs. [CI group] vs. [Control 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^2 for 10 minutes in 5 days per week for 3 weeks on the maximum pain region of lateral elbow.

(b) If you are allocated to the [CI group], you will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/ mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral

epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

(c) If you are randomized to the [Control group], you will neither receive US therapy nor corticosteroid injection. They will only receive the fundamental intervention, EBT program.

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 3 weeks, 2 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 3 weeks, 2 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

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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.

CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. The occurrence of these reactions depends on the individual patient, and usually does not require special treatment. In addition, during the injection, there may be a slight tingling sensation due to tissue and nerve damage in the skin. If the patient is physically sensitive, the pain may be more intense. Someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection. The drugs in the CI contain hormones, therefore, if are injected repeatedly and for a long time, it will cause damage to the tissues in the skin, so local calcification and skin stiffness occur. If the drug penetrates the bones, it can cause osteoporosis. After the injection, if the patient's physical condition decreases, and the wound is not kept clean, it may lead to bacterial invasion of the wound, so the wound healing speed will be slow, and there will develop infection and inflammation. These adverse reactions can be avoided by reducing the number of CIs and standardizing injection procedures.

EBT is exercise, and theoretically there are no complications.

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

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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 LET. 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, EBT, autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT, acupuncture, and surgery, etc.

Please discuss these and other possible options with your doctor.

Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied long-term (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

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worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture 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 COPENSATION

(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 LET, oral non-steroidal anti-inflammatory drugs, etc. There is no cost involved in EBT. The expenses related to US and CI injection 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 <u>Ziyang Sun</u> at <u>********</u>.

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

Legal Representative's Signature: Date:

Investigator Signature: Date: _____

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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 SPIRITreporting guidelines, and cite them as:

2 3 1	Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A,						
5	Schulz KF, Paruleka	ar WR, Krl	eža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanatior	i and g			
7 3 9)	Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586						
 <u>2</u> 3 1			Reporting Item	Pagean d Number a			
5	Administrative			r technolo			
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) 2 3 4	Title	<u>#1</u>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1			
5 5 7 3	Trial registration	<u>#2a</u>	Trial identifier and registry name. If not yet registered,	4/6			
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		name of intended registry	
Trial registration: dat	a <u>#2b</u>	All items from the World Health Organization Trial	4/6
set		Registration Data Set	
Protocol version	<u>#3</u>	Date and version identifier	5
Funding	<u>#4</u>	Sources and types of financial, material, and other support	3
Roles and	<u>#5a</u>	Names, affiliations, and roles of protocol contributors	2
responsibilities:			
contributorship			
Roles and	<u>#5b</u>	Name and contact information for the trial sponsor	2
responsibilities:			
sponsor contact			
information			
Roles and	<u>#5c</u>	Role of study sponsor and funders, if any, in study design;	2/3
responsibilities:		collection, management, analysis, and interpretation of	
sponsor and funder		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	
Roles and	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating	2/3
responsibilities:		centre, steering committee, endpoint adjudication	
committees		committee, data management team, and other individuals	
		or groups overseeing the trial, if applicable (see Item 21a	
		for data monitoring committee)	
Introduction			
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1 2	Background and	<u>#6a</u>	Description of research question and justification for	8-10
3 4	rationale		undertaking the trial, including summary of relevant studies	
5 6 7			(published and unpublished) examining benefits and harms	
, 8 9			for each intervention	
10 11 12	Background and	<u>#6b</u>	Explanation for choice of comparators	8-10
13 14 15	rationale: choice of			
16 17	comparators			
18 19 20	Objectives	<u>#7</u>	Specific objectives or hypotheses	10
21 22 23	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel	10
24 25			group, crossover, factorial, single group), allocation ratio,	
26 27			and framework (eg, superiority, equivalence, non-inferiority,	
28 29 30			exploratory)	
31 32 32	Methods:			
33 34 35	Participants,			
36 37	interventions, and			
38 39 40	outcomes			
41 42	Study setting	<u>#9</u>	Description of study settings (eg, community clinic,	11
45 44 45			academic hospital) and list of countries where data will be	
46 47			collected. Reference to where list of study sites can be	
48 49 50			obtained	
51 52	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If	11-12
53 54 55			applicable, eligibility criteria for study centres and	
56 57 58			individuals who will perform the interventions (eg,	
59 60	Fc	or peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2			surgeons, psychotherapists)	
3 4	Interventions:	<u>#11a</u>	Interventions for each group with sufficient detail to allow	13-15
5 6 7	description		replication, including how and when they will be	
, 8 9 10			administered	
11 12	Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated	13-15
13 14	modifications		interventions for a given trial participant (eg, drug dose	
15 16 17			change in response to harms, participant request, or	
18 19 20			improving / worsening disease)	
21 22	Interventions:	<u>#11c</u>	Strategies to improve adherence to intervention protocols,	13-15
23 24	adherance		and any procedures for monitoring adherence (eg, drug	
25 26 27 28			tablet return; laboratory tests)	
29 30	Interventions:	<u>#11d</u>	Relevant concomitant care and interventions that are	13-15
31 32 33	concomitant care		permitted or prohibited during the trial	
34 35	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the	16-20
36 37			specific measurement variable (eg, systolic blood	
38 39 40			pressure), analysis metric (eg, change from baseline, final	
41 42			value, time to event), method of aggregation (eg, median,	
43 44			proportion), and time point for each outcome. Explanation	
45 46			of the clinical relevance of chosen efficacy and harm	
47 48 49			outcomes is strongly recommended	
50 51 52	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any	22
53 54			run-ins and washouts), assessments, and visits for	
55 56			participants. A schematic diagram is highly recommended	
57 58			(see Figure)	
60		For peer rev	iew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	Sample size	<u>#14</u>	Estimated number of participants needed to achieve study	20-21
3 4			objectives and how it was determined, including clinical and	
5 6 7			statistical assumptions supporting any sample size	
7 8 9			calculations	
10 11 12	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to	11
13 14 15			reach target sample size	
15 16 17	Methods: Assignment			
18 19 20	of interventions (for			
20 21 22 23	controlled trials)			
24 25	Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg,	13
26 27	generation		computer-generated random numbers), and list of any	
28 29 20			factors for stratification. To reduce predictability of a	
30 31 32			random sequence, details of any planned restriction (eg,	
33 34			blocking) should be provided in a separate document that is	
35 36			unavailable to those who enrol participants or assign	
37 38 39			interventions	
40 41 42	Allocation	<u>#16b</u>	Mechanism of implementing the allocation sequence (eg,	13
42 43 44	concealment		central telephone; sequentially numbered, opaque, sealed	
45 46	mechanism		envelopes), describing any steps to conceal the sequence	
47 48 49			until interventions are assigned	
50 51	Allocation:	<u>#16c</u>	Who will generate the allocation sequence, who will enrol	13
52 53	implementation		participants, and who will assign participants to	
55 56			interventions	
57 58				
59 60	F	or peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg,	13
3 4			trial participants, care providers, outcome assessors, data	
5 6 7			analysts), and how	
8 9 10	Blinding (masking):	<u>#17b</u>	If blinded, circumstances under which unblinding is	13
11 12	emergency		permissible, and procedure for revealing a participant's	
13 14 15	unblinding		allocated intervention during the trial	
16 17	Methods: Data			
18 19 20	collection,			
20 21 22	management, and			
23 24	analysis			
25 26 27	Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline,	15-16,
28 29			and other trial data, including any related processes to	21-22
30 31 32			promote data quality (eg, duplicate measurements, training	
33 34			of assessors) and a description of study instruments (eg,	
35 36			questionnaires, laboratory tests) along with their reliability	
37 38 30			and validity, if known. Reference to where data collection	
39 40 41			forms can be found, if not in the protocol	
42 43 44	Data collection plan:	<u>#18b</u>	Plans to promote participant retention and complete follow-	15-16,
45 46	retention		up, including list of any outcome data to be collected for	21-22
47 48			participants who discontinue or deviate from intervention	
49 50 51			protocols	
52 53 54	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage,	15-16,
55 56			including any related processes to promote data quality	21-22
57 58			(eg, double data entry; range checks for data values).	
59 60	F	or peer re	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1			Reference to where details of data management	
2 3 4			procedures can be found, if not in the protocol	
5 6 7	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and secondary	21
7 8 9			outcomes. Reference to where other details of the	
10 11 12			statistical analysis plan can be found, if not in the protocol	
13 14	Statistics: additional	<u>#20b</u>	Methods for any additional analyses (eg, subgroup and	21
15 16 17	analyses		adjusted analyses)	
18 19 20	Statistics: analysis	<u>#20c</u>	Definition of analysis population relating to protocol non-	21
20 21 22	population and		adherence (eg, as randomised analysis), and any statistical	
23 24	missing data		methods to handle missing data (eg, multiple imputation)	
25 26 27	Methods: Monitoring			
28 29				
30 31	Data monitoring:	<u>#21a</u>	Composition of data monitoring committee (DMC);	15-16,
32 33	formal committee		summary of its role and reporting structure; statement of	21-22
34 35			whether it is independent from the sponsor and competing	
36 37			interests; and reference to where further details about its	
38 39			charter can be found, if not in the protocol. Alternatively, an	
40 41 42			explanation of why a DMC is not needed	
43 44 45	Data monitoring:	<u>#21b</u>	Description of any interim analyses and stopping	15-16,
46 47	interim analysis		guidelines, including who will have access to these interim	21-22
48 49 50			results and make the final decision to terminate the trial	
50 51 52	Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing	20
53 54			solicited and spontaneously reported adverse events and	
55 56 57 58			other unintended effects of trial interventions or trial	
59 60		For peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2			conduct	
2 3 4	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any,	21
5 6			and whether the process will be independent from	
/ 8 9			investigators and the sponsor	
10 11 12	Ethics and			
13 14 15	dissemination			
15 16 17	Research ethics	<u>#24</u>	Plans for seeking research ethics committee / institutional	22
18 19 20	approval		review board (REC / IRB) approval	
21 22 23	Protocol	<u>#25</u>	Plans for communicating important protocol modifications	22
23 24 25	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
26 27			relevant parties (eg, investigators, REC / IRBs, trial	
28 29			participants, trial registries, journals, regulators)	
30 31 32	Consent or assent	#26a	Who will obtain informed consent or assent from potential	22
33 34		<u> </u>	trial participants or authorised surrogates, and how (see	
35 36			Itom 22)	
37 38				
39 40	Consent or assent:	<u>#26b</u>	Additional consent provisions for collection and use of	22
41 42	ancillary studies		participant data and biological specimens in ancillary	
45 44 45			studies, if applicable	
46 47	Confidentiality	#27	How personal information about potential and enrolled	22
48 49	Conneontienty	<u></u>	narticipants will be collected, shared, and maintained in	
50 51			order to protect confidentiality before, during, and after the	
52 53			trial	
55 56			lia	
57 58	Declaration of	<u>#28</u>	Financial and other competing interests for principal	22
59 60		For peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1	interests		investigators for the overall trial and each study site		BMJ Ope
3 4 5 6	Data access	<u>#29</u>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such	20-22	n: first publi
7 8 9 10			access for investigators		shed as 1(F
11 12	Ancillary and post	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for	21-22).1136/ ^p rotect
13 14	trial care		compensation to those who suffer harm from trial		bmjop ed by
15 16 17			participation		en-2021 copyrigi
18 19	Dissemination policy:	<u>#31a</u>	Plans for investigators and sponsor to communicate trial	21-22	-05726 ht, inclı
20 21 22	trial results		results to participants, healthcare professionals, the public,		6 on 17 uding f
23 24			and other relevant groups (eg, via publication, reporting in		7 Janu En for use
25 26			results databases, or other data sharing arrangements),		ary 20; seigne s relat
27 28 29 30			including any publication restrictions		ement Sup ed to text
30 31 32	Dissemination policy:	<u>#31b</u>	Authorship eligibility guidelines and any intended use of	21-22	oaded oerieu and d
33 34 35	authorship		professional writers		from htt r (ABES) ata minir
36 37	Dissemination policy:	<u>#31c</u>	Plans, if any, for granting public access to the full protocol,	21-22	Al t
38 39	reproducible research		participant-level dataset, and statistical code		jopen. rainin
40 41 42 43	Appendices				bmj.com/ o g, and simil
44 45 46	Informed consent	<u>#32</u>	Model consent form and other related documentation given	22	n June ar tech
40 47 48 49	materials		to participants and authorised surrogates		9 12, 2025 nnologies
50 51	Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of	/	s.
52 53			biological specimens for genetic or molecular analysis in		ence E
54 55			the current trial and for future use in ancillary studies, if		3ibliog
56 57 58			applicable		raphiq
59 60	Fo	or peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		ue de l

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