



**HAL**  
open science

## **Transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: protocol for the randomised, double-blind, shamcontrolled ESTIVAL trial**

Alice Courties, Camille Deprouw, Alexandra Rousseau, Laurence Berard, Amel Touati, Johanna Kalsch, Margaux Villeveille, Emmanuel Maheu, Anne Miquel, Tabassome Simon, et al.

### ► To cite this version:

Alice Courties, Camille Deprouw, Alexandra Rousseau, Laurence Berard, Amel Touati, et al.. Transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: protocol for the randomised, double-blind, shamcontrolled ESTIVAL trial. *BMJ Open*, 2022, 12 (3), pp.e056169. 10.1136/bmjopen-2021-056169. hal-03642782

**HAL Id: hal-03642782**


**<https://hal.sorbonne-universite.fr/hal-03642782>**

Submitted on 22 Apr 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# BMJ Open Transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: protocol for the randomised, double-blind, sham-controlled ESTIVAL trial

Alice Courties <sup>1,2</sup>, Camille Deprouw,<sup>3</sup> Alexandra Rousseau,<sup>4</sup> Laurence Berard,<sup>4</sup> Amel Touati,<sup>4</sup> Johanna Kalsch,<sup>4</sup> Margaux Villeveille,<sup>4</sup> Emmanuel Maheu,<sup>3</sup> Anne Miquel,<sup>5</sup> Tabassome Simon,<sup>1,4</sup> Francis Berenbaum,<sup>1,2</sup> Jeremie Sellam,<sup>1,2</sup> on behalf of ESTIVAL study group

**To cite:** Courties A, Deprouw C, Rousseau A, *et al.* Transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: protocol for the randomised, double-blind, sham-controlled ESTIVAL trial. *BMJ Open* 2022;**12**:e056169. doi:10.1136/bmjopen-2021-056169

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-056169>).

Received 10 August 2021  
Accepted 07 February 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Professor Jeremie Sellam;  
[jeremie.sellam@aphp.fr](mailto:jeremie.sellam@aphp.fr)

## ABSTRACT

**Introduction** Patients with erosive hand osteoarthritis (EHOA) experience pain and inflammation, two features that can be targeted by vagus nerve stimulation using electrical auricular transcutaneous vagus nerve stimulation (tVNS). A pilot study demonstrated the feasibility of the procedure, so we designed a randomised sham-controlled trial to determine the safety and efficacy of tVNS in EHOA.

**Methods and analysis** ESTIVAL Study (Essai randomisé comparant la Stimulation auriculaire transcutanée du nerf Vague versus sham stimulation dans l'Arthrose Digitale Érosive symptomatique et inflammatoire) is a superiority, randomised, double-blind sham-controlled trial comparing two parallel arms: active and sham tVNSs in a 1:1 ratio. Patients with symptomatic EHOA (score  $\geq 40/100$  mm on a visual analogue scale (VAS) for pain of 0–100 mm) and inflammatory EHOA ( $\geq 1$  clinical and ultrasonography-determined interphalangeal synovitis) are included in 18 hospital centres (17 rheumatology and 1 rehabilitation departments) in France. Active and sham tVNSs use an auricular electrode connected to the Vagustim device, with no electric current delivered in the sham group. Patients undergo stimulation for 20 min/day for 12 weeks. The follow-up visits take place at weeks 4, 8 and 12. The enrolment duration is 2 years and started in April 2021; 156 patients are scheduled to be included. The primary outcome is the difference in self-reported hand pain in the previous 48 hours measured on a VAS of 0–100 mm between baseline and week 12. Secondary outcomes include other pain outcomes, function, quality of life, serum biomarker levels, compliance and tolerance. For a subset of patients, MRI of the hand is performed at baseline and week 12 to compare the change in Outcome Measures in Rheumatology/Hand Osteoarthritis MRI Scoring System subscores. The primary analysis will be performed at the end of the study according to the intent-to-treat principle.

**Ethics and dissemination** Ethics approval was obtained from the institutional review board (Comité de Protection des Personnes, 2020-A02213-36). All participants will be required to provide written informed consent. The findings will be published in peer-reviewed journals.

**Trial registration number** NCT04520516; Pre-results.

**Protocol version and number** V.2 of 11 March 2021.

## Strengths and limitations of this study

- The ESTIVAL study (Essai randomisé comparant Stimulation auriculaire transcutanée du nerf Vague versus sham stimulation dans l'Arthrose digitale érosive symptomatique et inflammatoire) is a large, multicentre, randomised controlled study that will provide data on an innovative treatment for erosive hand osteoarthritis (EHOA).
- A clinical, biological and imaging evaluation is planned to evaluate the efficacy of active auricular transcutaneous vagus nerve stimulation (tVNS) as compared with sham tVNS in symptomatic and inflammatory EHOA.
- Limitations can be due to blinding quality because some dysesthesia can be reported with tVNS, but several procedures will mitigate this issue as much as possible.

## INTRODUCTION

Among all locations of osteoarthritis (OA), symptomatic hand osteoarthritis (HOA) is frequent, affecting 8.2% of men and 16% of women in the general population older than 50 years.<sup>1</sup> Erosive hand osteoarthritis (EHOA) is a severe HOA subset, defined by the presence of central erosions and collapse of the subchondral bone plate on X-rays.<sup>2</sup> EHOA frequency varies, depending on the population studied: 2.8% in the general population over age 55 years and 3.6%–10.2% in HOA populations but could reach 25%–50% of symptomatic patients with HOA in secondary care centres.<sup>1,3–6</sup>

The main characteristics of EHOA are the higher level of pain and more inflammatory features than non-erosive HOA.<sup>3,4,7</sup> Patients with EHOA could even experience more articular symptoms than those with inflammatory arthritis.<sup>8</sup> Inflammation characterised



by joint clinical soft swelling or erythema (ie, synovitis) occurs more frequently in EHOA than in non-erosive HOA according to clinical assessment, ultrasonography (US) or MRI.<sup>9–11</sup> As well, ultra sensitive C reactive protein (usCRP) level is higher in EHOA than non-erosive HOA and is correlated with the number of painful or tender joints.<sup>12</sup>

Despite its burden and frequency, EHOA lacks effective treatments. Recent trials investigating hydroxychloroquine, colchicine and synthetic or biological disease-modifying antirheumatic drugs (DMARDs) give disappointing results.<sup>13–17</sup> A recent study showed that 6 weeks of 10 mg prednisolone per day was superior to placebo for HOA symptoms with inflammatory features, but this finding raises safety issues.<sup>18</sup> Hence, innovative therapies are expected.

Vagus nerve stimulation (VNS) could be a novel therapy because it may decrease the inflammation and pain. The binding of acetylcholine, the main mediator of the vagus nerve (VN), to one of its receptors, nicotinic acetylcholine alpha-7 receptor, decreases systemic tumour necrosis factor (TNF) production.<sup>19 20</sup> As well, afferent VNS signalling towards central nervous system (CNS) centres could limit pain signals and regulate the hypothalamic–pituitary–adrenal axis.<sup>21</sup>

Invasive VNS has shown promising results, with an anti-inflammatory effect in rheumatoid arthritis or inflammatory bowel disease.<sup>22–25</sup> More recently, non-invasive VNS has included auricular transcutaneous vagus nerve stimulation (tVNS), which stimulates a sensitive afferent branch of the VN located in the ear (the *cymba concha*).<sup>26</sup> tVNS is being evaluated in several chronic painful and inflammatory diseases.<sup>27</sup>

In an open-label pilot study, we showed that 1-hour auricular tVNS per day significantly decreased pain and the number of tender and swollen joints and improved function in 18 patients with EHOA, but more importantly was well tolerated.<sup>28</sup> However, the low number of patients and no control group could not allow us to rule out a placebo effect for effectiveness.

Therefore, in this superiority study, we aimed to assess the efficacy and safety of tVNS for EHOA symptoms versus sham tVNS in a multicentre randomised trial. We hypothesise that as compared with sham stimulation, tVNS will decrease hand pain and improve hand function in patients with EHOA.

## METHODS AND ANALYSIS

### Study design

ESTIVAL (Essai randomisé comparant STimulation auriculaire transcutanée du nerf Vague versus sham stimulation dans l'Arthrose digitale érosive symptomatique et inflammatoire) is a superiority double-blinded multicentre and sham-controlled randomised trial comparing two parallel arms. A total of 18 centres, all involved in caring for patients with EHOA, are participating in this trial. The sponsor is the Assistance Publique–Hôpitaux

de Paris (Délégation à la Recherche Clinique et à l'Innovation). The trial is funded by a grant from Programme Hospitalier de Recherche Clinique 2019 (French Ministry of Health). The study is conducted in accordance with the Declaration of Helsinki and has been approved by an ethics committee (Ile de France, number 2020-A02213\_36). The protocol follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.<sup>29 30</sup> ESTIVAL is registered at ClinicalTrials.gov.

All patients included undergo the auricular tVNS with the Vagustim or sham treatment with the same device, which has the same appearance but does not deliver any electric current. Patients are randomised to receive the active or sham tVNS for 12 weeks with no crossover design. Each patient is scheduled for a visit at baseline and at 4, 8 and 12 weeks (figure 1). At each visit, patients complete questionnaires and undergo a clinical examination for efficacy and safety assessments (table 1). An 8.5 mL blood sample is collected at baseline and at the 12-week visit. Patients followed up in Saint-Antoine Hospital Center undergo non-contrast MRI of the most symptomatic hand at the baseline visit and week 12.

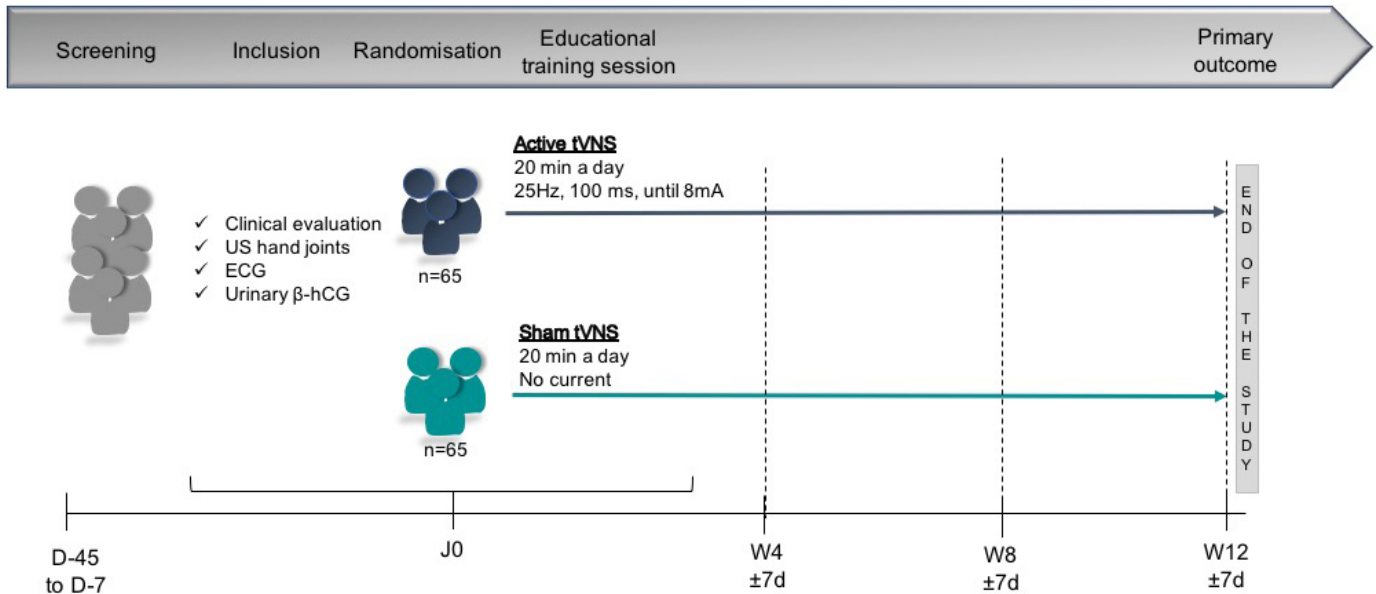
### Study participants

Patients are recruited during outpatient visits in each centre. During a screening visit, patients who fulfil inclusion criteria are informed about the trial and the protocol. They are informed about the two arms of the protocol and that they might be in the sham group. The investigator confirms the selection criteria (radiographic EHOA and presence of at least one joint with soft swelling or erythema, ie, synovitis) and then proposes the trial to the patient. If the patient agrees to participate, an inclusion visit is planned, and the patient is told to stop taking non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen 48 hours before the inclusion visit.

The inclusion visit is conducted by a medical doctor and includes checking inclusion and non-inclusion criteria, the patient giving informed written consent, a physical examination, completing questionnaires, hand US (to look for interphalangeal (IP) synovitis), electrocardiography, an urinary beta-human chorionic gonadotropin test for women of childbearing age, an 8.5 mL blood sample taken and bilateral anteroposterior hand radiography (table 2). A subset of patients, all included in Saint-Antoine Hospital Center, undergo MRI of the most symptomatic hand at IP joints.

### Inclusion, exclusion and randomisation criteria

The study includes patients aged  $\geq 18$  years with symptomatic HOA according to the American College of Rheumatology criteria and EHOA (defined by  $\geq 1$  erosive digital joint based on Verbruggen-Veys hand radiographic scoring).<sup>2 31 32</sup> Patients must have pain intensity of the hand of  $\geq 40/100$  mm on a visual analogue scale (VAS) at inclusion at least half of the last 30 days, at least  $\geq 1$  symptomatic proximal or distal IP (proximal or distal IP) joint with clinical soft swelling or erythema at inclusion,



**Figure 1** Schematic flow of the design of the randomised study comparing symptomatic effects of auricular tVNS versus sham tVNS in patients with symptomatic and inflammatory EHOA. Patients with symptomatic EHOA and inflammatory clinical and ultrasonography-evidenced synovitis are randomised (1:1) to active tVNS (n=65) or sham tVNS (n=65) for 20 min each day for 12 weeks. The two treatment arms are assessed at 4, 8 and 12 weeks. The primary outcome is assessed at 12 weeks. β-hCG, β-human Chorionic Gonadotropin; EHOA, erosive hand osteoarthritis; tVNS, transcutaneous vagus nerve stimulation.

and reported adverse effects with or inadequate response or contraindication to existing medication (including acetaminophen, topical and oral NSAIDs). Additionally, patients must give informed written consent (online supplemental file 1) and must be affiliated with a social security scheme. Exclusion criteria are in [table 1](#).

To be randomised, included patients must also have the following:

- ▶ At least  $\geq 1$  proximal or distal IP joint with presence of moderate or major grey scale synovitis (score 2 or 3) and/or power Doppler signal (score  $\geq 1$ ) on hand joint US.
- ▶ No contraindication to tVNS use, diagnosed on electrocardiography at inclusion (cardiac rhythm disturbances, atrioventricular block of >first degree or total bundle branch block >120 ms).
- ▶ Negative urine pregnancy test at inclusion, if appropriate.

### Interventions

The trial intervention is auricular active or sham tVNS for 20 min/day, every day for 12 weeks. Staff at each centre receive a training session by the main investigator or the clinical researcher associate (CRA) about the device and settings, how to use the device and how to explain its use to the patient to maintain blinding.

The tVNS device pack was graciously provided by Schwa-Medico (Rouffach, France) and contains the following ([figure 2](#)):

- ▶ The Vagustim device (EC certificate, registration number DD 60136841 0001; report number 28417062 004 dated 4 March 2019, CE0197-2020/04/28), which is a transcutaneous electrical nerve stimulation

(TENS) device from Schwa-Medico especially designed to connect to an ear electrode. The waveform is biphasic, asymmetrically balanced, with amplitude from 0 to 99 mA. Frequency preset modes are at 25, 10 and 1 Hz and will be set at 25 Hz, 100  $\mu$ s.

- ▶ One auricular electrode (Monath Electronic).
- ▶ Conductive gel medical device (C+V Pharma Depot GmbH, Versmold, Germany).

To properly stimulate the VN, a conductive gel is applied on the auricular electrode to ameliorate electrical transmission. The electrode is then applied on the left cymba concha for each daily use. The tVNS is performed on the left ear because efferent fibres to the heart that innervate the sinoatrial node are located on the right side and so could be connected to the VN afferent fibres of the right ear.<sup>23</sup> The participants randomised in the sham group receive the same device pack with a Vagustim device that looks exactly the same. The active and sham devices look exactly the same. All the procedures and daily settings are exactly the same for both devices; all patients will wear the auricular electrode with conductive gel, turn on the device, will see the same screen and will set the intensity to a maximum of 8 mA or less if they feel discomfort. For the sham device, the intensity will appear as a real intensity, but no current will be delivered.

After randomisation, the patients are thoroughly instructed in how to use the device, and the first active session is performed at the hospital. This training session is performed by a nurse, another medical doctor or the clinical research technician at the baseline visit and, if necessary, at visits on weeks 4 and 8. Furthermore, the person who performs the training calls the patient to

**Table 1** Exclusion criteria of ESTIVAL study (Essai Randomisé Comparant Stimulation Auriculaire Transcutanée du nerf Vague versus Sham Stimulation dans l'Arthrose Digitale Érosive Symptomatique et Inflammatoire)

Exclusion criteria	<ul style="list-style-type: none"> <li>▶ Isolated or a predominant pain thumb-base OA.</li> <li>▶ Other inflammatory joint disease (eg, gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis and Lyme disease), psoriasis, current skin disease of the left ear (eg, eczema, urticarial lesion, skin infection and external otitis).</li> <li>▶ Ear canal not adapted to apply the auricular electrode.</li> <li>▶ Known history of cardiac rhythm disturbances, atrioventricular block &gt;first degree or total bundle branch block.</li> <li>▶ Symptomatic orthostatic hypotension or repeated vasovagal syncope history and history of vagotomy.</li> <li>▶ Severe asthma and treated sleep apnoea.</li> <li>▶ Evidence of serious uncontrolled concomitant medical condition (including cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, gastrointestinal disease or epilepsy), which in the opinion of the investigator makes them unsuitable for the study.</li> <li>▶ Pregnant or breast feeding.</li> <li>▶ Existence of a pain syndrome of the upper limbs that would interfere with the monitoring of pain or fibromyalgia.</li> <li>▶ Use of other electrically active medical devices (eg, pacemaker or transcutaneous electrical nerve stimulation for chronic pain).</li> <li>▶ Use of oral/intramuscular or intra-articular or intravenous corticosteroids, disease-modifying antirheumatic drugs (eg, slow-acting antirheumatic drugs such as methotrexate and sulfasalazine) or intra-articular hyaluronic acid to the hand joints within the last 3 months.</li> <li>▶ Any new hand OA treatment in the previous 2 months (including physiotherapy or orthosis), planned hand surgery in the next 3 months or use of any investigational (unlicensed) drug within 3 months before screening.</li> <li>▶ Patients under legal protection measure (tutorship or curatorship) and patients deprived of freedom.</li> <li>▶ Use of vagus nerve stimulation before the study.</li> <li>▶ Use of non-steroidal anti-inflammatory drugs or acetaminophen less than 48 hours before the inclusion visit.</li> </ul>
--------------------	--

OA, osteoarthritis.

check on the proper use of the device at  $10 \pm 7$  days after the baseline visit.

Three parameters are set:

- ▶ Frequency at 25 Hz.
- ▶ 100  $\mu$ s.
- ▶ Intensity is progressively increased from 0 to 8 mA during the daily setting. If the patient starts to feel discomfort, the intensity level below this uncomfortable intensity is selected to obtain a non-painful and non-unpleasant intensity.

Then patients self-administer their treatment using the device for 20 min/day for 12 weeks. The following pain

treatments are allowed: acetaminophen (except during the 48 hours before each visit), hand orthosis if used for more than 2 months before inclusion, and physiotherapy or occupational therapy if prescribed at least 2 months before inclusion and stable during the trial. Topical or oral NSAIDs, opioids, hand surgery and hand joint infiltration (corticosteroids and hyaluronic acid) are prohibited.

Patients come for a medical visit every 4 weeks for 12 weeks (weeks 4, 8 and 12). At each visit, participants undergo hand and general clinical examinations, complete questionnaires, report the daily use of acetaminophen in a self-reporting notebook, report tolerance of the device and report adverse events (table 2). Adherence is evaluated by using a device tracker that provides information on its use with the daily time application and mean daily intensity since the previous visit. If necessary, patients undergo a new training session at weeks 4 and 8. The last visit at week 12 includes the same items of the follow-up visits plus a blood sample taken and a non-contrast MRI of the hand for the subgroup who had MRI at inclusion. Three specific additional assessments are added: asking about (1) satisfaction with the device; (2) ease of use of the device, rated on a 4-point scale; and (3) whether patients believed they had used the active or sham device. The investigators are asked whether they believe the patient has received the active or sham device.

Patients can withdraw from the study at any time for any reason. Patients will be withdrawn from the treatment if they comply with exclusion criteria but will continue to be monitored for the study.

### Randomisation

The investigator randomises patients to the active or sham tVNS groups by using the electronic case report form (e-CRF) CleanWeb (Telemedecine Technologies S.A.S.). The computer-generated, blocked, balanced randomisation is prepared in a 1:1 ratio by an independent biostatistician from the clinical research unit (URC-Est). The block width is not communicated to investigators. Randomisation is stratified by the centre. The investigator in charge of the randomisation is blinded to the randomisation group and selects the device according to the code number provided by CleanWeb and placed on the related device.

### Blinding

Active or sham devices look exactly the same. To homogenise between centres, the explanations given to the patients during the training session on the use of the device, a document with the verbatim to use for explanations was prepared by the coordinator and provided to the individuals in charge of training sessions in each centre. Manufacturing and preparation of the medical devices are handled by Schwa-Medico and are anonymised by the General Agency for Health Equipment and Products. Participants, investigators and all researchers involved in the data collection (investigators and nurses) or in biological and imaging analysis are blinded to the

**Table 2** Schedule of enrolment, interventions and assessments of the ESTIVAL study (Essai Randomisé Comparant Stimulation Auriculaire Transcutanée du nerf Vague versus Sham Stimulation dans l'Arthrose Digitale Érosive Symptomatique et Inflammatoire) according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines

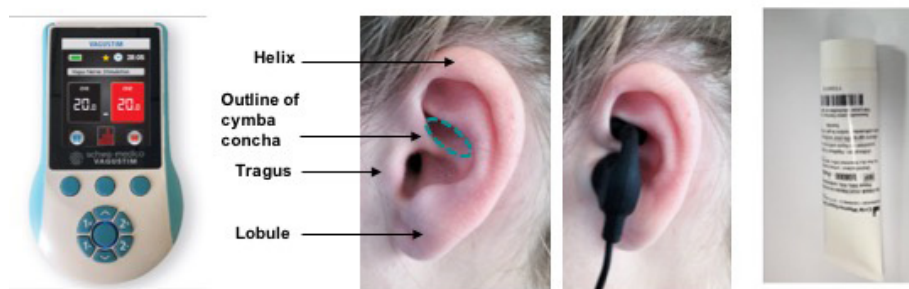
Timepoint	Study period				
	Screening Days 45–47	Allocation 0	Postallocation Week 4	Week 8	End of the study Week 12
<b>Enrolment</b>					
Eligibility screen	X	X			
Informed consent		X			
Hand radiography		X			
Hand joint ultrasonography		X			
Urinary $\beta$ -human chorionic gonadotropin test		X			
Electrocardiography		X			X
Randomisation		X			
<b>Interventions</b>					
Training session		X			
Active tVNS					
Sham stimulation					
<b>Assessments</b>					
Medical history	X				
Clinical general examination*		X	X	X	X
Hand clinical examination	X	X	X	X	X
VAS for hand pain in the last 48 hours	X	X	X	X	X
Morning stiffness		X	X	X	X
AUSCAN, FIHOA		X	X	X	X
Cochin Index		X			X
EQ-5D-5L		X			X
VAS for fatigue		X			X
HAD scale		X			X
DN-4 questionnaire		X			X
Knee/hip OA and WOMAC		X			X
Daily acetaminophen consumption (notebook)		X	X	X	X
PGIC					X
Patient and investigator beliefs					X
Device satisfaction/ease of use					X
Compliance			X	X	X
Adverse events			X	X	X
Blood samples		X			X
Hand MRI†		X			X

DN-4, a questionnaire about neuropathic pain.

\*Cardiopulmonary examination, blood pressure, search for orthostatic hypotension, heart rate, weight, height and left ear examination.

†Only a subset of patients undergo MRI of the most symptomatic hand at baseline and 12 weeks.

AUSCAN, Australian–Canadian Osteoarthritis Hand Index; DN-4, Douleur Neuropathique en Four Questions; EQ-5D-5L, EuroQol 5 Dimension 5 Level Quality of Life Questionnaire; FIHOA, Functional Index for Hand Osteoarthritis; HAD, Hospital Anxiety and Depression Scale; MRI, magnetic resonance imaging; OA, osteoarthritis; PGIC, Patient Global Impression of Changes Questionnaire; tVNS, transcutaneous vagus nerve stimulation; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.



**Figure 2** Description of the Vagustim device, the cymba concha, auricular electrode applied on the left cymba concha and the conductive gel provided to patients at the beginning of the study.

treatment allocation group until after the study completion and the analyses are fully performed at the end of the study. The investigator (outcome assessor) performs the clinical evaluation, and the clinical nurse or another medical doctor (different from the investigator) or the clinical study technician of each centre trains the patient in the device use. The investigating physician may request unblinding for any reason he considers essential to the health of the patient by contacting the project advisor. No unblinding is planned with the patient except in case of severe side effect.

During the follow-up visits, clinical efficacy is evaluated before recording potential minor stimulated site-treatment side effects. Because the clinical nurse or the person who performed the training session may guess the randomisation group according to the presence of these minor symptoms, no communication must occur between the investigator and the person who performed the training session and the patient during the study. We collect the initials of the person who performed the training session and the clinical assessor to ensure that they are different.

## Outcomes

### Primary outcome

The primary outcome is the difference between baseline and 12 weeks of self-reported hand pain in the previous 48 hours measured on a 100 mm VAS for the two groups. Patients are asked the standard question recommended by the Osteoarthritis Research Society International (OARSI): ‘How much pain in your hands did you experience during the past 48 hours?’ and give the answer on a VAS.<sup>33</sup>

### Secondary outcomes

Secondary outcomes are the Australian–Canadian Osteoarthritis Hand Index (AUSCAN) subscores (pain, function and stiffness),<sup>34</sup> modified Functional Index for Hand Osteoarthritis (FIHOA) score,<sup>35</sup> Cochin Functional Index, EuroQoL EQ-D5 score,<sup>36</sup> Hospital Anxiety and Depression Scale score,<sup>37</sup> fatigue intensity (0–100 mm VAS), number of painful and swollen hand joints (0–30) on pressure, patient global assessment on a 0- to 100 mm VAS and the Douleur Neuropathique en Four Questions questionnaire

score evaluating the neuropathic pain component<sup>38</sup> and total consumption of acetaminophen (in grams).

As well, we evaluate response defined by the Patient Acceptable Symptom State for pain (VAS score <40/100),<sup>39</sup> the Outcome Measures in Rheumatology (OMERACT)-OARSI definition or according to the Patient Global Impression of Change (0, no change or very much worse, to 7, considerable improvement; patients with scores 5, 6 or 7 are considered ‘responders’ vs 1–4, non-responders).<sup>40 41</sup>

Finally, the number of side effects (such as auricular local irritation, contact allergy, subjective side effects can occur such as slight pain, unpleasant ‘prickling’, ‘tingling’, ‘itching’, ‘tickling’, etc) and the mean time of daily use and cumulative time of use of Vagustim during the 30 days before each visit collected from the device’s tracker are recorded as secondary outcomes.

### Exploratory outcomes

Blood samples of 8.5 mL are collected at baseline and 12 weeks to explore change in serum levels of inflammatory or pain-related markers (usCRP, interleukin (IL)-6, IL-8, TNF, nerve growth factor) and serum markers (cartilage degradation (cartilage oligomeric matrix protein), collagen 2–1 (Col2-1) level, a marker of type II collagen denaturation) and Col2-1–NO<sub>2</sub>, cartilage-based biomarkers<sup>42</sup> (more information in online supplemental file 2). Other serum biomarkers will be measured according to the state-of-the-art OA-related biomarkers at the end of the study.

A subset of patients will undergo non-contrast MRI of the hand. MRI of the target hand (ie, the most symptomatic hand at the baseline visit) is acquired by using whole-body 1.5 or 3.0 T MRI. The hand is meticulously and consistently aligned in the coronal and axial planes to ensure a similar orientation at measurements separated in time. The acquisition uses a field of view covering the IP joints. One reader reads the baseline and 12-week MRI images with known time sequence for each treatment period but blinded to treatment allocation. Synovitis and bone-marrow lesions are scored by using a modified OMERACT/Hand Osteoarthritis MRI Scoring Systems core as an exploratory outcome.<sup>43</sup>

If patients have symptomatic OA pain at the knee or hip, the Western Ontario and McMaster Universities Arthritis Index score is recorded at baseline and 12 weeks to compare the effect of tVNS versus sham on other OA joints.<sup>44</sup>

To assess the efficacy of the blinding procedure and the ease of use of the device, we evaluate the following at 12 weeks: the patient's satisfaction with treatment assessed on a 5-point scale (very satisfied to not at all satisfied), ease of use on a 4-point scale (very easy to very difficult), and the patients and investigator's beliefs about whether the patient had used the active or sham device.

### Statistical power

The study is powered to detect a difference between groups in change of at least 13mm at 12 weeks on a 100mm pain VAS scale. Considering an improvement in the sham group of  $11.3 \pm 24$ mm, a two-sided alpha risk of 0.05, a non-parametric test and a 10% drop-out rate with a power of 80%, and an additional margin of 20%, 156 patients are needed to randomise 130 of them<sup>45</sup> (East 6 (2020), statistical software for the design, simulation and monitoring clinical trials; Cytel, Cambridge, Massachusetts, USA). The choice of this 13mm cut-off is based on the expected important placebo effect in the sham group (effect size of the TENS placebo in knee OA is 0.44, 95% CI 0.14 to 0.74), the stable placebo effect on pain level at 3 and 6 months in HOA and known minimal clinically important changes in pain level in OA.<sup>45 46</sup> The additional margin of 20% in recruitment is justified because some patients will not have US-evidenced synovitis. From the study of Vlychou *et al*, among 22 patients with EHOA, 19 had a thickened synovium; 18 had power Doppler signals; and thus 4 of 22 (18%) had no US features of joint inflammation.<sup>10</sup>

### Data collection and management

Data are collected in an e-CRF, devised by the study coordinator in collaboration with URC-Est. Data are completed by the investigators with the help of a clinical research technician. Data entry checks and a posteriori checks are planned. All information required by the protocol are recorded in physical or electronic report files, and an explanation must be provided for any missing data. All questionnaires used are validated. A CRA will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the standard operating procedures applied within the clinical research and innovation department. A steering committee with a coordinator, coinvestigators and a methodologist decides what to do in unexpected situations. The committee monitors the progress of the research and meets every 12 months.

Source documents (original document or item that can prove the existence or accuracy of a data or a fact recorded during the study) are kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

During and after the research involving human participants, all data collected concerning the participants are rendered anonymous. Under no circumstances are the names and addresses of the participants shown. Only the participant's initials are recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research.

### Data analysis

Analysis will be performed at the end of the study after a blind data review and database lock. A flowchart will be drawn according to the CONSORT statement. Continuous variables will be summarised with mean $\pm$ SD or median (IQR), depending on the distribution of the variable. Categorical variables will be described with frequency (percentage). Primary analysis will be performed on the intent-to-treat (ITT) population defined as all patients randomised.

### Primary outcome

Difference in VAS pain (baseline minus week 12) will be compared between groups by using a Wilcoxon rank-sum test. The effect size and its 95% CI will be estimated. Additional analysis will be made to study VAS pain over time using a linear mixed model. In case of non-normal distribution, adapted transformation will be made.

Sensitivity analysis will be performed in the ITT population with available data and on the per protocol population defined as all patients randomised without major protocol deviation.

### Secondary outcomes

Change in AUSCAN subscores and modified FIHOA score will be compared by Student t-test or Wilcoxon rank-sum test (depending on data distribution). Other outcomes will be described in both groups and the difference between them calculated with the 95% CI. The slope over time in VAS pain score, FIHOA score and AUSCAN subscores will be described graphically by randomisation group, and a linear mixed model may be used to compare groups.

Missing data replacement strategy for the primary endpoint will be fixed according to the structure of the missing data structure. Other missing values will not be replaced. Statistical analysis will be performed with SAS V.9.4. All tests will be two-sided and a p value of <0.05 will indicate statistical significance.

### Patient recruitment strategies

Recruitment of patients started in April 2021 and is expected for 2 years. In total, 18 French recruitment centres are involved: 17 rheumatology departments and 1 rehabilitation department in 18 hospitals (4 in Paris and 14 throughout France); 15 are academic hospitals (including 4 departments of Paris Assistance Publique des Hôpitaux de Paris (AP-HP) hospitals); 2 are regional



or departmental hospitals (Western region); and 1 is a private non-profit hospital (South of France, Marseille) for recruiting a wide range of patients with EHOA throughout France. However, because patients with EHOA are also often followed up in outpatient clinics, patients are also recruited from hospital consultations and by rheumatologists from private practice who work in collaboration with the investigator centres.

We used several communication channels to communicate about the study (French Society of Rheumatology and French Association for the Fight against Rheumatism (the largest patient's association devoted to musculoskeletal diseases in France)), the Arthritis Foundation, and publications in social network and the general media. We aimed also to contact the AP-HP network for communicating about ESTIVAL to the AP-HP patient community, which includes 39 hospitals. Flyers and posters are sent to the rheumatologists who participate to the OA study group of the French Society of Rheumatology. Finally, patients with EHOA can also contact us directly by letter or email. An ESTIVAL mailbox has been created for this purpose and is managed by the main investigator and/or the scientific director to refer patients to the nearest centre.

### Adverse events

Tolerance to the intervention was good in the pilot study and in studies in other indications with the only adverse event observed being an unpleasant sensation in the ear, mostly transitory, in a few patients.<sup>47</sup> However, information about adverse events and serious adverse events is collected throughout the study in the patient file and the eCRF. The investigator can temporarily or permanently withdraw a participant from the study or the patient may withdraw on their own for any safety reason or if it is in the participant's best interests.

### Patient and public involvement

There is no patient or public involvement.

### Ethics and dissemination

Ethics approval was obtained from the institutional review board at the main site (Comité de Protection des Personnes (CPP), 2020-A02213-36). All participants are required to provide written informed consent. Any substantial modification to the protocol by the coordinating investigator is sent to the sponsor for approval. After approval is given, the sponsor obtains approval from the CPP (research ethics committee) before the amendment can be implemented. The information note and the consent form can be revised if necessary, particularly in case of a substantial amendment to the study or if adverse reactions occur. Results of this study, whether positive or negative, will be presented at national and international congresses and published in a peer-reviewed journal.

## DISCUSSION

This is the first randomised study evaluating the tVNS in EHOA and in any OA joint. Here we chose a subset of patients with severe painful and inflammatory EHOA with clinical and US-confirmed synovitis to target the most severe and most symptomatic patients. We hypothesised that such a group will benefit most from tVNS because it targets pain as well as inflammation. We expect that tVNS will provide an analgesic effect over placebo in patients with EHOA and that it can be developed as a new non-pharmacological treatment in this subset of patients.

Recent randomised studies evaluating known synthetic or biological DMARDs failed to demonstrate efficacy in HOA or EHOA except for corticosteroids, which have a suspensive effect but also have safety concerns.<sup>14–18 48</sup> It is time to overcome the old scheme of already used rheumatic drugs and to develop innovative specific therapeutic targets in OA. Bioelectronic medicine is a new and promising field developed in several painful chronic conditions. Altered central sensitisation in patients with OA suggests altered CNS associated with chronic OA pain.<sup>49</sup> tVNS acts on CNS connectivity and plasticity involved in serotonergic and noradrenergic regulation, which may explain the analgesic effect in several contexts.<sup>50</sup> Moreover, tVNS also acts on inflammation, which is also involved in HOA-associated pain.<sup>51</sup>

We use here a non-invasive and usually very well-tolerated device. In a pilot study, the median decrease in hand pain on a VAS with tVNS applied with the same device was 23.5 mm (IQR 7.7–37.2) ( $p=0.001$ ) without any serious side effects. This encouraging study prompted us to conduct this randomised trial to determine the intrinsic efficacy of this device versus placebo with sham stimulation.

The design of the study follows the international guidelines for HOA clinical trials.<sup>33</sup> We considered previous data for calculating the sample size and considered possible limitations. Thus, the main issues in randomised trials evaluating tVNS are the quality and validity of the blinding.<sup>52</sup> Blinding of outcome assessors is essential, and we took additional measures, as recommended, to mitigate the potential bias from lack of blinding.<sup>53</sup> Concerning the sham procedure, some authors chose to perform stimulation at the same location (eg, cymba concha) but with low-frequency stimulation (1 Hz vs 25 Hz).<sup>54</sup> We did not choose this method because stimulation of the VN, although weak, cannot be excluded in this context. Other teams have preferred stimulation at another location (gastrocnemius or lobe of the ear), but then blinding is impossible for investigators, and we wanted to keep the blinding procedure as much as possible for the patient, nurse and investigator.<sup>55</sup> We decided on a sham stimulation at the same location (ie, cymba concha) to limit the possibility of unblinding patients and investigators. To appreciate the quality of the double-blinding, the final visit will include questions about whether the patients think they have had the active or the sham device. The same question will be asked of

the investigators concerning the active or sham device of the patient.

Regarding our primary and secondary outcomes, we expect that the tVNS treatment will decrease hand pain and improve hand function and quality of life in EHOA.

### Trial status

The recruitment started in April 2021 and will end in April 2023. The trial will end in July 2023, 3 months after the last inclusion.

### Author affiliations

<sup>1</sup>Sorbonne Université, Paris, France

<sup>2</sup>Hôpital Saint-Antoine, Service de Rhumatologie, Centre de Recherche Saint-Antoine, INSERM UMR\_S 938, APHP, Paris, France

<sup>3</sup>Hôpital Saint-Antoine, Service de Rhumatologie, APHP, Paris, France

<sup>4</sup>Hôpital Saint-Antoine, Unité de Recherche Clinique de l'Est Parisien (URC-Est), APHP, Paris, France

<sup>5</sup>Hôpital Saint-Antoine, Service de Radiologie, APHP, Paris, France

**Twitter** Emmanuel Maheu @emaheu1

**Acknowledgements** The authors thank Dr Camille Chesnel and Professor Gérard Amarengo for their help in the setting of transcutaneous vagus nerve stimulation in patients with osteoarthritis and for the ADEPT (traitement de l'Arthrose Digitale Erosive Par stimulation Transcutanée auriculaire du nerf vague) pilot trial. We thank Thomas Lobstein (Schwa-Medico) for helpful advice during the development of the project and Schwa-Medico, which graciously provided the Vagustim, electrode and conductive gel.

**Collaborators** ESTIVAL study group: Denis Arniaud; Jean-Philippe Bastard; Laurence Bérard; Francis Berenbaum; Julien Champey; Roland Chapurlat; Grégoire Cormier; Alice Courties; Camille Deprouw; Sandra Desouches; Florent Eymard; Soraya Fellahi; Jacques-Eric Gottenberg; Johanna Kalsch; Yves Henrion; Eric Lespessailles; Emmanuel Maheu; Hubert Marotte; Sylvain Mathieu; Anne Miquel; Paul Ornetti; Yves-Marie Pers; Nicolas Poursac; Francois Rannou; Anne-Christine Rat; Pascal Richette; Alexandra Rousseau; Christian H. Roux; Alain Saraux; Jérémie Sellam; Tabassome Simon; Amel Touati; Annick Tibi; Daniel Wendling.

**Contributors** AC, CD, AR, LB, AT, JK, MV, EM, AM, TS, FB and JS conceived and designed the study and participated in the implementation and data management of the study. AC and JS drafted the initial version of the manuscript. All the other authors provided critical revisions and approved the final revisions.

**Funding** This is an academic study sponsored by the Assistance Publique-Hôpitaux de Paris, Ministry of Health (Programme Hospitalier de Recherche Clinique National 2019). Schwa-Medico graciously donated the Vagustim device, electrodes and conductive gel.

**Disclaimer** Schwa-Medico graciously donated the Vagustim device, electrodes and conductive gel. Schwa-Medico was not involved in the design of the study or publication of the results and will not be involved in interpreting the data, preparing the manuscript or the decision to submit the article for publication.

**Competing interests** AC declares grants or contracts with Institut Servier, support for attending meetings and/or travel from Pfizer, Novartis, MSD, BMS and UCB. EM declares grants or contracts with Expanscience, Meda-Mylan, Sublimed, Pierre Fabre Labs, Fidia and Tand RB Chemedica; consulting fees from Fidia, Sublimed Expanscience and Meda-Mylan; payment or honoraria for lectures from Pierre Fabre and Fidia; and support for attending meetings and/or travel from Pfizer. TS declares grants from AstraZeneca, Bayer, Boehringer, Daiichi-Sankyo, Eli Lilly, GSK and Sanofi, and personal fees from AstraZeneca, Ablative Solutions, Bayer, Novartis and Sanofi. FB reports other conflicts from 4MovingG Biotech; personal fees from 4P Pharma during the conduct of the study; personal fees from Boehringer, Bone Therapeutics, CellProthera, Expanscience, Galapagos, Gilead, GSK, Lilly, Merck Sereno, MSD, Nordic, Novartis, Pfizer, Regulaxis, Roche, Sandoz, Sanofi, Servier, UCB and Peptinov; and grants from TRB Chemedica outside the submitted work; in addition, FB has a patent (WO2020104833A1); the co-inventors are R Rattenbach and Francis Berenbaum Composition, and methods for regulating chondrocyte proliferation and increasing of cartilage matrix production were issued. JS declares grants from Pfizer and Schwa-Medico.

**Patient consent for publication** Not applicable.

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

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

### ORCID iD

Alice Courties <http://orcid.org/0000-0001-8122-701X>

### REFERENCES

- Haugen IK, Englund M, Aliabadi P, *et al*. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham osteoarthritis study. *Ann Rheum Dis* 2011;70:1581–6.
- Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. *Clin Rheumatol* 2002;21:231–43.
- Kwok WY, Kloppenburg M, Rosendaal FR, *et al*. Erosive hand osteoarthritis: its prevalence and clinical impact in the general population and symptomatic hand osteoarthritis. *Ann Rheum Dis* 2011;70:1238–42.
- Bijsterbosch J, Watt I, Meulenbelt I, *et al*. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. *Ann Rheum Dis* 2010;69:1784–8.
- Hodkinson B, Maheu E, Michon M, *et al*. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. *Ann Rheum Dis* 2012;71:145–9.
- Sellam J, Maheu E, Crema MD, *et al*. The DIGICOD cohort: A hospital-based observational prospective cohort of patients with hand osteoarthritis - methodology and baseline characteristics of the population. *Joint Bone Spine* 2021;88:105171.
- Patrick M, Aldridge S, Hamilton E, *et al*. A controlled study of hand function in nodal and erosive osteoarthritis. *Ann Rheum Dis* 1989;48:978–82.
- Wittoek R, Cruyssen BV, Verbruggen G. Predictors of functional impairment and pain in erosive osteoarthritis of the interphalangeal joints: comparison with controlled inflammatory arthritis. *Arthritis Rheum* 2012;64:1430–6.
- Haugen IK, Mathiessen A, Slatkowsky-Christensen B, *et al*. Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthritis a separate inflammatory phenotype? *Osteoarthritis Cartilage* 2016;24:647–54.
- Vlychou M, Koutroumpas A, Malizos K, *et al*. Ultrasonographic evidence of inflammation is frequent in hands of patients with erosive osteoarthritis. *Osteoarthritis Cartilage* 2009;17:1283–7.
- Wittoek R, Carron P, Verbruggen G. Structural and inflammatory sonographic findings in erosive and non-erosive osteoarthritis of the interphalangeal finger joints. *Ann Rheum Dis* 2010;69:2173–6.
- Punzi L, Ramonda R, Oliviero F, *et al*. Value of C reactive protein in the assessment of erosive osteoarthritis of the hand. *Ann Rheum Dis* 2005;64:955–7.
- Kingsbury SR, Tharmanathan P, Keding A, *et al*. Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis: a randomized trial. *Ann Intern Med* 2018;168:385–95.
- Davis CR, Ruediger CD, Dyer KA, *et al*. Colchicine is not effective for reducing osteoarthritic hand pain compared to placebo: a randomised, placebo-controlled trial (COLAH). *Osteoarthritis Cartilage* 2021;29:208–14.
- Chevalier X, Ravaud P, Maheu E, *et al*. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697–705.
- ACR Meeting Abstracts. Methotrexate in patients with hand erosive osteoarthritis refractory to usual treatments: a randomized, double-blind, placebo-controlled trial. Available: <https://acrabstracts.org/abstract/methotrexate-in-patients-with-hand-erosive-osteoarthritis->

- refractory-to-usual-treatments-a-randomized-double-blind-placebo-controlled-trial/ [Accessed 14 Apr 2020].
- 17 Richette P, Latourte A, Sellam J, et al. Efficacy of tocilizumab in patients with hand osteoarthritis: double blind, randomised, placebo-controlled, multicentre trial. *Ann Rheum Dis* 2020;annrheumdis-2020-218547.
  - 18 Kroon FPB, Kortekaas MC, Boonen A, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019;394:1993–2001.
  - 19 Wang H, Yu M, Ochani M, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 2003;421:384–8.
  - 20 Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 2000;405:458–62.
  - 21 Randich A, Gebhart GF. Vagal afferent modulation of nociception. *Brain Res Brain Res Rev* 1992;17:77–99.
  - 22 Rong P, Liu A, Zhang J, et al. An alternative therapy for drug-resistant epilepsy: transcutaneous auricular vagus nerve stimulation. *Chin Med J* 2014;127:300–4.
  - 23 Nemeroff CB, Mayberg HS, Krahl SE, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology* 2006;31:1345–55.
  - 24 Koopman FA, Chavan SS, Miljko S, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci U S A* 2016;113:8284–9.
  - 25 Bonaz B, Sinniger V, Hoffmann D, et al. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. *Neurogastroenterol Motil* 2016;28:948–53.
  - 26 Yakunina N, Kim SS, Nam E-C. Optimization of transcutaneous vagus nerve stimulation using functional MRI. *Neuromodulation* 2017;20:290–300.
  - 27 Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in musculoskeletal diseases. *Joint Bone Spine* 2021;88:105149.
  - 28 Courties A, Deproux C, Maheu E, et al. Effect of transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: results from a pilot trial. *J Clin Med* 2022;11:1087.
  - 29 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191–4.
  - 30 Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–94.
  - 31 Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601–10.
  - 32 Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39:308–20.
  - 33 Kloppenburg M, Maheu E, Kraus VB, et al. OARSI clinical trials recommendations: design and conduct of clinical trials for hand osteoarthritis. *Osteoarthritis Cartilage* 2015;23:772–86.
  - 34 Bellamy N, Campbell J, Haraoui B, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: development of the Australian/Canadian (AUSCAN) osteoarthritis hand index. *Osteoarthritis Cartilage* 2002;10:855–62.
  - 35 Dreiser RL, Maheu E, Guillou GB, et al. Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed* 1995;62:43S–53.
  - 36 EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
  - 37 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
  - 38 Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005;114:29–36.
  - 39 Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. *Arthritis Care Res* 2012;64:1699–707.
  - 40 Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976.
  - 41 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–21.
  - 42 Henrotin Y, Sanchez C, Bay-Jensen AC, et al. Osteoarthritis biomarkers derived from cartilage extracellular matrix: current status and future perspectives. *Ann Phys Rehabil Med* 2016;59:145–8.
  - 43 Haugen IK, Østergaard M, Eshed I, et al. Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. *J Rheumatol* 2014;41:386–91.
  - 44 Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833–40.
  - 45 Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. *Arthritis Rheum* 2011;63:3383–91.
  - 46 Zhang W, Robertson J, Jones AC, et al. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008;67:1716–23.
  - 47 Mertens A, Raedt R, Gadeyne S, et al. Recent advances in devices for vagus nerve stimulation. *Expert Rev Med Devices* 2018;15:527–39.
  - 48 Kloppenburg M, Ramonda R, Bobacz K, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018;77:1757–64.
  - 49 Loggia ML, Edwards RR. Brain structural alterations in chronic knee osteoarthritis: what can treatment effects teach us? *Pain Med* 2018;19:2099–100.
  - 50 Garcia RG, Lin RL, Lee J, et al. Modulation of brainstem activity and connectivity by respiratory-gated auricular vagal afferent nerve stimulation in migraine patients. *Pain* 2017;158:1461–72.
  - 51 Kortekaas MC, Kwok W-Y, Reijnierse M, et al. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010;69:1367–9.
  - 52 Neugebauer EAM, Rath A, Antoine S-L, et al. Specific barriers to the conduct of randomised clinical trials on medical devices. *Trials* 2017;18:427.
  - 53 Boutron I, Moher D, Tugwell P, et al. A checklist to evaluate a report of a nonpharmacological trial (CLEAR NPT) was developed using consensus. *J Clin Epidemiol* 2005;58:1233–40.
  - 54 Bauer S, Baier H, Baumgartner C, et al. Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). *Brain Stimul* 2016;9:356–63.
  - 55 Addorisi ME, Imperato GH, de Vos AF, et al. Investigational treatment of rheumatoid arthritis with a vibrotactile device applied to the external ear. *Bioelectron Med* 2019;5:4.