# A feasibility study of non-invasive auricular vagus nerve stimulation in people with rheumatoid arthritis.

# STUDY PROTOCOL (Version 5, 20/10/2023) Ankit Parikh

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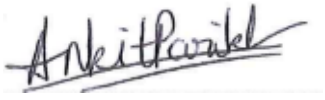
**AGREEMENT**

This document is confidential. The Investigators will conduct the study according to the procedures specified in the study protocol, and in accordance with the principles of the "Declaration of Helsinki" and HDEC National Statement on Ethical Conduct in Research Involving Humans.



20/10/2023

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Investigator Date

# PROTOCOL SYNOPSIS

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|---|
| **Title of Study:** Is a future single-centre clinical trial of home-based taVNS feasible in people with rheumatoid arthritis (RA)? |
| **Principal Investigator/Site:**<br><br>Associate Professor David Rice<br>Auckland University of Technology North Campus<br>90 Akoranga Drive,<br>Northcote,<br>Auckland 0627<br><br>**Co-ordinating Investigator/ Site:**<br><br>Ankit Parikh<br>Auckland University of Technology North Campus<br>90 Akoranga Drive,<br>Northcote,<br>Auckland 0627 |
| **Objectives:** The primary objective of this study is to determine if a future single-centre clinical trial of home-based taVNS is feasible in people with rheumatoid arthritis (RA). |
| **Methods:** This is a 14-day intervention. To address the primary objective, we will conduct 3 combined assessment and intervention sessions at the North Shore Hospital and participants will be required to complete another 12 sessions at home. |
| **Number of participants: 12** |
| **Inclusion criteria:**<br><br>• Aged 18 years and over<br>• Diagnosed with adult-onset RA according to ACR/EULAR 2010 RA classification criteria<br>• Have the presence of at least 3/28 swollen and/or at least 3/28 tender joints with 1 tender joint being in the hand or wrist |
| **Exclusion criteria:**<br><br>• Ear infection (otitis media or otitis externa)<br>• Poor hand dexterity and no access to a helper at home who could assist in fitting the in-ear taVNS device and the respiration sensor strap |

- Changes in oral or biologic disease-modifying antirheumatic drugs (DMARDs) in the last 4 weeks
- Have had intraarticular or intramuscular corticosteroids within 2 weeks prior to study entry
- Unstable dosing regimen of NSAIDs or analgesics in the last 2 weeks
- History of arrhythmia, myocardial infarction in the last 12 months, currently on beta-blocker medication or history of stroke affecting the brainstem
- Previous vagotomy
- Currently implanted electrical and/or neurostimulator device
- Active malignancy or history of active malignancy in the last 2 years, with the exception of non-melanoma skin carcinoma or carcinoma in situ
- Severe comorbidities which in the judgement of the study physicians would deem the participant not suitable as it may impact the safety of study conduct
- Known cognitive impairments
- Psychiatric illness with active psychosis
- Pregnant

**Data Collection:** During the intervention, all participants will wear the prototype taVNS device that contains the auricular stimulation electrodes placed on the concha of their left ear, an HRV sensor on their left index finger and a respiration sensor strap. During the 1$^{st}$, 8$^{th}$ and 15$^{th}$ day visits, a 1-hour assessment will take place, whereby resting HRV, patient-reported outcomes, quantitative sensory testing and a blood sample of the participant will be collected for the evaluation of inflammatory biomarkers.

**Data Analysis:** During the 1$^{st}$, 8$^{th}$ and 15$^{th}$ day visits, patient-reported outcomes and quantitative sensory testing results will be logged for each participant in a log file. The results of blood sample assessments will also be added to the above log file.

A user application will log and upload all the heart rate sample data for each session to Exsurgo's secure cloud infrastructure for each user. These data will stay in a secure location and will be post-processed for analysis.

**Statistical Analysis:**

Feasibility outcomes will be reported for

- **Participant eligibility and recruitment:** This will be reported based on the people with RA screened, ineligible, eligible, consented and declined.
- **Intervention adherence:** Reported by the number of sessions completed out of 14.

- **Usability and Acceptability:** Scores from usability and acceptability questionnaires will be evaluated.
- **Estimates of mean intervention effect and variance:** Intervention effect sizes will be calculated from baseline to 7 sessions and baseline to 14 sessions for the patient-reported scores, HRV parameters of RMSSD and HF-HRV and blood inflammatory biomarkers.
- **Adverse events/safety:** Safety-related events and withdrawals will be reported in absolute numbers and as a percentage out of 12 participants.
- **Relationships between HRV biomarkers and pain measures:** A correlation between changes in HRV and changes in pain and pain sensitivity will be reported.

# Background

## Transcutaneous auricular vagus nerve stimulation (taVNS) as an alternative treatment for managing pain

Current treatments for chronic pain are difficult to access and often only partially effective. There is a need for novel, more efficacious therapeutic approaches, particularly those that can be delivered remotely and/or facilitate self-management of pain and other symptoms. Neuromodulation is a fast-growing area that enables modulation of the central or peripheral nervous system circuits by delivering electrical, magnetic, optical, acoustic or mechanical energy to the body [1]. Transcutaneous auricular vagus nerve stimulation (taVNS), a type of neuromodulation, is a potential non-pharmacological alternative to manage pain. Vagus nerve stimulation activates several brainstem regions involved in descending pain inhibition [2], [3], likely increases the release of endogenous opioids [4], may alter nociceptive processing at a cortical level and has anti-inflammatory effects [5]–[7]. All these actions have been hypothesised to have an antinociceptive effect [8], [9]. taVNS is also advantageous in terms of feasibility and costs. An auricular device can be made small enough to be housed in a pocket-size or in-ear enclosure that is highly portable, allowing the treatment to be administered remotely or as a self-management device at home.

While there are several commercially available taVNS devices [10]–[14], only one of them offers closed-loop stimulation [10]. Closed-loop stimulation enables automatic modification of stimulation parameters while reducing the need for manual intervention and monitoring of the effects of stimulation. For example, a continuous glucose monitoring system tracks the blood glucose levels and adjusts insulin injection doses to maintain the blood glucose levels within a therapeutic range. In this way, a closed-loop design has the theoretical advantage of ensuring a standardised therapeutic dose of taVNS based on its physiological effect, rather than the potentially inconsistent stimulation delivered by open-loop devices. To enable closed-loop stimulation, it is essential to establish one or more potential biomarkers that can be monitored to assess the effects of stimulation.

In addition, the ability to deliver taVNS in synchronisation with the exhalation phase of the respiratory cycle is likely to improve its application for pain management. Activity in the vagal brainstem nuclei is cyclically modulated by respiration [3]. Recent functional magnetic resonance imaging (fMRI) studies [5],[15] have shown exhalation respiratory-gated auricular vagal nerve stimulation (eRAVANS) evoked fMRI signal increase in brain regions associated with enhanced VN activity and descending pain modulation.

## Why target people with RA?

RA is an autoimmune disease, the most common form of inflammatory arthritis and frequently leads to recurrent or chronic pain and disability. Inflammation within the joint contributes to the activation of peripheral nociceptors, leading to neuroplastic changes in both peripheral and central nervous systems [16]. There is also evidence that pain in RA can persist in the absence of overt inflammation, which is thought to be driven largely by central sensitisation, including impaired descending modulation of nociceptive pathways [17]. Also, lower HRV is associated with increased reported pain and increased inflammation in people with RA [18]. Hence, people with painful RA may have ongoing inflammation, impaired descending modulation of nociceptive pathways and evidence of ANS dysregulation, making them a good candidate population for taVNS.

## The prototype taVNS system

We intend to design and build a novel taVNS device that is capable of synchronising stimulation with the exhalation phase of the respiratory cycle and uses real-time HRV as feedback for monitoring the physiological effects of stimulation. While possible to do this in a laboratory environment using existing gold standard equipment (e.g. 12 lead ECG to measure HRV parameters and a respiration strap to measure the respiration phase), it would be preferable to develop alternative, more portable methods of measuring HRV to allow the future taVNS device to be used more easily in both clinical and home-based settings. An alternative way of measuring heart rate and HRV is through the use of photoplethysmography (PPG), where inexpensive and non-invasive optical sensors are placed on the skin and infrared light is used to derive measures of heart rate [19], [20]. From these measures, it is possible to calculate HRV parameters [21], [22].

This study will inform if the prototype device is feasible to be used in a future single-centre clinical trial of home-based taVNS in people with RA.

## Objectives

1. To determine if a future single-centre clinical trial of home-based taVNS is feasible in people with RA. This will be determined by
    a. Estimating the proportion of patients with RA that meet the eligibility criteria.
    b. Estimating how many eligible patients can be recruited.
    c. Estimating the intervention adherence based on the percentage of the taVNS sessions started and completed.

d. Evaluating the usability challenges and acceptability of in-home use of the prototype system and the user application.
e. Identifying any adverse events/issues related to safety.

2. To explore potential dose-response relationships by estimating the mean intervention effect and variance on
   a. Pain intensity (resting visual analogue scale (VAS), gripping VAS)
   b. Pain sensitivity (pressure pain threshold)
   c. Pain interference (Brief Pain Inventory)
   d. Psychological distress (Depression, Anxiety and Stress Scale [DASS-21])
   e. Health assessment (PGA [patient global assessment of disease activity] and HAQ [health assessment questionnaire])
   f. C-reactive protein (CRP), Tumor Necrosis Factor-α (TNF-α), Interleukin (IL)-1β, IL-10 and IL-17A
   g. Resting vagal tone (RMSSD, HF HRV), based on the assessment after the 7th and the 14th session.
3. To determine whether HRV is a feasible biomarker for a future closed-loop taVNS device, we will explore the relationships between immediate post-taVNS change in HRV parameters and pain and pain sensitivity measures.

## Study Design

A single-arm, repeated measures feasibility study will be undertaken. Participants will receive 14 sessions of daily taVNS for 20 minutes. Two of these sessions will be supervised and take place at North Shore Hospital, as part of an assessment session, while 12 of these sessions will be completed unsupervised, in the participant's home. The participants will be required to visit North Shore Hospital for three 1-hour assessment sessions on day 1, day 8 and day 15, during which patient-reported outcomes, resting HRV, quantitative sensory testing and a blood sample of the participant will be collected for the evaluation of inflammatory biomarkers.

## Location

The study will be conducted at the North Shore Hospital and in the participant's home.

## Participants

Twelve participants will be recruited from the Rheumatology outpatient departments in the Auckland region. This sample size is based on the number of participants that have been considered feasible to

recruit over 6 months rather than any formal power calculation. Participants will be included based on the following criteria:

- Aged 18 years and over
- Diagnosed with adult-onset RA according to ACR/EULAR 2010 RA classification criteria
- Have the presence of at least 3/28 swollen and/or at least 3/28 tender joints with 1 tender joint being in the hand or wrists

Participants will be excluded from the study if they have any of the following:

- Ear infection (otitis media or otitis externa)
- Poor hand dexterity and no access to a helper at home who could assist in fitting the in-ear taVNS device and the respiration sensor strap
- Changes in oral or biologic disease-modifying antirheumatic drugs (DMARDs) in the last 4 weeks
- Have had intraarticular or intramuscular corticosteroids within 2 weeks prior to study entry
- Unstable dosing regimen of NSAIDs or analgesics in the last 2 weeks
- History of arrhythmia, myocardial infarction in the last 12 months, currently on beta-blocker medication or history of stroke affecting the brainstem
- Previous vagotomy
- Currently implanted electrical and/or neurostimulator device
- Active malignancy or history of active malignancy in the last 2 years, with the exception of non-melanoma skin carcinoma or carcinoma in situ
- Severe comorbidities which in the judgement of the study physicians would deem the participant not suitable as it may impact the safety of study conduct
- Known cognitive impairments
- Psychiatric illness with active psychosis
- Pregnant

Participants will be free to withdraw from this study at any time without affecting their right to receive further treatment. In addition, participants may be withdrawn after the initial assessment session(s) if the study team determines that they do not have sufficient finger dexterity to fit and operate the equipment at home or a person living with them who is able to assist them. Finally, participants may be withdrawn if the study physicians (Dr Ng, Dr Kluger) consider it inappropriate for them to continue for any reason, including intervention-emergent adverse events, a serious adverse event, or medical reasons unrelated to the study. Reasons for withdrawal will always be documented and reported.

## Intervention

Participants will be asked to complete one 20-minute session of taVNS each day during the 14-day intervention period, using a specially developed prototype system. A user application, developed to accompany the prototype system, will be loaded on a mobile tablet that will be supplied to the participant. The application will instruct the participant to be seated in a chair and fit the equipment appropriately. It will check that the finger pulse sensor and respiration belt have been worn correctly and are transmitting the data to the application. The application will set the taVNS stimulation intensity to ensure it is strong but not uncomfortable. During each taVNS session, the stimulation will be administered for 1.0 second during exhalation only, and the HRV parameters will be continuously recorded by the application for a total of 20 minutes, after which the session will be completed.

## Other treatments

In addition to taVNS, participants will receive usual care as deemed appropriate by the study physicians (Dr Ng, Dr Kluger), provided this is stable in the 4 weeks leading up to the baseline assessment and throughout the 14-day intervention period. Usual care may include medications and other regular treatments deemed appropriate by the study physicians. Changes to existing medications (e.g. DMARDs, corticosteroids) will not be permitted during the 14-day intervention period.

## Study Procedures

Following screening and informed consent, participants will be booked in to visit the laboratory at the North Shore Hospital for three assessment sessions (Day 1, Day 8, Day 15). Blood samples will be taken at the beginning of each assessment session to track the changes in inflammatory biomarkers for the duration of the intervention. Patient-reported outcomes (e.g. Brief Pain Inventory, DASS-21,) will then be collected. A supervised 20-minute taVNS session will then be undertaken, with appropriate instruction. As part of the induction during the first assessment session, participants will be trained on how to insert the stimulation electrodes in the left ear and how to position the heart rate sensor. They will also be instructed on how to wear the respiration sensor strap. If the participant has poor hand dexterity that would make it difficult for them to fit/wear the in-ear taVNS device and the respiration strap (e.g. they report being unable to fit in-ear headphones by themselves) then they will be asked to be accompanied by a person living with them who can assist them in the fitment of the equipment during the home sessions. Before and immediately after 20 mins taVNS at each assessment session, pain at rest (VAS), pain during a standardised movement (VAS completed after 5 repetitions of 5kg grip) and pressure pain

thresholds will be assessed. An algometer (SBmedic, Sweden) will be used to assess the pressure pain threshold at two sites, the wrist of the dominant hand and the contralateral tibialis anterior (in a randomised order) at a ramping rate of 30kpa/sec. To assess pressure pain threshold, pressure will be increased until the participant feels any pain, at which point they will push a button. A mean of two measurements will be taken at each site, with a 30-second rest between repetitions.

After the first assessment session, participants will carry the equipment kit home. This kit will include the prototype system with a finger pulse sensor, a respiration belt, a commercial taVNS (Vagustim) device, a tablet running the mobile application and alcohol wipes. The finger pulse sensor and respiration belt have been chosen after the completion of a prior study conducted from April to July 2023 at Auckland University of Technology's North Shore campus. This study was approved by the AUT ethics committee. It recruited 35 participants who wore these sensors along with additional sensors for a duration of 60 to 90 minutes. The finger pulse sensor demonstrated excellent correlation (> 97%) and acceptable accuracy (24% error margin), with 95% confidence intervals and a p-value of < 0.001, in measuring the participant's heart rate variability when compared to a 12-lead electrocardiogram (ECG) system. The respiration belt achieved a true positive rate of 85%, with 95% confidence intervals and a p-value of < 0.001, in measuring the start of exhalation when compared to a gold standard respiration belt. These sensors will be housed in the sensor box shown in the following figure.

The participant will be required to complete 12 further 20-minute sessions at the rate of 1 session/day over the next 14 days and return to the North Shore Hospital laboratory for 2 more occasions for assessments, with the equipment kit. Participants will be provided with the researcher's contact details for any kind of technical support or other assistance required.

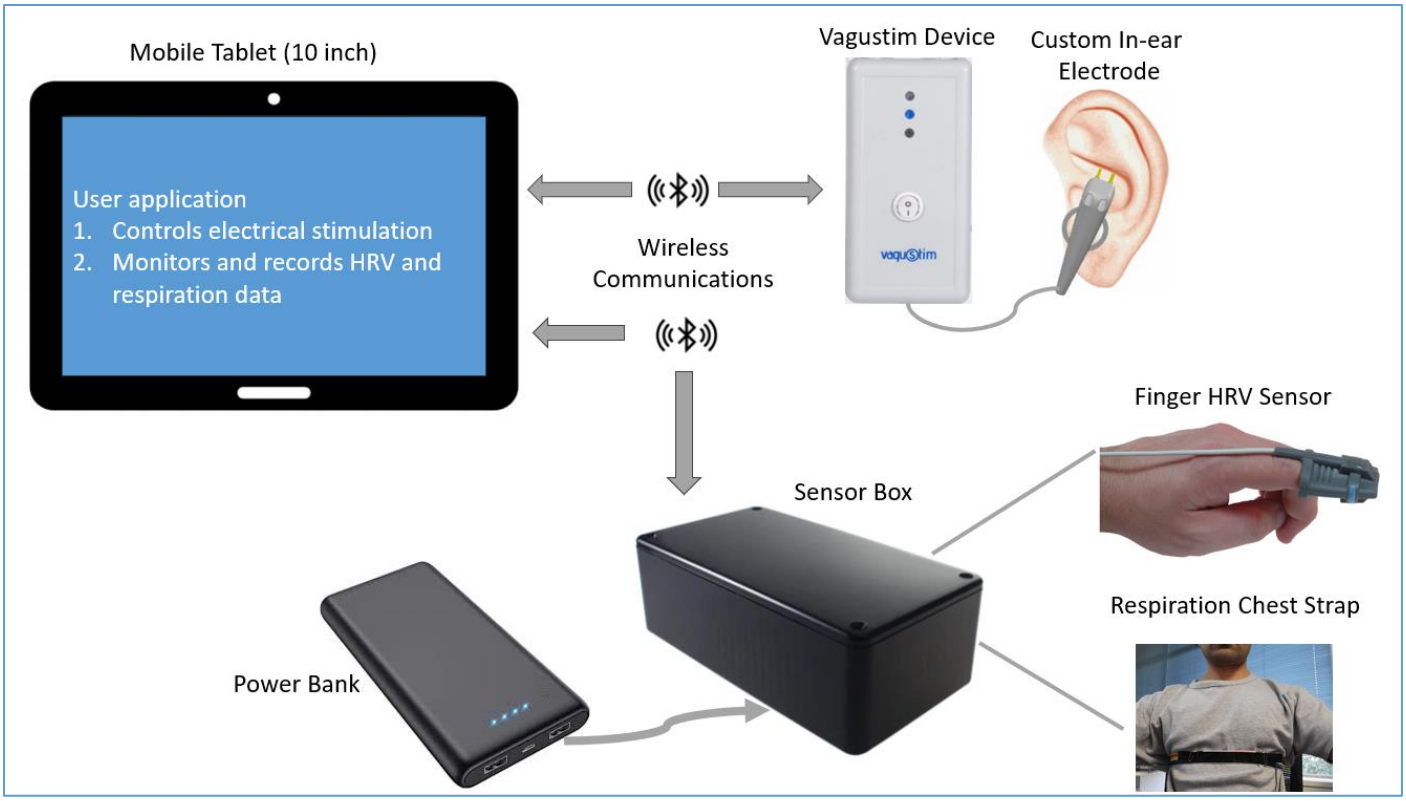



**Figure 1. Participant kit containing a 10-inch mobile tablet, Vagustim device with custom left ear electrode, sensor box with connections to finger sensor, respiration belt and power bank.**

Treatment adherence, including completion of daily sessions, will be automatically captured by the mobile application. If participants miss a single session, a follow-up text message and email will be sent reminding them to complete the next session as planned. If participants fail to complete 2 consecutive sessions, a follow-up phone call will be made by a member of the study team to encourage adherence and troubleshoot any issues with the training. A phone number and email address will be made available for participants to seek technical assistance throughout the intervention.

Additionally, the responses to the questionnaires completed during each hospital visit will be evaluated within 24 hours. If the responses indicate a moderate or severe concern (eg. scores from the DASS21 form indicating moderate to severe stress or depression), the clinical team involved in the study will be notified. They will contact the participant to discuss the findings and notify their GP if needed.

In addition to other patient-reported outcomes, participants will be asked to complete short usability and acceptability questionnaires during the final assessment session (Day 15) to get feedback on the use of the prototype taVNS system at home. The usability questionnaire will ask the participants to rate the usability questions on a scale of 1 (Strongly Agree) to 10 (Strongly Disagree). These questions will be based on the guidelines provided from a systematic review of e-health applications [23] and a study evaluating the usability of mobile health applications by participants suffering from chronic health conditions [24].

The acceptability questionnaire will be based on the theoretical framework of acceptability [25] for healthcare interventions. The responses to this questionnaire will be rated on a scale of 1 to 5 with ratings of 4 or above suggesting general acceptability.

The following figures show the timeline of the study protocol for the 2 weeks and the flow of the user application from the start to the end of the session.

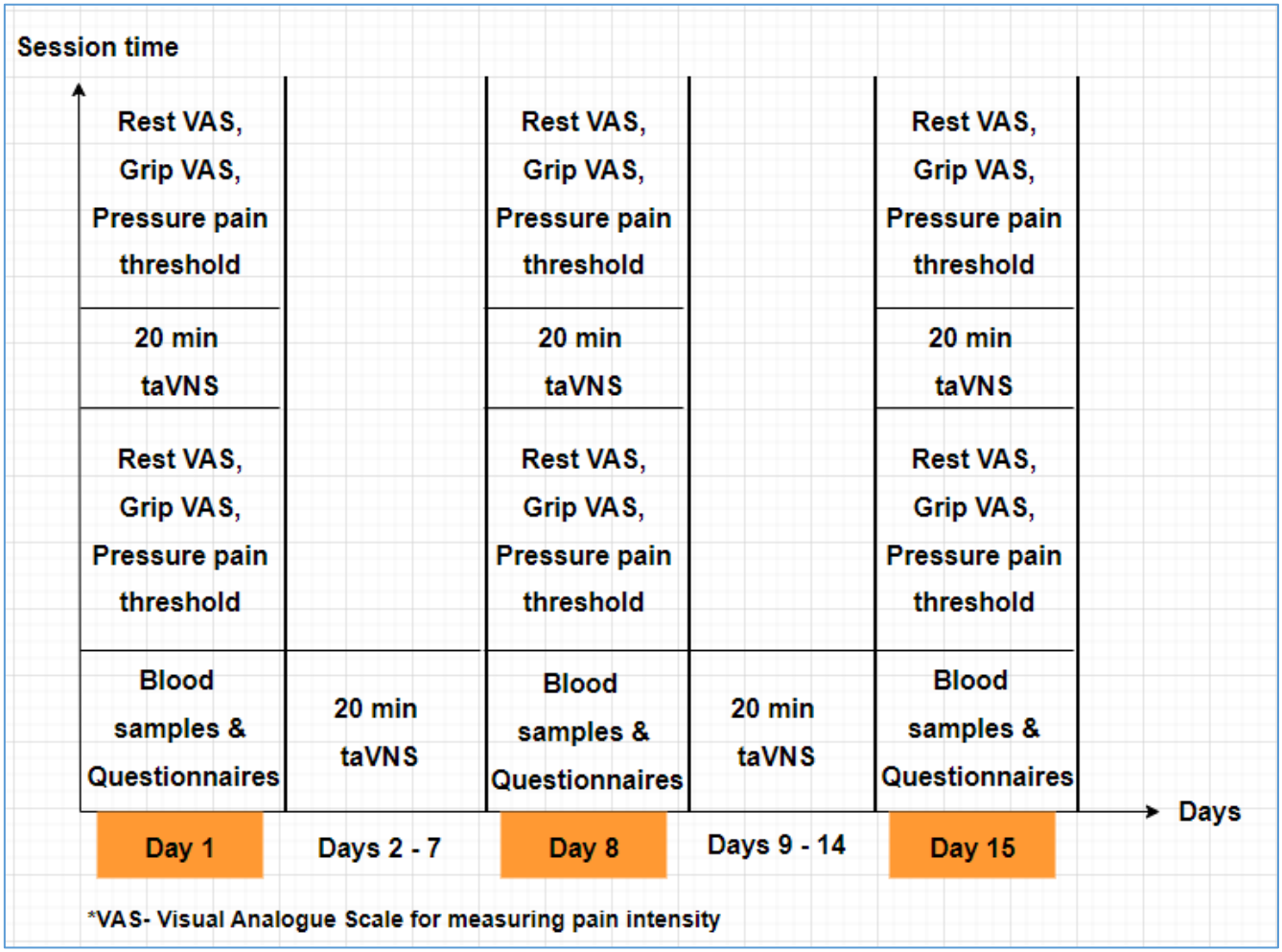



**Figure 2. Study protocol for the 2 weeks, outlining the flow of events during the 3 hospital visits.**

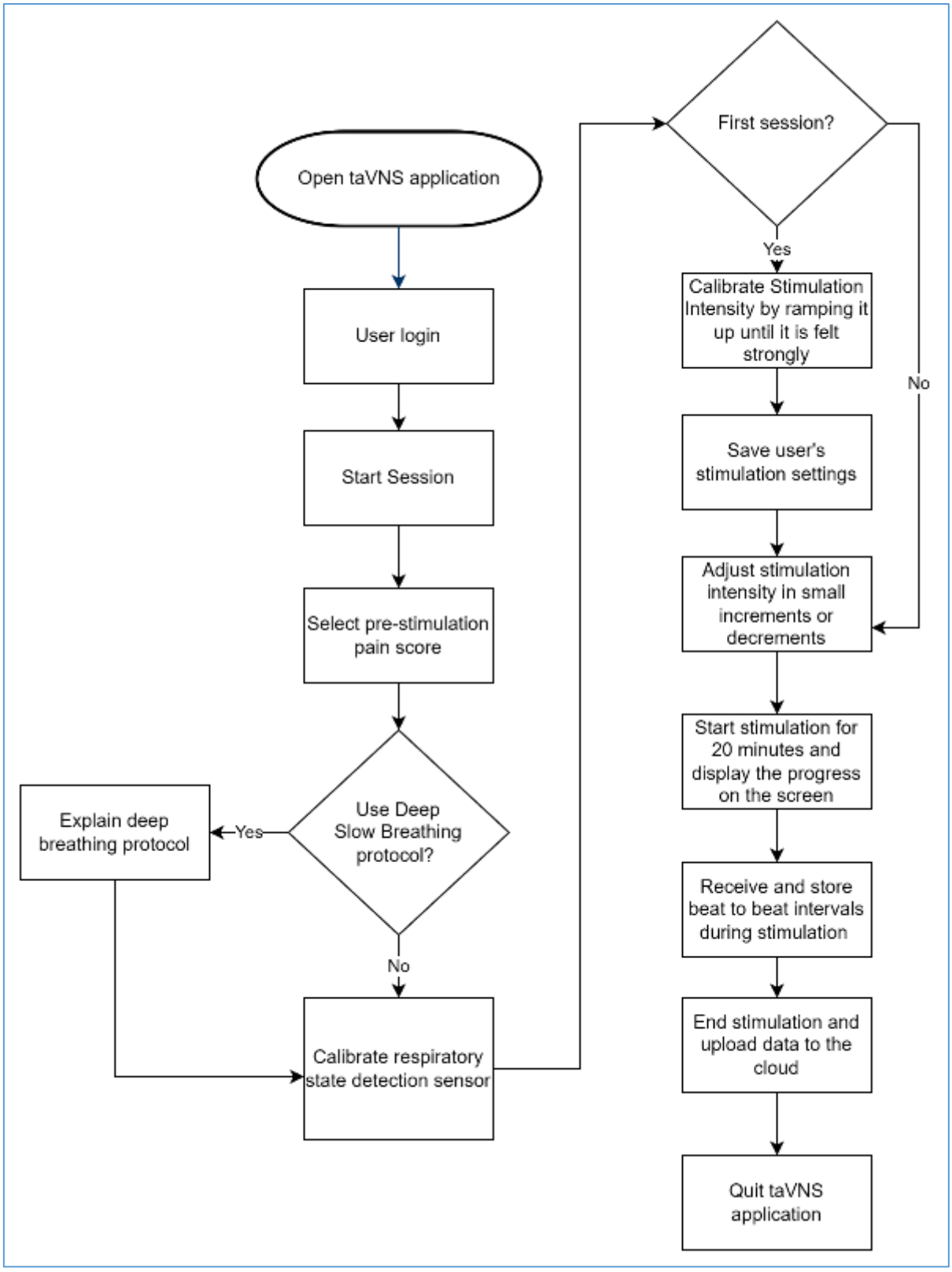



**Figure 3. User application flow during a taVNS session.**

## Outcome measures

**Participant eligibility and recruitment*:*** A log will be kept documenting the number of people with RA screened, ineligible, eligible, consented and declined. Feasibility outcomes will be reported on

- The proportion of screened people with RA who meet the inclusion criteria as a percentage of the total screened people
- The percentage of eligible participants that consented to be a part of the intervention

**Intervention adherence*:*** The user application will record the number of taVNS sessions started and completed. Adherence will be reported as a percentage of possible sessions completed prior to the final assessment (out of 14).

**Usability and Acceptability:** Individual items and total scores from both questionnaires will be evaluated. Overall acceptability of 60% or higher will be considered adequate, given the prototype design.

**Adverse events/safety:** Any participant withdrawals, reasons for withdrawal and any intervention-emergent adverse events during the intervention period will be documented and reported both in absolute numbers and as a percentage out of 12 participants. An intervention-emergent adverse event (TEAE) will be considered any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs during the intervention period and may or may not be considered related to the intervention. During the Day 8 and Day 15 assessment sessions, participants will be asked the open question: 'Have you experienced any health problems or had any unusual symptoms or abnormal changes in bodily function in the last week?' If the participant answers yes, they will be asked to list any health problems/symptoms/changes in body function they have experienced, and a series of follow-up questions will be posed for each problem identified including: Can you describe it? When did it start? How long did it last for? How frequently did you experience it? Are you still experiencing it? Did it affect your usual daily activities? In what way? Did you seek any medical treatment? If so, what was this? This information will be used to create a TEAE log and then to classify and grade each TEAE using the Common Terminology Criteria for Coding Adverse Events (CTCAE).

**Estimates of mean intervention effect and variance**: Intervention effect sizes, using Cohen's d method [26], will be calculated from baseline to 7 sessions and baseline to 14 sessions for resting and grip pain intensity, pain interference, psychological distress, patient global assessment of disease activity, and health assessment questionnaire, SF36 pressure pain thresholds, resting vagal tone (RMSSD, HF-HRV) and inflammatory biomarkers (CRP, TNF-α, IL-1β, IL-10 and IL-17A).

**Relationships between HRV biomarkers and pain measures**: We will examine and report the relationships between changes in resting pain, grip pain, and pressure pain thresholds in each assessment

session (pre to immediately post 20 mins taVNS), and the change in each of the HRV parameters over the same time using Pearson correlation coefficients [27] or Spearman rank coefficients [28].

## Ethics, data management and responsibilities

### Ethics

This study has received ethics approval from the Northern A Health and Disability Ethics Committee (reference **18139**). The study will be conducted according to the procedures specified in the study protocol, and in accordance with the principles of the "Declaration of Helsinki", CHMP GCP Guidelines on Good Clinical Practice E6(R2) and HDEC National Statement on Ethical Conduct in Research Involving Humans. All participants will be informed about the nature and objectives of the study and possible risks associated with participation. Written informed consent will be obtained from each participant before any study-specific activity is performed. The primary investigator will retain a copy of each participant's signed consent form. A copy of the signed and dated consent form will be provided to participants. Only participants who provide informed consent will enter the study.

### Data management

Confidentiality will be maintained throughout the trial. Investigators involved in accessing health information are employees of the Te Whatu Ora and are bound by its relevant privacy and confidentiality policies. Co-investigators who are not Te Whatu Ora employees and any research assistants who become involved in data collection at a future date will be required to sign a confidentiality agreement. Upon signing a consent form, participants will be assigned a unique participant code and no personal identifiers (e.g. name, date of birth, contact details) will be contained in the main data set. Deidentified (coded) data (i.e. questionnaire responses, HRV data) will be collected on the Exsurgo application and will be sent to a central data storage point using end-to-end encryption. Coded data will be kept by Exsurgo in secure, HIPAA-compliant, cloud-based storage on a password-protected database. Any data transferred/downloaded from the database during the study (e.g. for data safety monitoring and/or data analysis purposes) will remain deidentified and stored on a password-protected computer or external hard drive. For qualitative interviews, participants will be asked to choose their pseudonym, which will not be associated with any other data apart from their unique participant code. All consent forms and data related to the trial will be securely stored for a period of at least ten years. Data backups will be completed on at least a weekly basis and all data will be checked using range checks for data values prior to data analysis.

## Roles and responsibilities

Assoc. Prof David Rice is the primary investigator and will take overall responsibility for the conduct of the study, ensuring that it is conducted in accordance with both New Zealand law and Good Clinical Practice standards. Dr Rice is responsible for notifying and seeking approval for any changes to the study protocol to HDEC and AUT and for ensuring that serious adverse events and intervention-emergent adverse events are reported to the sponsor, HDEC and Medsafe as required, as well as completing and submitting relevant progress reports.

Ankit Parikh is the co-ordinating investigator and will be responsible for gaining written informed consent, organising participant appointments, data collection procedures and ensuring that data is managed and analysed in accordance with the data management plan. Ankit will help to complete and submit relevant progress reports, under the supervision of Assoc Prof. Rice.

Assoc Profs. Hamid GholamHosseini and Gwyn Lewis have contributed to the study design and will be involved in supervising data collection procedures and in the analysis and interpretation of data.

Dr Kristine (Pek Ling) Ng and Assoc. Prof. Michal Kluger have contributed to the study design and will act as the study physicians. They may be involved in recruitment as well as taking overall responsibility for medical supervision of the study. They will supervise the screening process and be involved in communications with the primary and co-ordinating investigators regarding the identification, coding and (if necessary) appropriate management of intervention-emergent adverse events. They will decide whether participants should be withdrawn from the trial for medical reasons.

All investigators will be involved in the dissemination of the study findings.

## Role of the sponsor

The sponsor will have a role in supporting data collection and storage and access to the final reports before dissemination.

# Appendix

## Brief Pain Inventory

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

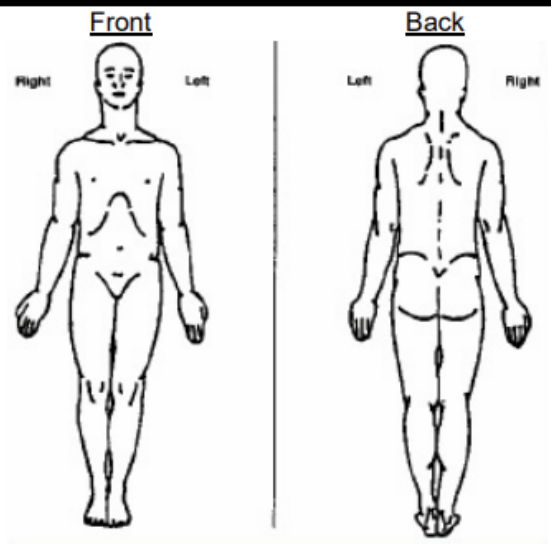
Revision: 07/01/05

### Brief Pain Inventory (Short Form)

**1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?**

☐ Yes ☐ No

**2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.**




**3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

**4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

**5. Please rate your pain by marking the box beside the number that best describes your pain on the average.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

**6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

**7. What treatments or medications are you receiving for your pain?**

**8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.**

| 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|---|---|---|
| ☐ No Relief | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ Complete Relief |

**9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:**

**A. General Activity**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**B. Mood**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**C. Walking ability**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**D. Normal Work (includes both work outside the home and housework)**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**E. Relations with other people**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**F. Sleep**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**G. Enjoyment of life**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

# Patient Global Assessment of Disease Activity

## AMERICAN COLLEGE OF RHEUMATOLOGY

### Patient Assessment

**Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing:**

Very Well ——————————— Very Poorly

**How much pain have you had because of your condition over the past week? Place a mark on the line below to indicate how severe your pain has been:**

No Pain ——————————— Pain as Bad as It Could Be

Please answer the following questions, even if you feel that they may not be related to you at this time. Answer exactly as you think or feel – there are no right or wrong answers. Check the one best answer for each question.

| **Activity Level**<br>**Right now, are you able to:** | **Without any difficulty** | **With some difficulty** | **With much difficulty** | **Unable to do** |
|---|---|---|---|---|
| 1. Dress yourself, including tying shoelaces and doing buttons? | 0 | 1 | 2 | 3 |
| 2. Get in and out of bed? | 0 | 1 | 2 | 3 |
| 3. Lift a full cup or glass to your mouth? | 0 | 1 | 2 | 3 |
| 4. Walk outdoors on flat ground? | 0 | 1 | 2 | 3 |
| 5. Wash and dry your entire body? | 0 | 1 | 2 | 3 |
| 6. Bend down to pick up clothing from the floor? | 0 | 1 | 2 | 3 |
| 7. Turn regular faucets on and off? | 0 | 1 | 2 | 3 |
| 8. Get in and out of a car, bus, train or airplane? | 0 | 1 | 2 | 3 |
| 9. Walk two miles? | 0 | 1 | 2 | 3 |
| 10. Participate in sports and games as you like? | 0 | 1 | 2 | 3 |
| 11. Get a good night's sleep? | 0 | 1.1 | 2.2 | 3.3 |
| 12. Deal with feelings of anxiety or being nervous? | 0 | 1.1 | 2.2 | 3.3 |
| 13. Deal with feelings of depression or feeling blue? | 0 | 1.1 | 2.2 | 3.3 |

**For Office Use Only**

**GL** ☐

**PN** ☐

**FN** ☐

1=0.33
2=0.67
3=1.0
4=1.33
5=1.67
6=2.0
7=2.33
8=2.67
9=3.0
10=3.33
11=3.67
12=4.0
13=4.33
14=4.67
15=5.0
16=5.33
17=5.67
18=6.0
19=6.33
20=6.67
21=7.0
22=7.33
23=7.67
24=8.0
25=8.33
26=8.67
27=9.0
28=9.33
29=9.67
30=10.0

**Your Name**_____ **Today's Date**_____ **Time of Day** _____

**Instructions for Office Staff**

Activity Level Index Scoring: For FN (questions 1-10) add total points and convert using scale on right. For PS (questions 11-13), add total points.

Visual Analog Scales: measure with metric ruler. Line is exactly 10 cm long. Scores should be recorded in cm.mm format.

Adapted from
Pincus T, Swearingen C, Wolfe F. Toward a Multidimensional Health Assessment Questionnaire. Arthritis Rheum 1999; 42:2220-2230.

# Health Assessment Questionnaire (HAQ)

Please try to answer each question, even if you do not think it is related to you at this time. There are no right or wrong answers. Please answer exactly as you think or feel. Thank-you.

**1. Please check (✓) the ONE best answer for your abilities OVER THE PAST WEEK:**

| **OVER THE PAST WEEK**<br>**Were you able to:** | Without **ANY** Difficulty | With **SOME** Difficulty | With **MUCH** Difficulty | **UNABLE** To Do |
|---|---|---|---|---|
| ***DRESSING & GROOMING*** | | | | |
| a. Dress yourself, including tying shoelaces and doing buttons? | ❑ | ❑ | ❑ | ❑ |
| *b.* Shampoo your hair? | ❑ | ❑ | ❑ | ❑ |
| ***ARISING*** | | | | |
| *c.* Stand up from an armless chair? | ❑ | ❑ | ❑ | ❑ |
| *d.* Get in and out of bed? | ❑ | ❑ | ❑ | ❑ |
| ***EATING*** | | | | |
| *e.* Cut your meat? | ❑ | ❑ | ❑ | ❑ |
| *f.* Lift a full cup or glass to your mouth? | ❑ | ❑ | ❑ | ❑ |
| *g.* Open a new milk carton? | ❑ | ❑ | ❑ | ❑ |
| ***WALKING*** | | | | |
| *h.* Walk outdoors on flat ground? | ❑ | ❑ | ❑ | ❑ |
| *i.* Climb up five steps? | ❑ | ❑ | ❑ | ❑ |

Please check any **AIDS OR DEVICES** that you usually use for any of these activities:

- ❑ Cane
- ❑ Walker
- ❑ Crutches
- ❑ Wheelchair
- ❑ Devices used for dressing (button hook, zipper puller, etc)
- ❑ Built-up or special utensils
- ❑ Special or built up chair
- ❑ Other (specify):_____

Please check any categories for which you need **HELP FROM ANOTHER PERSON**

- ❑ Dressing and Grooming
- ❑ Arising
- ❑ Eating
- ❑ Walking

| | | | | |
|---|---|---|---|---|
| ***HYGIENE*** | | | | |
| *j.* Wash and dry your entire body? | ❑ | ❑ | ❑ | ❑ |
| *k.* Take a tub bath? | ❑ | ❑ | ❑ | ❑ |
| *l.* Get on and off the toilet? | ❑ | ❑ | ❑ | ❑ |
| ***REACH*** | | | | |
| *m.* Reach and get a 5-lb object (such as a bag of n. sugar) from just above your head? | ❑ | ❑ | ❑ | ❑ |
| *o.* Bend down and pick up clothing from the floor? | ❑ | ❑ | ❑ | ❑ |
| ***GRIP*** | | | | |
| *p.* Open car doors? | ❑ | ❑ | ❑ | ❑ |
| *q.* Open jars which have been previously opened? | ❑ | ❑ | ❑ | ❑ |
| *r.* Turn faucets on and off? | ❑ | ❑ | ❑ | ❑ |
| ***ACTIVITIES*** | | | | |
| *s.* Run errands and shop? | ❑ | ❑ | ❑ | ❑ |
| *t.* Get in and out of a car? | ❑ | ❑ | ❑ | ❑ |
| *u.* Do chores such as vacuuming, yard work? | ❑ | ❑ | ❑ | ❑ |

***Please Turn Over***

Please check any **AIDS OR DEVICES** that you usually use for any of these activities:

- ❑ Raised toilet seat
- ❑ Bathtub seat
- ❑ Jar opener
- ❑ Other (Specify):_____
- ❑ Long-handled appliances for reach
- ❑ Long-handled appliances in bathroom
- ❑ Bathtub bar

Please check any categories for which you **NEED HELP FROM ANOTHER PERSON**

- ❑ Hygience
- ❑ Reach
- ❑ Gripping and opening things
- ❑ Errands and chores

2. **How much PAIN have you had because of your illness in the PAST WEEK? Please indicate on the scale below how severe your pain has been:**

NO PAIN ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 VERY SEVERE PAIN

3. **How much of a problem has UNUSUAL fatigue or tiredness been for you OVER THE PAST WEEK?**

FATIGUE IS NO PROBLEM ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 FATIGUE IS A MAJOR PROBLEM

4. **How much of a problem has sleeping been for you OVER THE PAST WEEK?**

SLEEP IS NO PROBLEM ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 SLEEP IS A MAJOR PROBLEM

5. **How active has your arthritis been in the LAST 24 HOURS?**

VERY WELL ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 VERY POORLY

6. **When you get up in the morning do you feel stiff?** ❑ YES ❑ NO
   If you answer NO please go to item number 7.
   If you answer YES, please write the number of minutes: _____, OR number of hours:_____
   until you are as limber as you will be for the day?

7. **How do you feel today compared to ONE MONTH AGO? Please check only one:**

❑ MUCH BETTER(1) ❑ BETTER(2) ❑THE SAME(3) ❑WORSE(4) ❑MUCH WORSE(5)

***For office use only***

| HAQ | PN | FT | SL | GL | AM | CH |
|---|---|---|---|---|---|---|
| | | | | | | |

| | | | |
|---|---|---|---|
| 1=0.125 | 7=0.875 | 13=1.625 | 19=2.375 |
| 2=0.25 | 8=1.0 | 14=1.75 | 20=2.5 |
| 3=0.375 | 9=1.125 | 15=1.875 | 21=2.625 |
| 4=0.5 | 10=1.25 | 16=2.0 | 22=2.75 |
| 5=0.625 | 11=1.375 | 17=2.125 | 23=2.875 |
| 6=0.75 | 12=1.5 | 18=2.25 | 24=3.0 |

**0-0.5** Mild ➔ **0.5-1.0** Mild-Mod ➔ **1.0-1.5** Mod ➔ **1.5-2.0** Mod-Sev ➔ **2.0-3.0** Sev

## Depression Anxiety and Stress Scale 21 (DASS21)

# DASS21

Name: Date:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you **over the past week**. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree or a good part of time
3 Applied to me very much or most of the time

| | | | | | |
|---|---|---|---|---|---|
| 1 (s) | I found it hard to wind down | 0 | 1 | 2 | 3 |
| 2 (a) | I was aware of dryness of my mouth | 0 | 1 | 2 | 3 |
| 3 (d) | I couldn't seem to experience any positive feeling at all | 0 | 1 | 2 | 3 |
| 4 (a) | I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion) | 0 | 1 | 2 | 3 |
| 5 (d) | I found it difficult to work up the initiative to do things | 0 | 1 | 2 | 3 |
| 6 (s) | I tended to over-react to situations | 0 | 1 | 2 | 3 |
| 7 (a) | I experienced trembling (e.g. in the hands) | 0 | 1 | 2 | 3 |
| 8 (s) | I felt that I was using a lot of nervous energy | 0 | 1 | 2 | 3 |
| 9 (a) | I was worried about situations in which I might panic and make a fool of myself | 0 | 1 | 2 | 3 |
| 10 (d) | I felt that I had nothing to look forward to | 0 | 1 | 2 | 3 |
| 11 (s) | I found myself getting agitated | 0 | 1 | 2 | 3 |
| 12 (s) | I found it difficult to relax | 0 | 1 | 2 | 3 |
| 13 (d) | I felt down-hearted and blue | 0 | 1 | 2 | 3 |
| 14 (s) | I was intolerant of anything that kept me from getting on with what I was doing | 0 | 1 | 2 | 3 |
| 15 (a) | I felt I was close to panic | 0 | 1 | 2 | 3 |
| 16 (d) | I was unable to become enthusiastic about anything | 0 | 1 | 2 | 3 |
| 17 (d) | I felt I wasn't worth much as a person | 0 | 1 | 2 | 3 |
| 18 (s) | I felt that I was rather touchy | 0 | 1 | 2 | 3 |
| 19 (a) | I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat) | 0 | 1 | 2 | 3 |
| 20 (a) | I felt scared without any good reason | 0 | 1 | 2 | 3 |
| 21 (d) | I felt that life was meaningless | 0 | 1 | 2 | 3 |

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