

# BMJ Open Temporal summation of pain and ultrasound Doppler activity as predictors of treatment response in patients with rheumatoid arthritis: protocol for the Frederiksberg hospitals Rheumatoid Arthritis, pain assessment and Medical Evaluation (FRAME-cohort) study

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## ABSTRACT

**Introduction:** Chronic pain is common in rheumatoid arthritis (RA) and may still persist despite regression of objective signs of inflammation. This has led researchers to hypothesise that central pain sensitisation may play a role in the generation of chronic pain in RA. Application of the disease activity score DAS28 can classify some patients with active RA solely based on a high tender joint count and poor patient global health score. In such cases, intensified treatment with anti-inflammatory drugs would be expected to yield poorer results than in cases with DAS28 elevation due to a high score for swollen joints and C reactive protein (CRP). Evaluation of central pain sensitisation in patients with few inflammatory indices may be a predictive tool regarding the effect of anti-inflammatory treatment. Computerised pneumatic cuff pressure algometry (CPA) is a method for assessing temporal summation (ie, degree of central sensitisation). The main objective of this study was to examine the prognostic values of pressure pain-induced temporal summation, ultrasound Doppler activity and the interaction between them in relation to treatment response (DAS28-CRP change) in patients with RA initiating any anti-inflammatory therapy.

**Method and analysis:** 120 participants  $\geq 18$  years of age will be recruited. Furthermore, they must be either (1) diagnosed with RA, untreated with disease-modifying antirheumatic drugs for at least 6 months and about to initiate disease-modifying antirheumatic drug treatment or (2) about to begin or switch treatment with any biological drug for their RA. Data (clinical, imaging, blood samples, patient reported outcomes and CPA measurements) will be collected from each participant at baseline and after 4 months of anti-inflammatory treatment.

## Strengths and limitations of this study

- This is the first prospective cohort study to explore the relationship between central pain sensitisation and inflammation as prognostic factors for treatment response in patients with rheumatoid arthritis (RA).
- The RA population studied is heterogeneous.
- The observation period is limited to 4 months.

**Ethics and dissemination:** This study has been approved by the ethics committee for the Copenhagen region (H-4-2013-007). Dissemination will occur through presentations and publication in international peer-reviewed journals.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease causing synovial joint destruction, disability and pain.<sup>1</sup> Over the past 10–15 years the trend in RA treatment has shifted to a more aggressive approach with early treatment to achieve remission.<sup>2</sup> Despite better disease control, patients with RA still rate pain as a significant priority.<sup>3</sup> The majority of US and European patients with RA report dissatisfaction with their arthritis pain,<sup>4</sup> and even among patients in remission according to the disease activity score-28 based on C-reactive protein (DAS28-CRP), the prevalence of clinically significant pain is 11.9%.<sup>5</sup> DAS28-CRP is a widely used composite score for assessing

disease activity in RA. DAS28-CRP consists of a tender joint count, a swollen joint count, plasma CRP and a global health score (0–100).<sup>6</sup> In patients with RA a high DAS28-CRP due to high tender joint count and poor global health score could indicate a significant component of central pain sensitisation. In these patients, it is plausible that alterations in central pain modulation are the cause of persistent pain, rather than ongoing inflammatory activity. This notion is supported by registry data showing decreased efficacy of biologicals in cases with a low swollen-tender joint ratio.<sup>6a</sup>

The fact that pain can persist despite regression of signs of inflammation has led researchers to hypothesise that central pain sensitisation plays a central role in the generation of chronic pain in RA<sup>7</sup> analogous to chronic widespread pain conditions.<sup>8</sup> This may also partially explain why a significant proportion of patients with RA apparently do not respond to treatment with biologicals.<sup>9</sup> Mechanical hyperalgesia or allodynia in a patient will consistently yield high tender joint counts, poor global health scores and reports of pain. This may lead to overestimation of disease activity by composite scores. It would, therefore, be desirable for the treating health-care professional to have knowledge concerning contributing pain mechanisms, including the degree of central pain sensitisation, when considering the initiation or intensification of medical therapy.

Computerised pneumatic cuff pressure algometry (CPA) is a method for quantitative sensory measurements. The method was originally developed for pain research in healthy controls to avoid some of the observer bias and other sources of error seen when using hand-held algometry.<sup>10</sup> The CPA uses an inflatable tourniquet cuff as a stimulus, which predominantly activates deep tissue nociceptors.<sup>11</sup> The compression rate is controlled by a computer, and the participant's pain response is recorded continuously during measurements, which avoids interference from the observer.<sup>10 12</sup>

## Rationale and hypothesis

Since its development CPA has been used to quantify pressure pain in patients with osteoarthritis, lateral epicondylitis, fibromyalgia and chronic whiplash-associated disorder.<sup>13–16</sup> Low pressure pain thresholds (pain threshold and pain tolerance) are an indication of pain hypersensitivity, but these measures do not differentiate between central and peripheral sensitisation. Facilitated temporal summation, on the other hand, indicates central sensitisation.<sup>17 18</sup> Temporal summation has previously been shown to be of greater magnitude in patients with fibromyalgia compared with healthy controls.<sup>19</sup> On the basis of these findings, we hypothesise that facilitated temporal summation (ie, central sensitisation) in combination with low inflammatory indices in patients with RA at baseline predicts poorer treatment response following the initiation or intensification of medical treatment.

## Objectives

Our objective was to determine whether pressure pain-induced temporal summation, ultrasound Doppler score and the interaction between them can be used as prognostic factors for treatment effect following initiation/intensification of medical treatment.

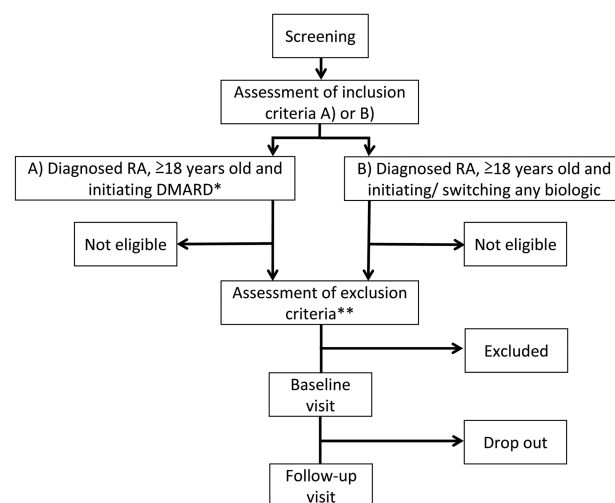
## METHODS

### Study design

The 'FRAME-cohort' (Frederiksberg hospitals Rheumatoid Arthritis, pain assessment and Medical Evaluation) study will be designed as a 'closed cohort' with prospective enrolment of patients with RA over time.<sup>20</sup> Information about the patients and their exposures (including temporal summation of pain and ultrasound Doppler) will be collected at a single centre at two time points (figure 1), at baseline and after approximately 4 months of treatment, according to the clinical standards in Denmark. Examinations will be carried out consecutively in the same order and on the same day. Participant inclusion will begin on 1 March 2013 and is expected to be completed by August 2014, with follow-up concluding in December 2014.

### Participants

Participants will be recruited from the Department of Rheumatology, Frederiksberg Hospital and from private rheumatology clinics in the Copenhagen area.



**Figure 1** Overview of participant flow. \*Either disease-modifying antirheumatic drugs (DMARD) naïve or untreated with DMARD ≥6 months. \*\*Exclusion criteria: (1) No consent; (2) Pregnancy; (3) Does not understand Danish; (4) Other known inflammatory rheumatic diseases; (5) Diagnosed with a condition with risk of neuropathic pain; (6) Claudicatio intermittens; (7) Intra-articular or intramuscular corticosteroids given <3 weeks; (8) Treatment with oral corticosteroids at doses equivalent to more than 10 mg prednisolone/day <3 weeks; (9) Inability to suspend usage of central acting analgesics 1 week prior to examination; (10) Inability to suspend usage of mild analgesics 24 h prior to examination; (11) For (A): treatment with DMARD >3 weeks; (12) For (B): treatment with any biologicals >1 week.

To be considered for inclusion, participants must be diagnosed with RA according to the 1987 or 2010 ACR criteria<sup>1 21</sup> and be at least 18 years of age. Furthermore, potential participants must be untreated with disease-modifying antirheumatic drugs (DMARD) within the past 6 months (including patients with newly diagnosed RA) and initiate DMARD treatment in the inclusion period (group A) or begin treatment (including switch) with any biological agent during the inclusion period (group B). In an attempt to minimise selection bias, all referrals will be scrutinised to identify the patients with RA who might be eligible for inclusion. Inclusion of all patients where biological treatment is considered by their rheumatologist will be discussed at the department's biological conference. AWC and SR-M will screen potential participants regarding fulfilment of the inclusion criteria and none of the exclusion criteria (figure 1). Informed consent will be obtained for all eligible participants prior to the baseline visit. Participants will be excluded from the study if any of the following criteria are present: (1) no consent, (2) pregnancy, (3) does not understand Danish, (4) other known inflammatory rheumatic diseases, (5) diagnosed with a condition with risk of neuropathic pain (eg, diabetes), (6) intermittent claudication, (7) intra-articular or intramuscular glucocorticoids given within the past 3 weeks, (8) treatment with oral corticosteroids at doses equivalent to more than 10 mg prednisolone/day within the past 3 weeks, (9) inability to suspend usage of centrally acting analgesics 1 week prior to examination (eg, anticonvulsants, antidepressants or opioids), (10) inability to suspend usage of mild analgesics 24 h prior to examination (eg, acetaminophen, non-steroidal anti-inflammatory drugs, acetylsalicylic acid). Participants will not be included in group A (11) if DMARD therapy was initiated more than 3 weeks prior to the baseline visit; and in group B (12) if treatment with biological agents was initiated more than 1 week prior to the baseline visit. The participants who for any reason are not assessed at the 4-month follow-up will be regarded as drop-outs. During 4 months between assessments the participants will receive routine care at the Department of Rheumatology, Frederiksberg Hospital.

### Variables and outcome measures

Included patients will undergo an examination programme to extract the variables shown in table 1. Response to treatment will primarily be assessed using changes in DAS28-CRP<sup>6</sup> and visual analogue scale (VAS<sub>pain</sub>) from baseline to the follow-up visit. The degree of inflammation will primarily be assessed using the summed semiquantitative ultrasound Doppler score. The response according to the EULAR response criteria,<sup>22</sup> transition questionnaire score and changes in the following variables will also be explored: DAS28-CRP components, the number of tender points assessed by manual tender point examination, Health Assessment Questionnaire (HAQ) total score, major depression inventory (MDI) score, generalised anxiety disorder (GAD-10)

score, 36-Item Short-Form Health Survey (SF-36) mental and physical composite scores, VAS<sub>fatigue</sub>, semiquantitative ultrasound Doppler score, ultrasound Doppler colour fraction (CF), pain threshold, pain tolerance and CRP.

### Clinical examination and blood samples

A trained healthcare professional will perform a 46-joint count (44 joint index with the addition of the temporomandibular joints) ad modum EULAR and the manual tender point examination according to the guidelines in the 1990-ACR-criteria for fibromyalgia.<sup>23</sup> Medication variables as specified in table 1 will be recorded and blood pressure will be measured. Blood samples as specified in table 1 will be collected by a trained laboratory technician and treated according to set procedures.

### Computerised pneumatic cuff pressure algometry

The CPA consists of a tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany), a computer-controlled air compressor (DoloCuff, UE unique electronics, DK) and an electronic 10 cm VAS that enables continuous feedback. The 0 and 10 cm extremes on the VAS are defined as 'no pain' and 'worst imaginable pain'. Data will be recorded using the DoloCuff pain measuring system 'LePainS'. CPA will be carried out with the participant in the supine position, and will be performed on the side where the participant reports most pain. If the pain is equal bilaterally, the side of the dominant extremity will be chosen. Prior to fixing the cuff, the widest circumference (cm) on the chosen arm and leg will be determined. The cuff will be placed where the forearm muscles are widest and on the widest part of the lower leg. The cuff size for arm measurements is 6.75 cm×35 cm and that for leg measurements is 13.5 cm×76 cm. CPA measurements will be carried out in two sequences: short and long. During the short sequence measurements, the cuff will be inflated at a rate of 1 kPa/s to determine the following variables: (1) pain threshold: the pain threshold is defined as the pressure of the cuff at the moment of transition from a sensation of strong pressure to the first sensation of pain (unit kPa). (2) Pain tolerance: pain tolerance is defined as the pressure of the cuff at the time where the pressure is switched off due to the highest tolerable pain caused by pressure stimulation (unit kPa). (3) VAS-pain limit: the VAS-pain limit is defined as the score on the VAS meter when the participant reaches pain tolerance (unit: VAS cm). The first short sequence measured is solely to familiarise the participant with the procedure and will not be considered further. Following this, the short sequence will be repeated three times on one arm and three times on one leg. Between each measurement the participant will have a 3 min break. The mean values for the leg will be used to determine the stimulation intensity for the long sequence. The degree of temporal summation will be determined during the long sequence, which is always conducted on the lower leg. The cuff will be filled to obtain a calculated pressure ( $P = \text{Pain Threshold}_{\text{mean}} + 0.50 \times (\text{Pain Tolerance}_{\text{mean}} - \text{Pain Threshold}_{\text{mean}})$ ) with a rate of

**Table 1** Summary of measures to be collected

		Baseline	4 Months
<b>Demographics</b>			
Sex (M/F)		X	–
Age (year)		X	–
Disease duration (months)		X	–
Height (cm)		X	–
Weight (kg)		X	X
<b>Medication</b>			
MTX dose (mg/week)		X	X
Other current DMARD therapy (yes/no)		X	X
No. of previous biologicals used (if any)		X	–
Name of current biological agent		X	–
No. of treatment weeks since baseline		–	X
Dose of prednisolone orally at assessment week (mg/week)		X	X
Dose of prednisolone orally 1 week prior to assessment week (mg/week)		X	X
Dose of prednisolone orally 2 weeks prior to assessment week (mg/week)		X	X
Intra-articular glucocorticoid injections in the previous 3 months (no.)		X	X
Intramuscular glucocorticoid injection in the previous 3 months (mg)		X	X
Consumption of analgesics		X	X
<b>Clinical examination</b>			
Blood pressure (mm Hg)		X	X
46 swollen joint count		X	X
46 tender joint count		X	X
Swollen joint count/tender joint count ratio		X	X
Manual tender point examination		X	X
DAS28-CRP		X	X
<b>Patient-reported outcomes</b>			
HAQ		X	X
SF-36		X	X
GAD-10		X	X
MDI		X	X
VAS <sub>fatigue</sub>		X	X
Transition questionnaire		–	X
<b>Ultrasound Doppler activity</b>			
Semiquantitative scoring system (Doppler score)		X	X
Quantitative scoring system (colour fraction)		X	X
<b>CPA measurements</b>			
Pain threshold		X	X
Pain tolerance		X	X
VAS-pain limit		X	X
Temporal summation		X	X
<b>Blood samples</b>			
	mL blood		
Glass 1*			
CRP, ALAT, alkaline phosphatase, creatinine, estimated GFR, sodium, potassium	4.0	X	X
Glass 2*			
Haemoglobin, erythrocyte volume fraction MCHC, MCV, leucocytes, differential count, thrombocytes	4.0	X	X
Glass 3			
IgM-RF, anti-CCP	4.0	X	–

\*Will not be repeated if already taken within the past week.

ALAT, alanine transaminase; CPA, computerised cuff pressure algometry; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drugs; GAD-10, generalised anxiety disorder 10 items; GFR, glomerular filtration rate; HAQ, Health Assessment Questionnaire; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDI, major depression inventory; MTX, methotrexate; SF-36, 36-Item Short-Form Health Survey; VAS, visual analogue scale.

20 kPa/s. This will be maintained for 10 min while the participant continuously reports the pain intensity via an electronic VAS scale. The participant will be notified that the pressure in the cuff will increase rapidly in order to

minimise VAS increase solely due to surprise. Termination of the stimulation will be possible before the end of the defined 10 min if the participant feels that the pain intensity has reached the strongest pain imaginable caused by



pressure stimulation. These  $VAS_{\text{pain}}$ -time plots will be analysed, and for each a value representing the degree of temporal summation will be calculated as previously reported elsewhere.<sup>15</sup>

### Ultrasound Doppler examination

Two trained ultrasound investigators, AWC and KE, will conduct the ultrasound Doppler (USD) examinations and analyse the images according to a pre-established plan. The ultrasound examiner will be blinded to the reported joint count and USD measurements will be performed on the same side as the CPA. Scanning will be performed with a General Electric Logiq E9 (Milwaukee, Wisconsin, USA) using a linear array matrix transducer (ML6–15) with 15 MHz centre frequency. Colour Doppler will be chosen over power Doppler, as it is more sensitive on the machine used. The same colour Doppler preset will be used for all examinations, and no readjustment of Doppler parameters will be performed. The machine settings will be adjusted as recommended.<sup>24</sup> All images must depict specific anatomical landmarks and while keeping the landmarks in the image the transducer will be moved until the scanning plane with most Doppler activity is found.<sup>25</sup> The following projections will be examined with USD: metacarpophalangeal joint 2–4, wrist central, radial, ulnar and m. extensor carpi ulnaris tendon, elbow posterior, knee supra-patellar, lateral and medial, ankle central, medial and lateral, tarsometatarsal central, medial and lateral, metatarsophalangeal joint 2–4, m. tibialis posterior tendon, m. peroneus longus and brevis tendons. Altogether this comprises a total of 24 projections.

To grade the degree of inflammation seen on ultrasound we will primarily use a summed Doppler score that will consist of Szkudlarek's semiquantitative Doppler score<sup>26</sup> for joints and a semiquantitative assessment of tenosynovitis.<sup>27</sup> In the semiquantitative score, inflammation is graded according to the flow signal in the synovium on a four-grade scale from 0 to 3 with the following definitions for each category: grade 0: absence of signal, no intra-articular flow; grade 1: mild, one or two vessel signals (including one confluent vessel) for small joints and two or three signals for large joints (including two confluent vessels); grade 2: moderate confluent vessels (>grade 1) and less than 50% of synovial area; grade 3: marked vessel signals in more than half of the synovial area.<sup>28</sup> Assessment of tenosynovitis will be carried out longitudinally and transversally, but participants will receive only one score per locus. The severity will be graded semiquantitatively from 0 to 3 as described elsewhere.<sup>27</sup> Each projection will be scored 0–3, and the range of achievable Doppler score points will therefore be 0–72 per participant. This method will give a greater weight to larger joints (several projections), which also have more synovial tissue.

Subsequently, four joint projections will be selected, based on having the most inflammation according to the examiner. If the degree of inflammation is equal in several projections, we will prioritise projections of larger joints. These projections will be quantified using Qvistgaard

*et al's* CE, as conducted by the ultrasound machine's built-in 'colour quantification' software. A region of interest (ROI) corresponding to the synovial tissue will be drawn by the examiner, and the computer software will then calculate the CE, which is the number of coloured pixels in the ROI divided by the total number of pixels. For each of the selected projections, two CEs will be calculated: one depicting minimal Doppler activity (end diastolic flow) and the other maximal Doppler activity (peak systolic flow). At follow-up, the projections chosen at baseline will be selected for CE evaluation.

### Patient demographics and patient-reported outcomes

Patient demographics and medication history will be collected from the participant by interview and from the patient record. Sampling of patient-reported outcomes will be based on computerised health status questionnaires that are stored in a designated research database.

The Medical Outcomes Study SF-36 is a generic health status questionnaire that was developed as a tool to compare various aspects of health status across a general and broad patient population.<sup>29–31</sup> The SF-36 examines eight general health domains: physical functioning, role limitations due to physical health problems (RP), bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems (RE) and mental health. Furthermore, a physical (PCS) and mental (MCS) component summary score can be calculated. We will use the Danish version of SF-36 Danish,<sup>32</sup> which uses a 4-week recall period.

The HAQ is a measure of impairment of activities of daily living used for patients with RA. HAQ assesses the responder's ability to complete everyday tasks. HAQ consists of 20 questions in eight different areas of activity of daily living. In each area, the highest scores are summed and divided by 8. Final scores range from 0 to 3, with 3 indicating a high level of disability.<sup>33</sup> The HAQ also contains a VAS for pain and global health ( $VAS_{\text{pain}}$ ,  $VAS_{\text{global health}}$ ).

The MDI is a questionnaire used to measure DSM-IV and International Classification of Diseases (ICD)-10 diagnoses of major (moderate to severe) depression and rating of depression by the patients' self-reported symptoms.<sup>34</sup> The questionnaire has been used for prevalence studies of major depression in the Danish general population.<sup>35</sup>

The GAD-10 is a 10-item questionnaire developed from the Hamilton 6-item anxiety scale (HAM-A6). The instrument measures generalised anxiety according to severity scales by scoring the simple total sum of the items, the total score ranging from 0 to 50.<sup>36</sup> In GAD-10, a score of 15–19, 20–29 and 30–50 points indicates a mild, moderate and severe condition of anxiety, respectively.

The transition questionnaire consists of three main questions addressing change in pain, change in function and overall change between the two visits. For each question, the participants will first be asked whether there has been an improvement, deterioration or no change. If they indicate improvement or deterioration, they will

subsequently be asked to rate the magnitude on a 7-point scale as described elsewhere.<sup>37</sup>

In addition to the aforementioned questionnaires, the participants will also be asked to indicate their fatigue on a VAS (VAS<sub>fatigue</sub>).

### Power and sample size considerations

This study was designed as an exploratory study. It is anticipated that 120 participants are likely to be included during a period of 1.5 years. For a paired *t* test with a two-sided significance level of 0.05, assuming a common SD of 1.5 and the correlation between the prescores and post-scores being  $r=0.30$ ,<sup>38</sup> a sample size of 120 patients with RA (ie, pairs) has a power of 87% (0.865) to detect a mean change of 0.5 DAS28-CRP units. In case that the study period does not allow us to include more than 100 participants, the study would still have a reasonable power to detect a mean change of 0.5 DAS28-CRP units; a sample size of 100 pairs has a power of 80% (0.797).

### Statistical analyses

All analyses will be carried out using SAS software (V9.3; SAS Institute Inc, Cary, North Carolina, USA). The PROC UNIVARIATE statement will be used to summarise the data and the PROC CORR (Spearman) statement will be applied for correlation analyses. In order to evaluate the data distributions of the continuous outcomes, visual inspections of the studentised residuals will be used to suggest whether the assumption of normality is reasonable. All descriptive statistics and tests will be reported in accordance with the recommendations of the “Enhancing the QUALity and Transparency Of health Research” (EQUATOR) network<sup>39</sup>; the STROBE Statement.<sup>20</sup> Primary analyses will be conducted based on the ‘full analysis set’ according to the intention-to-treat principle; that is, analysing all participants who enter the study, even if some participants withdraw during the study period. Missing data at follow-up will be imputed with a non-responder assumption—using the baseline observations carried forward technique. We consider *p* values less than 0.05 to be statistically significant.

To study the prognostic value of the degree of temporal summation regarding changes in DAS28-CRP simultaneously accounting for the level of inflammation (ie, summed USD score) we will use a multivariable regression model with both measures applied as main effects as well as their interaction (ie, ‘crude model’). This model will be handled using analysis of covariance fitted in SAS using PROC GLM. Furthermore, the crude model will be adjusted for the following confounders: age (years), sex (M/F), disease duration (months), disease activity, group (A vs B), anti-CCP positive (yes/no) and concomitant prednisolone (ie, ‘adjusted model’).

### DISCUSSION

The proposed study will give an insight into the value of central sensitisation assessed by CPA in relation to

inflammation assessed by ultrasound Doppler as prognostic factors associated with treatment outcome in patients with RA following the initiation of DMARD therapy or initiation/switch of biological therapy. Knowledge about the presence of central pain sensitisation in an individual may be useful for rheumatologists when confronted with a patient with a high DAS28 score predominantly due to tender joints and/or persistent pain, since this may help identify those patients with little potential to respond to anti-inflammatory therapy. Increasing our ability to predict the potential for response to treatment is mandatory for several reasons. First of all, it can help shift focus to other areas of importance, for example, optimising analgesic treatment, but it will also spare some patients from unnecessary immunosuppressive therapy with subsequent risks of side effects. Furthermore, avoiding the unnecessary use of drugs, some of which are very costly, is beneficial for health economic reasons. It is our hope that the results of this study may add to the knowledge of the mechanisms behind persistent pain in RA.

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**Contributors** AWC and SR-M are co-responsible for all phases of the Frederiksberg hospitals Rheumatoid Arthritis, pain assessment and Medical Evaluation (FRAME) cohort setup, from which data for this study will be obtained. AWC serves as the principal investigator for this study. AWC, SR-M, RC, EMB, AJ, KE, KA, HL, STP, PCT, BD-S and HB participated in the design of the study and drafting of the protocol. All authors have given final approval for the protocol to be published.

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**Competing interests** None.

**Ethics approval** This study has been approved by the Ethics Committee for the Copenhagen region (H-4-2013-007) and will be carried out in accordance with the Helsinki Declaration.

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

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