BMJ Open

Sensory alterations and immunological changes during the chronification of postsurgical pain: a study protocol for a prospective observational cohort study

Marjelle E C van Driel ,[1] Nadine van Veenendaal,[1] Lisette Margaretha Vernooij ,[1,2] Niels Eijkelkamp,[3] Leo Koenderman ,[3] L Timmerman,[4] Roel J H Custers,[5] Diyar Delawi,[6] Frank J P M Huygen,[1] M Rijsdijk[1]

To cite: van Driel MEC, van Veenendaal N, Vernooij LM, *et al*. Sensory alterations and immunological changes during the chronification of postsurgical pain: a study protocol for a prospective observational cohort study. *BMJ Open* 2025;**15**:e094249. doi:10.1136/bmjopen-2024-094249

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-094249).

Received 26 September 2024
Accepted 06 December 2024

For numbered affiliations see end of article.

Correspondence to
Marjelle E C van Driel;
m.e.c.vandriel-4@umcutrecht.nl

ABSTRACT

Introduction Chronic postsurgical pain (CPSP) represents a widely underdiagnosed and often poorly treated medical problem, affecting 10–50% of all surgical patients, exhibiting neuropathic features in 35–60%. It is hypothesised that surgery-induced tissue damage and the subsequent immune response cause sensory alterations in the early postoperative period, ultimately leading to a chronic neuropathic or nociplastic pain state. The 'Sensory Changes and Immunological parameters in Postsurgical pain' study (SCIP-Pain study) was designed to test this hypothesis and identify sensory alterations and changes in the immunological response that are related to the development of CPSP with neuropathic features.

Methods and analysis This protocol describes the SCIP-Pain study—an ongoing prospective observational cohort study involving 150 adult patients undergoing elective lower extremity orthopaedic surgery. Study participants complete questionnaires, undergo quantitative sensory testing (QST) and provide blood samples to assess the immunological response at various time points: before surgery, 2 weeks and 3 months after surgery. To reduce dimensionality, cluster analyses will be conducted on QST and immunological parameters. Cluster allocation, along with other preselected candidate predictors, will subsequently be used in a generalised mixed-effects model to predict CPSP with neuropathic features within 3 months after surgery as the primary outcome.

Ethics and dissemination This study received approval from the Medical Ethics Committee NedMec (protocol NL77085.041.21), as well as from all participating centres. The study results are expected to be published in peer-reviewed journals and disseminated at international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Sensory Changes and Immunological Parameters in Postsurgical Pain study is a prospective observational cohort study that allows for the longitudinal assessment of sensory and immunological parameters in a population at high risk for chronic postsurgical pain (CPSP).
⇒ The use of the complete DFNS (German Research Network on Neuropathic Pain) protocol for quantitative sensory testing in this study offers a more objective pain assessment compared with relying on self-report questionnaires alone.
⇒ While the 3-month follow-up period aligns with the CPSP definition set by the International Association of the Study of Pain and International Classification of Diseases, 11th Revision, it may potentially lead to an overestimation of CPSP prevalence.
⇒ The presence of the CPSP with neuropathic features is adjudicated by a pain specialist blinded to the study measurements according to the updated grading system for neuropathic pain in research and clinical practice.
⇒ Loss to follow-up represents a form of selection bias related to the study design and the inherently eventful nature of the postoperative period.

INTRODUCTION

Chronic postsurgical pain (CPSP) is a widely underdiagnosed and often poorly treated medical problem affecting 10–50% of all surgical patients.[1–4] Postsurgical pain is generally classified and treated as nociceptive pain with opioids because it is assumed to result from surgery-induced tissue damage. Over time, however, as postsurgical nociceptive pain transitions into CPSP, 35–60% of patients exhibit neuropathic features such as burning, squeezing, lancinating pain with electric shocks or painful cold.[2 3 5] In the absence of sufficient evidence for a lesion or disease of the somatosensory nervous system itself, the diagnostic criteria for neuropathic pain are not fulfilled.[6] Nociplastic pain might be a more applicable label, as it refers to pain arising from altered nociception without clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors, nor evidence of disease or lesion of the somatosensory system causing the pain.[7 8] A dynamic interplay of

biopsychosocial mechanisms can drive or amplify pain, with psychological factors being particularly relevant for the expression of nociplastic pain.[7] Nevertheless, the role of altered nociception and the influence of psychological factors in the transition from acute to chronic pain after surgery remain insufficiently clarified.

It is suggested that surgery-induced tissue damage and the subsequent immune response cause sensory alterations in the early postoperative period, which may ultimately lead to the development of CPSP with neuropathic features. Cytokines and damage-associated molecular pattern molecules are known mediators in the pathophysiology of neuropathic pain.[9–12] Neutrophils, essential in the early stages of inflammation and tissue repair, respond to these mediators. Differential expression of neutrophil markers is thought to reflect the extent of tissue damage and the subsequent immune response. It is, however, unknown whether this potential marker of postsurgical immune response dysregulation predisposes individuals to altered pain processing.

Quantitative sensory testing (QST) is a clinical method for monitoring pain processing and its alterations in patients by measuring sensory thresholds and tolerance levels to thermal and mechanical stimuli.[13] Multiple studies have examined the association between one or more QST parameters and CPSP. Systematic reviews have reported a significant association between QST variables and CPSP in 58–68% of studies across various types of surgery.[14 15] However, the strengths of the associations ranged from weak to strong, and none of the QST parameters showed a consistent association with CPSP due to large heterogeneity in QST methodologies.

To date, neither the changes in postsurgical immune response nor the sensory alterations occurring within the first 3 months after surgery have been thoroughly described. The Sensory Changes and Immunological parameters in Postsurgical pain study (SCIP-Pain study) was designed to identify sensory alterations and changes in the immunological response that are related to the development of CPSP with neuropathic features after elective lower extremity orthopaedic surgery.

METHODS AND ANALYSIS

Study design, setting and patient involvement

This prospective, observational cohort study is being conducted in patients undergoing elective lower extremity orthopaedic surgery at the University Medical Centre Utrecht and the St. Antonius Hospital in Utrecht, the Netherlands. Recruitment for the study commenced in September 2021 and is expected to continue for 5 years. The Medical Research Ethics Committee (EC) NedMec approved the study prior to participant inclusion (protocol NL77085.041.21).

Patient and public involvement statement

Patients were not actively involved in the design of this study. Nevertheless, the burden of the study procedures on participants is carefully monitored. Once the results of this study have been published, participants will be informed of the results by sending a study newsletter suitable for a non-specialist audience.

Study population

Inclusion and exclusion criteria

All patients aged 18 years or older scheduled for elective lower extremity orthopaedic surgery are eligible to participate. However, patients meeting any of the following criteria will be excluded from participation in this study:

- Major cognitive or psychiatric disorders and communication problems, as QST is prone to bias related to attention, motivation, cognitive functioning, psychiatric comorbidity and feigning.[16 17]
- Acute infection confirmed by clinical, laboratory and standard radiological examination interfering with the assessment of the immunological response.
- Pre-operative definite neuropathic pain condition of the lower extremities according to the updated grading system for neuropathic pain in research and clinical practice by Finnerup *et al*[6]

Recruitment and informed consent

After the indication for elective lower extremity orthopaedic surgery, eligible patients receive written study information and are asked to consent to be contacted by the study team.

Patients who agree to be contacted receive a follow-up phone call from an investigator for further explanation and to answer any questions if needed. Patients willing to participate are scheduled for the first research appointment. Inclusion is completed during the first research appointment once the informed consent form is signed by both the patient and a member of the study team. Participants are informed that participation in the study is voluntary and that they are free to withdraw at any time. Recruitment and consent of study participants by members of the study team are in accordance with Good Clinical Practice.

Study procedures

After written informed consent is obtained, study participants complete questionnaires, undergo QST and provide blood samples at various time points in the perioperative period (figure 1).

Questionnaires

Study participants are asked to complete questionnaires at different time points during follow-up (figure 1). Pain severity and its interference with activities and affect are addressed in the International Pain Outcome Questionnaire.[18] Neuropathic features are assessed using the Douleur Neuropathique en 4 (DN4) questionnaire.[19 20] In addition, participants are asked to complete a daily pain diary (either electronic or on paper) for 2 weeks after surgery to evaluate pain intensity and the pain medication used.

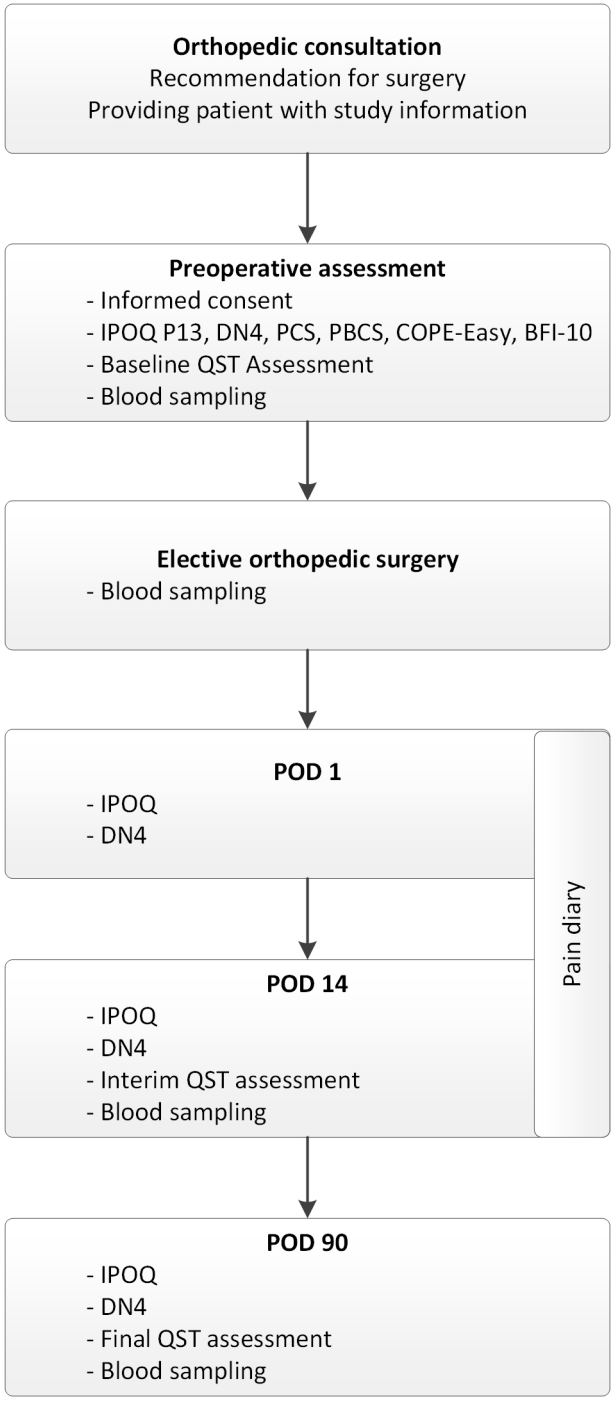

Figure 1 Study procedures over follow-up time. BFI-10, Big Five Inventory-10; COPE-Easy, Coping Orientation to Problems Experienced; DN4, Douleur Neuropathique en 4; IPOQ, International Pain Outcome Questionnaire; PCS, Pain Catastrophising Scale; PBCS, Private Body Consciousness Scale; QST, quantitative sensory testing.

The perception and severity of pain are influenced by various psychological factors. For this reason, participants' personality traits, tendencies toward pain catastrophising, interoceptive accuracy and coping strategies are being assessed using the Big Five Inventory-10, the Pain Catastrophising Scale, the Private Body Consciousness Scale and the Coping Orientation to Problems Experienced survey, respectively.[21–24]

Quantitative sensory testing

QST is a panel of clinical psychophysical tests that quantify somatosensory function by assessing the patient's sensory thresholds and tolerance to a variety of standardised stimuli on the skin.[13] QST is performed before surgery, 2–4 weeks (POD14) and 3 months (POD90) after surgery.

This study uses the QST protocol of the German Research Network on Neuropathic Pain (DFNS). This protocol consists of seven standardised tests measuring thirteen parameters that assess the functioning of somatosensory nerve fibres, which are necessary for sensing pain, warmth and cold (see table 1).[13 25]

The tests are performed as close as possible to the site of the surgical incision (test area) and the mirror-image contralateral area (control area). For example, for knee surgery, tests are performed on the dermatome L4 above the knee, while for hip surgery, dermatome L2/3 is used. If the contralateral side is not available (e.g., due to skin conditions) the cheek is assessed as the control area.

Each test starts with a brief demonstration in an area not included in the actual QST assessment, followed by QST of the control area and then QST of the test area.

Blood sampling and analysis

Blood samples are collected by an experienced physician or research nurse during the first research appointment prior to surgery, immediately after surgery, POD14 and on POD90. At each time point, 10 mL of blood is collected. After collection, the sodium-heparin blood vial is placed in the automated AQUIOS CL 'Load & Go' flow cytometer (Beckman Coulter, Miami, Florida, USA). The AQUIOS combines robotic automated sample preparation with automated analysis of single cells. The AQUIOS automatically mixes and pipettes the blood into two wells: one without and one pre-coated with the bacterial/mitochondrial-derived activator N-Formyl-norleucyl-leucyl-phenylalanine (BioCat GmbH, Heidelberg, Germany) at a concentration of 10–5 M. When blood is pipetted into the wells, the machine proceeds with the antibody staining. The antibody mix consists of anti-CD16-FITC (clone 3G8), anti-CD11b-PE (clone Bear1), anti-CD62L-ECD (clone DREG56), anti-CD10-PC5 (clone ALB1) and anti-CD64-PC7 (clone 22; all clones from Beckman Coulter).

After 15 min of incubation, the blood is lysed by adding 335 µl of lysing reagent A, followed by 100 µl of lysing reagent B. Lysing reagent A is a cyanide-free lytic reagent that lyses red blood cells. Lysing reagent B slows the reaction caused by reagent A and preserves the white blood cells for measurement in the flow cell. Finally, the prepared sample is aspirated for analysis. The absolute white blood cell count is measured based on an electronic volume measurement. Fluorescent intensity of the bound fluorochromes is assessed by excitation with a 488 nm

Table 1 Quantitative sensory testing parameters, the modalities tested and the equipment used in the standardised DFNS (German Research Network on Neuropathic Pain) protocol

QST parameter		Modality of somatosensory system tested	Equipment used
Thermal tests	Cold detection threshold	C and Aδ fibres	Thermal sensory testing device with thermode and stop button.
	Warm detection threshold		
	Cold pain threshold		
	Heat pain threshold		
	Thermal sensory limen	Thermodiscriminative function for alternating cold and warm stimuli. Number of paradoxical heat sensations*	
Mechanical detection threshold		Aβ fibre function	Von Frey filaments that exert forces between 0.25 and 512 mN.
Mechanical pain threshold		Aδ fibre mediated hyperalgesia or hypoalgesia	Weighted pinprick stimulators that exert forces between 8 and 512 mN.
Stimulus-response functions	Mechanical pain sensitivity	Aδ-mediated sensitivity to sharp stimuli. Measure of central sensitisation	Weighted pinprick stimulators that exert forces between 8 and 512 mN applied in a balanced order, five times each.
	Dynamic mechanical allodynia	Aβ fibre-mediated pain sensitivity to stroking light touch. Measure of central sensitisation	Cotton wisp (~3 mN) Cotton wool tip (~100 mN) Brush (~200–400 mN) Each applied five times with a single stroke of 1–2 cm in length.
Wind-up ratio		Temporal pain summation. Measure of central sensitisation	Pinprick stimulus (128 mN for the face and 256 mN for the body) in trains of 5 single stimuli and 10 repetitive stimuli.
Vibration detection threshold		Aβ fibre function	Rydel-Seiffer 64 Hz tuning fork with 8/8 scale on bony prominence in three series of descending stimulus intensities.
Pressure pain threshold		Deep pain sensitivity, most probably mediated by muscle C and Aδ fibres	Pressure gauge device, exerting pressure up to 20 kg/cm^2/~200 N/cm^2/~2000 kPa in three series of ascending stimulus intensity.

This table was published in BJA Education, Vol 24, issue 9, M.E.C. van Driel, F.J.P.M. Huygen, M. Rijsdijk, Quantitative sensory testing: a practical guide and clinical applications, 326–334, Copyright Elsevier (2024), with permission from Elsevier.[17]
*When cooling stimuli during the TSL are mistaken as heating stimuli.
CDT, Cold detection threshold; CPT, Cold Pain threshold; DFNS, German Research Network on Neuropathic Pain; DMA, Dynamic mechanical allodynia; HPT, Heat pain threshold; MDT, Mechanical detection threshold; MPS, Mechanical pain sensitivity; MPT, Mechanical pain threshold; PPT, Pressure pain threshold; QST, Quantitative sensory testing; TSL, Thermal sensory limen; VDT, Vibration detection threshold; WDT, Warm detection threshold; WUR, Wind-up ratio.

laser and measurement in five different channels (one for each fluorochrome).

In addition, the multiplex proximity extension assay inflammation panel Target 96 (Olink Bioscience, Uppsala, Sweden) is used to measure 92 different biomarkers for inflammatory and immune processes in serum. A complete list of measured immunological parameters can be found in the online supplemental table S1.

Outcome

The primary outcome of this study is CPSP with neuropathic features, defined as a numerical rating scale≥4 in combination with a DN4≥4, 3 months after surgery. The presence of the outcome is adjudicated by a pain specialist blinded to the study measurements, according to the updated grading system for neuropathic pain in research and clinical practice.[6]

Statistical analysis

Sample size justification

This study was powered to detect at least one significant difference in QST results between patients with CPSP with neuropathic features and those without the study outcome. Previous research showed that 91.9% of neuropathic pain patients had at least one QST abnormality, compared with 59.4% in healthy subjects.[26] To detect a 33% difference in the occurrence of at least one QST abnormality between these groups, with an alpha level (α) of 0.05 (two-sided) and a statistical power (1-β) of 0.8, the study anticipates including 18 patients with at least one QST abnormality experiencing CPSP with neuropathic features.

Given the previously reported ratio of absence to presence of CPSP with neuropathic features in the orthopaedic population is 0.85: 0.15, a sample size of 121 patients will be required.[27] To account for a reported dropout rate of 27%, the final sample size needed to ensure sufficient statistical power and precision was set at 150 patients.

Statistical analysis plan

The primary objective is to identify sensory alterations and changes in immunological response that are related to the development of chronic pain with neuropathic features in postsurgical patients within 3 months after surgery.

Because of the large number of variables (13 QST parameters and the broad panel of immunological

parameters), data reduction is necessary. Prior to analysis, the dataset will be examined for completeness, outliers and normality. When the proportion of missing values for a given variable exceeds 10%, the variable may be removed, or imputation techniques will be applied if this is deemed important for the analysis.

To reduce dimensionality and avoid multicollinearity, correlation analysis and cluster analyses techniques will be employed. Using correlation matrices, the correlation between QST parameters will be estimated in order to preselect one of the two predictors in the presence of collinearity. Cluster analyses will be performed on both QST and immunological parameters at each time point to identify relevant phenotypes based on these parameters. Cluster allocation will subsequently be used in a generalised mixed-effects model, along with predictors preselected based on a critical review of the relevant literature, clinical expertise, pathophysiological reasoning and practical considerations for future implementation in clinical practice. Generalised mixed-effects models will be fitted to predict the development of CPSP with neuropathic features at 3 months.

As the preferred automated variable selection method in multivariable modeling, backward elimination based on the Akaike Information Criterion will be used. The discriminatory performance of the final model will be assessed by calculating the area under the receiver operating characteristic curve. A calibration plot will be constructed to examine the agreement between the predicted probabilities and the observed frequencies. For internal validation of the final model, discrimination and calibration measures will be estimated using bootstrapping to account for overfitting and optimism.

For all analyses, statistical significance will be considered when the two-sided p-value is less than 0.05. All analyses will be performed using R V.3.6.2 (RStudio team (2015). RStudio: Integrated Development for R. RStudio, Boston, Massachusetts, USA).

Data management and monitoring

Patient-level data is pseudonymised before storage, with the key being accessible only to authorised personnel. Data will be stored for a minimum of 15 years after study termination.

An external, independent monitoring team will review the progress of the trial, verify the accuracy and completeness of the case report forms and ensure that all protocol requirements and investigator obligations are being fulfilled.

Study safety and reporting adverse events

Because completing questionnaires and undergoing QST testing are non-invasive procedures with negligible health risk, and blood collection via venipuncture is considered a low-risk procedure with a minimal chance of severe adverse events (SAEs), the sponsor will not report the SAEs to the accredited EC. Reporting SAEs is not deemed to add value to the authorities in evaluating participant safety or in ensuring the quality/validity of the data of this observational study.

DISCUSSION

The SCIP-Pain study investigates the extent of sensory alterations through QST and the immune response over time in the development of CPSP in adult patients undergoing elective lower extremity orthopaedic surgery.

By assessing perioperative QST patterns and immune responses, the study aims to provide insights into the aetiology of CPSP and the identification of patients at risk, which could ultimately lead to better-targeted treatments and improved long-term outcomes.

The following sections address key methodological considerations related to the study design, selection of the study population and outcome measures.

Study design

The prospective observational design of this cohort study enables the longitudinal assessment of sensory and immunological parameters within a clinical setting. However, loss to follow-up represents a form of selection bias specific to this study design, particularly in the postoperative period, which is often an eventful time for patients. Data collection through additional research visits can be challenging during this phase. To mitigate this, the sample size was adjusted to account for potential loss to follow-up. Additionally, resources were allocated to maximise follow-up rates by sending reminders via mail and/or telephone to initial non-responders.[28]

In this study, participants will complete questionnaires, undergo QST and provide blood samples. Previous studies investigating postoperative sensory changes using QST have been limited by significant heterogeneity in the choice of QST parameters and methodologies. One possible explanation may be the resource-intensive nature of QST, requiring expensive equipment, specialised training and significant time commitment to obtain reliable results. Despite these practical issues, the complete DFNS QST protocol will be performed in this study. Unravelling perioperative QST patterns, up to 3 months after surgery, may contribute to the development or refinement of simplified QST protocols in this setting.

As pain is a subjective experience that cannot be directly observed by others, it is typically measured through subjective report. Simple scales or complex questionnaires require patients to convert a subjective feeling into a quantitative number. The use of QST in this study provides a more objective assessment of pain. It is, however, not clear how the response to evoked pain as assessed by QST correlates with spontaneous pain. Clarifying this relationship is one of the secondary objectives of this study.

Choice of study population

This study includes patients undergoing elective orthopaedic surgery, due to the high prevalence of CPSP in this

population and the finding that bone surgery is a significant predictor of CPSP.[5 26] From a practical perspective, it is decided to include only procedures involving the lower extremities. Orthopaedic procedures on the lower extremities are among the most common surgeries performed, providing a substantial sample size. Furthermore, the anatomical and functional symmetry of the lower extremities allows for reliable comparisons between the right and left sides, enhancing the reliability of the data collected. Emergency procedures were excluded from the study, as performing baseline measurements would be impossible.

Outcome measures

The primary outcome of the study is the presence of CPSP with neuropathic features, indicative of a nociplastic pain syndrome. The 7-item DN4 questionnaire is used to screen for neuropathic features in the perioperative period, despite not being validated in this specific setting. Given its validation in chronic pain, using the DN4 as part of the composite endpoint 3 months post-surgery appears legitimate.

The follow-up period of 3 months was chosen in accordance with the definition of CPSP provided by the International Association of the Study of Pain and International Classification of Diseases, 11th Revision, which require that pain persists for a minimum of 3 months.[29 30] In non-malignant pain, 3 months is the most convenient point of division between acute and chronic pain, but for research purposes 6 months is often preferred.[31] However, significantly longer follow-up may reduce the likelihood that the pain is directly related to surgery.[32]

The assessment of pain intensity, neuropathic features and time criterion could carry a potential risk of overestimating the prevalence of clinically significant CPSP. To avoid overclassification, a pain specialist blinded to study measurements adjudicates the presence of the outcome according to the updated grading system for neuropathic pain in research and clinical practice.

In conclusion, this study will advance the understanding of pathophysiological processes involved in the transition from acute to chronic postsurgical pain. Combining information on sensory processing and the immune response during the perioperative period will provide the understanding of CPSP development and may eventually lead to improved outcomes through more mechanism-based treatment regimens.

ETHICS AND DISSEMINATION

This study has been approved by the Medical Research Ethics Committee NedMec (protocol NL77085.041.21), as well as by all participating centres. Written informed consent will be obtained from all participants before the participant is submitted to any aspect of the study procedure. The study will be conducted in accordance with the Declaration of Helsinki (V.64 WMA General Assembly, Fortaleza, Brazil, October 2013), the GCP guidelines, and the Dutch Medical Research Involving Human Subjects Act.

The study results are expected to be published in peer-reviewed journals and presented at international conferences.

Author affiliations
[1]Pain Clinic, Department of Anesthesiology, University Medical Centre Utrecht, Utrecht, The Netherlands
[2]Anesthesiololgy, Intensive Care and Pain Management, Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands
[3]Centre for Translational Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands
[4]Anesthesiology, St Antonius Hospital, Nieuwegein, Utrecht, The Netherlands
[5]Orthopaedic Surgery, University Medical Centre Utrecht, Utrecht, The Netherlands
[6]Orthopaedic Surgery, St Antonius Hospital, Nieuwegein, Utrecht, The Netherlands

Contributors Conception and design: MECvD, MR, LMV, NE and LK. Acquisition, analysis or interpretation of data: All authors. Drafting of the article: MECvD and NvV. Critical revision of article for important intellectual content: All authors. Statistical analysis: MECvD, LMV and MR. Administrative, technical or logistic support: MECvD, LT, RJHC and DD. Supervision: FJPMH, MR and MECvD is the guarantor.

Funding This research is partially supported by Erasmus Fonds, Rotterdam, the Netherlands. The funding body has no role in the study design, data collection, analysis, interpretation of data, or in manuscript preparation. This research receives no specific grant from any funding agency in the commercial sector.

Competing interests MR and NE are consultants for Synerkine Pharma, not receiving funding related to present study. FJPMH reports institutional fees from Synerkine, grants from Boston Scientific, grants and personal fees from ABOTT, Saluda and personal fees from Grunenthal outside the submitted work. MECvD, NvV, LMV, LK, LT, RJHC and DD declare that they have no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Marjelle E C van Driel http://orcid.org/0009-0006-4151-6531
Lisette Margaretha Vernooij http://orcid.org/0000-0002-9153-087X
Leo Koenderman http://orcid.org/0000-0002-5636-6453

REFERENCES

1 Crombie IK, Davies HTO, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. *Pain* 1998;76:167–71.
2 Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001;87:88–98.
3 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;367:1618–25.
4 Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008;101:77–86.

5 Fletcher D, Stamer UM, Pogatzki-Zahn E, *et al*. Chronic postsurgical pain in Europe: An observational study. *Eur J Anaesthesiol* 2015;32:725–34.
6 Finnerup NB, Haroutounian S, Kamerman P, *et al*. Neuropathic pain: an updated grading system for research and clinical practice. *Pain* 2016;157:1599–606.
7 Fitzcharles M-A, Cohen SP, Clauw DJ, *et al*. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet* 2021;397:2098–110.
8 Kosek E, Cohen M, Baron R, *et al*. Do we need a third mechanistic descriptor for chronic pain states? *Pain* 2016;157:1382–6.
9 Bäckryd E, Lind A-L, Thulin M, *et al*. High levels of cerebrospinal fluid chemokines point to the presence of neuroinflammation in peripheral neuropathic pain: a cross-sectional study of 2 cohorts of patients compared with healthy controls. *Pain* 2017;158:2487–95.
10 Kuffler DP. Injury-Induced Effectors of Neuropathic Pain. *Mol Neurobiol* 2020;57:51–66.
11 Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. *Pain* 2018;159:595–602.
12 Bjurstrom MF, Giron SE, Griffis CA. Cerebrospinal Fluid Cytokines and Neurotrophic Factors in Human Chronic Pain Populations: A Comprehensive Review. *Pain Pract* 2016;16:183–203.
13 Rolke R, Baron R, Maier C, *et al*. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006;123:231–43.
14 Petersen KK, Vaegter HB, Stubhaug A, *et al*. The predictive value of quantitative sensory testing: a systematic review on chronic postoperative pain and the analgesic effect of pharmacological therapies in patients with chronic pain. *Pain* 2021;162:31–44.
15 van Helmond N, Aarts HM, Timmerman H, *et al*. Is Preoperative Quantitative Sensory Testing Related to Persistent Postsurgical Pain? A Systematic Literature Review. *Anesth Analg* 2020;131:1146–55.
16 Backonja MM, Attal N, Baron R, *et al*. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain* 2013;154:1807–19.
17 van Driel MEC, Huygen FJPM, Rijsdijk M. Quantitative sensory testing: a practical guide and clinical applications. *BJA Educ* 2024;24:326–34.
18 Rothaug J, Zaslansky R, Schwenkglenks M, *et al*. Patients' perception of postoperative pain management: validation of the International Pain Outcomes (IPO) questionnaire. *J Pain* 2013;14:1361–70.
19 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.
20 van Seventer R, Vos C, Giezeman M, *et al*. Validation of the Dutch version of the DN4 diagnostic questionnaire for neuropathic pain. *Pain Pract* 2013;13:390–8.
21 Wheeler CHB, Williams AC de C, Morley SJ. Meta-analysis of the psychometric properties of the Pain Catastrophizing Scale and associations with participant characteristics. *Pain* 2019;160:1946–53.
22 Miller LC, Murphy R, Buss AH. Consciousness of body: Private and public. *J Pers Soc Psychol* 1981;41:397–406.
23 Kleijn WC, Heck GL, Waning A. Experiences with a Dutch adaptation of the COPE coping questionnaire: The COPE-Easy. *Gedrag Gezondheid: Tijdschr voor Psychol en Gezondh* 2000.
24 Rammstedt B, John OP. Measuring personality in one minute or less: A 10-item short version of the Big Five Inventory in English and German. *J Res Pers* 2007;41:203–12.
25 Rolke R, Magerl W, Campbell KA, *et al*. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain* 2006;10:77–88.
26 Maier C, Baron R, Tölle TR, *et al*. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010;150:439–50.
27 van Driel MEC, van Dijk JFM, Baart SJ, *et al*. Development and validation of a multivariable prediction model for early prediction of chronic postsurgical pain in adults: a prospective cohort study. *Br J Anaesth* 2022;129:407–15.
28 Meyer VM, Benjamens S, Moumni ME, *et al*. Global Overview of Response Rates in Patient and Health Care Professional Surveys in Surgery: A Systematic Review. *Ann Surg* 2022;275:e75–81.
29 Schug SA, Lavand'homme P, Barke A, *et al*. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain* 2019;160:45–52.
30 MG30.21 chronic postsurgical pain. international classification of diseases, eleventh revision (ICD-11), World Health Organization (WHO). n.d. Available: https://icd.who.int/browse/2024-01/mms/en#302680255
31 Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? *Br J Anaesth* 2014;113:1–4.
32 Papadomanolakis-Pakis N, Uhrbrand P, Haroutounian S, *et al*. Prognostic prediction models for chronic postsurgical pain in adults: a systematic review. *Pain* 2021;162:2644–57.