

Sep 16, 2025

IMPETUS: Integrated Mechanisms, Phenotypes, and Translational Underpinnings of Chronic Pain after Surgery

DOI

<https://dx.doi.org/10.17504/protocols.io.261gekw1og47/v1>

Simon Haroutounian, PhD¹, Pratik Sinha, MD, PhD², Thomas Kannampallil, PhD³, Katie Holzer, PhD²

¹Division of Clinical and Translational Research, Department of Anesthesiology, Washington University School of Medicine;

²Department of Anesthesiology, Washington University School of Medicine;

³Department of Anesthesiology, and Institute for Informatics, Washington University School of Medicine

Washington University i...



Harutyun Alaverdyan

Create & collaborate more with a free account

Edit and publish protocols, collaborate in communities, share insights through comments, and track progress with run records.

Create free account

OPEN  ACCESS



DOI: <https://dx.doi.org/10.17504/protocols.io.261gekw1og47/v1>

Protocol Citation: Simon Haroutounian, PhD, Pratik Sinha, MD, PhD, Thomas Kannampallil, PhD, Katie Holzer, PhD 2025.
IMPETUS: Integrated Mechanisms, Phenotypes, and Translational Underpinnings of Chronic Pain after Surgery. **protocols.io**
<https://dx.doi.org/10.17504/protocols.io.261gekw1og47/v1>

License: This is an open access protocol distributed under the terms of the **Creative Commons Attribution License**, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Protocol status: Working

We use this protocol and it's working

Created: September 15, 2025

Last Modified: September 16, 2025

Protocol Integer ID: 227354

Keywords: expertise from pain neurobiology, pain neurobiology, clinical pain research, translational underpinnings of chronic pain, chronic pain, surgery chronic postsurgical pain, pain medicine, postsurgical pain, specific clinical phenotypes of cpsp, cpsp phenotype, based cpsp phenotype, patients with cpsp, distinct cpsp phenotype, clinical trials for cpsp intervention, treating cpsp, cpsp intervention, discrete cpsp phenotype, affective mechanism, functional impairment, specific clinical phenotype, cognitive mechanism, novel therapeutic development, cognitive neuroscience, distinct clinical phenotype, peripheral neural, clinical psychology, immune mechanism

Funders Acknowledgements:

NIH

Grant ID: 1RM1NS135283-01A1

Abstract

Chronic postsurgical pain (CPSP) is a major healthcare burden, affecting nearly 20% of patients undergoing major surgery. CPSP is associated with diminished quality of life, mood disturbances, functional impairment, and increases the risk of opioid use disorder. Considerable research suggests that a combination of somatosensory, immune, affective and cognitive mechanisms contribute to CPSP, and that CPSP phenotypes are highly heterogeneous, even after identical surgical procedures. However, most prior research has explored peripheral or central mechanisms in isolation, preventing an integrated insight into underlying biological factors that drive these distinct clinical phenotypes. Preclinical models of CPSP have also failed to capture this phenotypic heterogeneity or meaningful clinical outcome measures, significantly limiting forward translation of basic discoveries. As a result, current strategies for predicting, preventing and treating CPSP are extremely limited. To address this need, we have developed the IMPETUS program that draws expertise from pain neurobiology, clinical pain research, clinical psychology, cognitive neuroscience, immunology, proteomics, genomics, transcriptomics, bioinformatics, machine learning, and pain medicine. Our goal is to gain integrated mechanistic insights into peripheral and central biological processes that contribute to CPSP, and to understand how these processes contribute to CPSP heterogeneity. Aim 1. Characterize peripheral neural and immune mechanisms contributing to CPSP. In patients with CPSP subsequent to abdominal or genitourinary surgery (n=220) and contemporaneous controls (n=100), we will characterize somatosensory profiles of mechanical and thermal sensitivity, the neural and immune milieu at the cutaneous site of injury, and circulating immune host profiles, and compare them with correlates across the same domains in a mouse model of laparotomy. Aim 2. Characterize cognitive and affective mechanisms contributing to CPSP. In patients with CPSP and controls, we will use granular longitudinal data collection methods to characterize affective, cognitive, and activity/sleep measures of CPSP, and compare them with animal model correlates across these domains, using translational outputs of amotivation, punishment-sensitivity, reversal learning task, and actigraphy. Aim 3. Identify and back-translate mechanism-based CPSP phenotypes. Using state-of-the-art machine learning approaches applied to multidimensional data generated in Aims 1 and 2, we will identify discrete CPSP phenotypes, and recapitulate them in animal models for improved translatability. We expect the IMPETUS program to 1) identify distinct somatosensory, neural, immune, affective and cognitive mechanisms that contribute to distinct CPSP phenotypes and explain inter-patient heterogeneity, with cross-species validation; 2) Characterize distinct phenotypic clusters within CPSP to inform personalized patient care and stratified clinical trials for CPSP interventions; and 3) Develop animal models that recapitulate specific clinical phenotypes of CPSP to accelerate for mechanistic exploration and novel therapeutic development.

Guidelines

Baseline Visit

- Collection of patient demographic, comorbidity, and medications data
- Brief Pain Inventory
- Michigan Body Map
- DN4 questionnaire
- Neuropathic Pain Symptom Inventory (NPSI) questionnaire
- Fibromyalgia survey questionnaire
- TAPSI (Tobacco, Alcohol, Prescription medication, and other Substance use) screener for substance use
- Quantitative sensory testing protocol to determine warmth and cold detection thresholds (WDT, CDT), heat and cold pain thresholds (HPT and CPT), mechanical detection and pain thresholds (MPT, MDT), mechanical pain sensitivity (MPS), vibration detection threshold (VDT), dynamic mechanical allodynia (DMA), thermal sensory limen (TSL), paradoxical heat sensations (PHS), pressure pain threshold (PPT), and conditioned pain modulation (CPM).
- Sensory mapping for areas of sensory loss and sensory gain
- Two 3-mm skin punch biopsies from around the surgical area (separate specimens for morphology and spatial transcriptomics)
- Blood draw for proteomic and transcriptomic analyses, and for simulated ex-vivo immune response.
- Pain Catastrophizing Scale (PCS)
- Assessment of depression: PHQ-2, and PROMIS depression short-form
- Assessment of anxiety: GAD-2 and PROMIS anxiety short-form
- PROMIS Sleep disturbance
- PROMIS Cognitive abilities
- PROMIS Physical Functioning short form
- Tampa Scale 11 (TSK-11) of Kinesiophobia
- 2-item WHO QOL instrument
- Patient Global Impression of Change (PGIC)
- The Veterans Rand 12 item Health Survey (VR-12)
- Color Word Matching Stroop Test (CWMSST)
- Eriksen Flanker task
- Wisconsin Card Sorting Task
- Stop-Signal Task

30-day post-baseline follow-up:

- Ecological Momentary Assessments (EMA) of mood, pain, sleep, analgesic use and cognitive function (daily, 30 days after baseline visit)
- Actigraphy monitoring with a Fitbit device (daily, 30 days after baseline visit) collecting measures such as heart rate, steps, and sleep.
- Eriksen-Flanker Task (weekly, for 4 weeks after baseline visit)

Pre-Study Period

- Identification of potential participants using the P5 perioperative cohort study at Washington University or Electronic Health Record (EHR)
- Informed consent

Enrollment/Baseline Visit

- Verify inclusion/exclusion criteria
- Obtain written informed consent
- Obtain demographics, comorbidity, and medications data
- Confirm diagnosis of CPSP or identify participants as controls, with no chronic pain at the surgical site
- Complete assessments and neurocognitive tests
- Download the LifeData app for Ecological Momentary Assessments (EMA), and train the participants how to use it.

30-day follow-up after baseline visit

- EMA - Participants will be asked to complete EMA ratings three times a day, with the first rating of the day dependent upon preferred participant schedule (e.g., from 8:00 AM to 8:00 PM). Data collected via EMA will include pain severity (with movement and rest), pain interference, analgesic medication use, symptoms related to anxiety and depression, sleep disturbances, and cognitive abilities.
- Eriksen-Flanker task will be administered once a week for 4 weeks after the baseline visit, in an on-line format task
- Participants will be asked to wear a Fitbit device for 30 days to collect data on activity (e.g., steps, heart rate) and sleep.

Study Procedures

- Consented subjects will be asked to participate in the study for up to 5 weeks. We will aim to complete the consent process and baseline visit on the same day. If this is not possible, the baseline visit may take place on another day after signing informed consent.
- Patients' data collected at baseline will include their age, sex, race and ethnicity, education, marital status, weight, height, BMI, comorbidities, smoking status, and alcohol and substance use history and status. We will document participants' current and past medical and surgical history, current medications (including current and past opioid use and other analgesics) and corresponding Morphine Milligram Equivalents (MME), pre-existing painful conditions and presence of widespread pain. We will collect details about the index surgery, including patients' reason for surgery, date of surgery, duration of surgery, and type of anesthesia received.
- We will document existing diagnoses of depression, anxiety, post-traumatic stress disorder, and other mental health conditions. Participants will complete anxiety and depression symptom assessment on PROMIS surveys, and GAD-2 and PHQ-2 surveys, and the Pain Catastrophizing Scale (PCS). For cognitive flexibility assessment, participants will complete the Color-Word Matching Stroop Test (CWMST), Stop-Signal Test and Eriksen Flanker Task, as well as the Wisconsin Card Sorting Task. Additionally, patients will fill out PROMIS short versions for sleep disruption, cognitive function, and physical performance. The TAPS1 questionnaire will serve as a screening tool for substance use.
- The evaluation of pain syndrome will utilize the Brief Pain Inventory and Michigan Body Map tools. The neuropathic component will be assessed using the DN4 and Neuropathic Pain Symptom Inventory (NPSI)

questionnaires. A fibromyalgia survey questionnaire will be administered to gather information on widespread pain symptoms.

Quantitative sensory testing:

- Quantitative sensory testing will be performed on painful area in CPSP group or area near to surgery scar in control group.
- A description of the QST procedures follows [24, 25]:

Thermal detection and thermal pain thresholds

- **Equipment:** The Thermal Sensory Analyzer (TSA-II platform - Medoc, Ramat Yishai, Israel) will be used to determine thermal detection and pain thresholds. This equipment is used globally for functional assessment of pain and temperature-conducting nerve fibers (C and A-delta fibers).
- **Method and Background:** Using the thermal sensory analyzer, cold and warm detection thresholds (CDT and WDT, respectively), as well as cold and heat pain thresholds (CPT and HPT, respectively) will be determined. The thermode with contact area of 9.0 cm² is applied to the tested site, and all thresholds are determined by continuous ramping of temperature from 32°C baseline temperature by 1°C/S until the subject presses the 'stop' button. Cut-off temperatures are 0°C and 50°C, to minimize thermal damage to the skin. The baseline temperature to which the thermode returns before each test is 32°C. The average threshold is calculated from three measurements in each area.
- The thermal sensory limen (TSL) and paradoxical heat sensations (PHS) procedure is a sequence of alternating warming and cooling of the skin. The subject is instructed to press a button every time a temperature change is felt, and to verbally describe the sensations for six consecutive temperature changes. The number of PHS is defined based on a qualitative report of a warm or burning sensation, during cooling of the skin, and corresponded to a value between 0 and 3. Vice versa, the number of paradoxical cold sensations (PCS) is defined as the report of a cold sensation during warming of the skin (0–3 PCS).
- The individual TSL is calculated by subtracting the mean of the cold detection threshold from the mean of the warm detection threshold as measured by the TSL test.

Determination of mechanical detection threshold (MDT)

- **Equipment:** A set of standardised von Frey filaments (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128 and 256mN). The contact area of the hairs with the skin is of uniform size (1 mm²) and texture.
- **Methods and Background:** Standardised von Frey filaments will be used in a modified "method of limits" manner using 5 series of increasing and decreasing stimulus intensities to determine the geometric average as the tactile detection threshold of the painful and non-painful skin areas [26].
- Von Frey filaments of different stimulus intensities are used to determine the tactile detection thresholds. A filament eliciting 16mN force* is applied first, followed by filaments of consecutively lower intensity until the patient cannot detect the stimulus being applied. This respective force represents the first threshold value. The order in which the stimuli are applied is then reversed and stimuli of consecutively greater intensity are applied until sensation is detected (this intensity becomes the second value). Again filaments with decreasing intensity are applied until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

* In case the first von Frey filament with an intensity of 16mN is not detected, the next highest intensity filament which can be detected must be used as a starting intensity. However, the relevant force of this stimulus is not documented. Filaments with consecutively lower intensity are applied until the patient cannot detect the stimulus being applied. The procedure is followed as above; until in total 5 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

Determination of mechanical pain thresholds (MPT) and Mechanical pain sensitivity (MPS)

- **Equipment:** A set of standardized weighted metal probes (Nervetest, MRC systems) exerting pressure of 8, 16, 32, 64, 128, 256 and 512 mN.
- **Methods and Background:**
 - The standardized metal probes will be used in a modified method of levels manner, 5 series of increasing stimulus intensities to detect the mechanical pain threshold. Beginning with an applied force of 8mN, stimuli increase in intensity until the sensation induced by increased pressure can be described as 'painful'. The corresponding force is used to represent the first MPT value. The procedure is then repeated a total of 3 times and until a total of 5 values are obtained, from which the mean MPT is determined.
 - For Mechanical pain sensitivity (MPS) metal probes will be applied in a balanced order, five times each, and the subject will be asked to give a pain rating for each stimulus on a 0–100 numerical rating scale (0 indicating "no pain", and 100 indicating "most intense pain imaginable").

Determination of dynamic mechanical allodynia

- **Equipment:** a cotton wisp exerting a force of ~3 mN, a cotton wool tip fixed to an elastic strip exerting a force of ~100 mN, and a standardized brush exerting a force of ~200–400 mN.
- **Methods and Background:**
 - Stimulus–response–functions for dynamic mechanical allodynia (ALL) will be determined using a set of three light tactile stimulators: a cotton wisp, a cotton wool tip fixed to an elastic strip, and a standardized brush. The three tactile stimuli will be applied five times each with a single stroke of approximately 1–2 cm in length over the skin. They were intermingled with the pinprick stimuli in balanced order and subjects will be asked to give a rating on the same scale as for pinprick stimuli.

Determination of vibration detection thresholds (VDT)

- **Equipment:** A standard tuning fork.
- **Methods and Background:**
 - The tuning fork will be applied at the closest bony prominence to the surgical site, and vibration detection threshold (the moment patient stops feeling the vibration of the tuning fork applied to the skin) will be measured on a scale of 1–8. The test will be repeated a total 3 times. VDT is determined as an average of the three measures.

Determination of wind-up ratio (WUR)

- **Equipment:** A standardized weighted metal probes (Nervetest, MRC systems) exerting pressure of 256mN.
- **Methods and Background:** In this test a pinprick (256mN) is first applied singularly. After that a series of 10 identical pinprick stimuli are applied with a frequency of 1 s⁻¹ within an area of 1 cm². Immediately following the single stimulus and series of stimuli, an evaluation of the sensation must be provided according to NRS (0–10, '0':

'no pain', '10': 'worst pain imaginable'). A ratio is calculated using these values. This procedure will be repeated 3 times. A geometric average of the 'wind-up' is calculated from the two ratios [27, 28].

Determination of muscular pressure pain threshold (PPT)

- **Equipment:** Pressure pain threshold will be determined with a handheld algometer (Somedic AB, Sweden).
- **Methods and Background:** Pressure will be increased continually (approx.. 0.5 kg/s equivalent to 50 kPa/s) until pain is indicated by the patient. An average of three measurements will be taken.

Determination of conditioned pain modulation (CPM)

- **Equipment:** A temperature-controlled water bath, and a hand-held pressure algometer (Wagner instruments).
- The efficiency of conditioned pain modulation (CPM) as a surrogate measure of endogenous top-down pain control efficiency will be determined. CPM is derived from a patient report of pain intensity following application of a calibrated painful (test) stimulus with and without another ongoing aversive (conditioning) stimulus. A temperature-controlled water bath, and a hand-held pressure algometer (Wagner instruments) will be used for CPM. The conditioning stimulus will consist of 60-second immersion of the dominant hand in 12°C cold water [29].
- The pain stimulus will consist of applying the pressure algometer on the trapezius muscle at 0.5kg/sec rate, until achieving pressure pain threshold (i.e. participant responding that the sensation changed from pressure to pain).
- The test stimulus will be applied twice at the trapezius muscle, during the last 30 seconds of the conditioning stimulus, and averaged. The difference between test stimulus intensity (average of 2 measures of pressure pain threshold (PPT), in kg) with and without conditioning is defined as Δ CPM. Higher PPT with conditioning implies descending inhibition (rather than facilitation) [30, 31].

Sensory mapping

- We will also perform sensory mapping (i.e. sensitivity surgery incision area to cold, warm, brushing and pricking stimuli) for areas of sensory gain and sensory loss. We will create personalized diagrams of pain mapping and sensory mapping to characterize the pain and sensory sign distribution in CPSP and contrast them with controls.

Skin Biopsy:

- Two 3-mm skin punch biopsy specimens will be collected from the painful area in CPSP group or next to surgical scar in control group.[32] The first biopsy specimen will be exposed to overnight fixation, followed by transfer to a glycerol-based cryoprotectant fluid., and subsequently frozen and stored at -80°C. For analysis, tissues will be sectioned into 50- μ m slices for immunostaining with PGP 9.5 antibody, adhering to published guidelines for the determination of intraepidermal nerve fiber density. [33] The second biopsy will be freshly frozen and stored under -80°C.
- We will perform a detailed exploratory examination of epidermal and dermal neural and immune cell types to understand their impact on CPSP.

Ex vivo LPS-stimulation of cytokine response and inhibition by dexamethasone:

- Blood (approximately 24mL in EDTA tubes and 26mL in Heparin tubes) will be drawn at the study visit. Cytokine production using the endotoxin lipopolysaccharide (LPS; 10 ng/ml; Escherichia coli) will be stimulated.[34-39] Within 45 minutes of sample collection, heparinized whole blood (3200 μ l) will be added to 400 μ l of saline solution or 400 μ l of LPS solution (to achieve a final 15 ng/ml concentration prepared using sterile saline solution The

volumes may change without changing the proportions to maintain the same final concentration of LPS. An additional 2.5 ml each of stimulated and unstimulated heparin blood sample will be distributed to PAXgene RNA tubes for mRNA expression analyses to assess gene expression under basal, LPS-stimulation, and dexamethasone suppression conditions.[38] After incubating for 4-6 hours at 37° C in 5% CO₂, samples will be centrifuged at 1500g before the plasma is collected and stored.

- We will collect blood samples for the following analyses:

-Proteomics and specific biomarkers– either to be analyzed by OLINK 96-protein immune and inflammatory panel, or 700-protein mass spectrometry assay at Washington University Mass Spec core at McDonell Genome Institute, or other conventional methodology.

-Whole blood bulk RNA sequencing

-Whole genome sequencing, for patients recruited outside of P5 cohort (DNA for P5 patients is already collected and stored)

- The total amount of blood collected will be approximately 50mL.

Ecological Momentary Assessment (EMA)

- To capture detailed data on patient experiences with CPSP (rather than ask a patient to make a general summative judgement over a given period of time in standard surveys), we will use a statistical method for time-series data to examine causes over time. We will use LifeData – a HIPAA-compliant EMA service. The service used will be functional on a variety of smartphones, including iPhone and Android phones. If possible, we will extend the service further to participants who can receive SMS messages.

- EMA items will include pain severity, anxiety, depression, cognitive function items drawn from PROMIS measures, pain catastrophizing items drawn from the Pain Catastrophizing Scale, and an item asking about subjective psychological impairment due to analgesic use (ranging from “none” [0] to “as much as I could handle” [100]). Patients will be asked these questions about the present moment at each time point; the measure of analgesic use will ask about consumption since last survey response. A subjective measure of analgesic use will be used, since a purely objective accounting of use would depend upon specific drug, formulation, and dose, which cannot be assessed readily by a rapid self-report.

- We will also obtain EMA ratings on subjective cognitive functioning. Participants will self-report via EMA on items of cognitive flexibility (using items adapted from the Attentional Control Scale),[40-42] memory (using items from the Memory Complaint Questionnaire (MAC-Q)), [43] and processing speed (using an item from the PROMIS Cognitive abilities scale), see Appendix 1. Self-report of cognitive ability displays relatively weak associations with objective performance,[40, 44] and thus provides unique information regarding functioning.

- Participants will be asked to complete EMA ratings three times a day, based upon preferred participant schedule (e.g., from 8:00 AM to 8:00 PM). EMA will continue through 30 days post-operatively. Missing data, whether caused by participants not having a device or intermittent failure to answer surveys will be handled either at the EMA modeling stage or the machine learning stage.

Actigraphy Assessment

- Each participant will be provided with a Fitbit Inspire 3 wristband device. The devices will be registered and connected to the appropriate Fitbit mobile application on their smart phones. Subjects will be followed for 30 days. During this period, subjects will be asked to wear the activity tracker as much as possible, including when they sleep, and sync their devices using the associated mobile app on their smartphone.

- Fitbit collects step count, heart rate, and sleep stages at minute-granularity, which results in long time series for each patient. To facilitate data analysis, we will employ our established two-level feature engineering framework to extract high-level features from the time series.[45-47] The daily features will include semantic features related to physical activity, sedentary behaviors, and sleep (e.g., active vs. very active minutes; calories burned, wear time, sleep time) and statistical features (e.g., skewness and kurtosis) of the time series.
- To avoid collection of PHI for the Fitbit device use, we will set a dummy account for each participant, so that only study ID information is registered in Fitbit.

Cognitive flexibility measurement

- We will capture week-to-week variability in cognitive flexibility to examine its associations with pain and mood. The Eriksen Flanker task will be administered remotely at the end of each week, resulting in 5 total measurements to estimate within-person performance variability.

Materials

- Smart phone
- Fitbit device
- 3-mm skin punch biopsy tools
- Equipment for blood draw
- Various questionnaires and scales (e.g., Brief Pain Inventory, Michigan Body Map, DN4 questionnaire, etc.)
- Thermal Sensory Analyzer (TSA-II platform - Medoc, Ramat Yishai, Israel)
- Set of standardised von Frey filaments (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128 and 256mN)
- Set of standardized weighted metal probes (Nervetest, MRC systems) exerting pressure of 8, 16, 32, 64, 128, 256 and 512 mN
- Cotton wisp
- Cotton wool tip fixed to an elastic strip
- Standardized brush exerting a force of ~200–400 mN
- Standard tuning fork
- Handheld algometer (Somedic AB, Sweden)
- Temperature-controlled water bath
- Hand-held pressure algometer (Wagner instruments)
- EDTA tubes
- Heparin tubes
- PAXgene RNA tubes

Safety warnings

Potential Risks

- **Blood Collection:** Likely/common risks include pain, bruising, and/or bleeding at site of blood draw. A less common risk is infection at the site of the blood draw.
- **Skin Biopsy:** Potential risks include local pain, infection, and minor bleeding. Pain is transient, and cutaneous infiltration with lidocaine will be offered to reduce discomfort. Slight chance of scarring, but site expected to look the same as surrounding skin after a few months.
- **Thermal and Mechanical Testing:** Minimal risk of injury. Pain is transient and subsides immediately. Participants may stop any procedure at any time. Slight risk of burn with thermal stimulation, minimized by positive lockout of stimulus parameters above 52°C and built-in shut-down system. CPM testing involves ice water bath at 12°C, posing minimal risk of tissue damage from cold exposure.
- **Breach of Confidentiality:** Subjects may experience a breach of confidentiality. Investigators will keep subjects' participation confidential unless disclosure is required by law. However, it is possible that others may become aware of subjects' participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies subjects.

Ethics statement

We have established a longitudinal surgical patient cohort at Barnes-Jewish Hospital as a part of P5 (Personalized Prediction of Persistent Postsurgical Pain) project, WashU IRB # 202101123.

Potential Benefits of the Proposed Research to the Subjects and Others

- 1 Participants will be provided \$200 for participating in the baseline visit. Thereafter, they will receive \$10 for the end of each of the 4 subsequent weeks for completing assessment, and another \$10 when returning their Fitbit device – i.e. an additional \$50 payment when the Fitbit device is returned in a prepaid FedEx envelope (minus \$10 for any missed weekly assessment). Alternatively, participants may opt for retaining the Fitbit device (\$70 value) in lieu of \$50 reimbursement for the post-baseline assessments. We will use Advarra gift cards to provide study-related payments to the participants.

Inclusion of Women and Minorities

- 2 There is no exclusion of any sex/gender or racial/ethnic group for the IMPETUS studies. The study and its advertisements actively encourage the participation of women in the research. Women of childbearing potential are not excluded from our research protocols. Women are reported to have a higher risk of developing chronic postsurgical pain (CPSP), and will be accordingly, carefully characterized to identify particular risk factors in this patient group. The IMPETUS cohort is designed to over-represent women, since the P5 observational study from which IMPETUS will mainly recruit patients has ~70% female composition. This is due to the fact that some surgeries with high risk of CPSP (e.g., hysterectomy), are performed exclusively/predominantly on women.
- 3 All of our studies and their advertisements actively encourage the participation of minorities in the research. Our minority recruiting typically matches the demographic composition of the St Louis and Washington University community from which subjects will be recruited. Our current race and ethnicity representation in the P5 sub-cohort of abdominal and genitourinary surgeries is 72.5% White, 21% Black, 4.3% Asian or Native American; 3% Hispanic. This is the expected distribution in the overall IMPETUS study.

Inclusion of Individuals across the Lifespan

- 4 Patients who are 18 to 80 years of age, who underwent major abdominal or genitourinary surgery within 6-36 months prior to the baseline study visit will be approached for consent to this study. Adults 3e80 years old will not be included, as our enrollment will be primarily from the P5 (Personalized Prediction of Persistent Postsurgical Pain) observational cohort, which has inclusion criteria that limit the age range to 18-75 year old. In addition, adults 3e80 have been consistently shown to be at a lower risk of chronic postsurgical pain (CPSP), making the results less generalizable for this group. In addition, the ecological momentary assessment (EMA) includes smartphone-based daily data entry and it is our experience that participants 3e80 years old have low consent rates and high attrition rates due to the requirement of these assessments.



- 5 Children younger than 18 years old will not be studied in these experiments. The cognitive, pain, behavioral and EMA tools proposed in these studies have been validated in adult subjects. We were unable to justify using a different set of tools in pediatric patients, as the introduction of the additional variability in patient-reported tools and outcomes would substantially limit the ability to combine the data and would negatively affect methodological rigor. Insights gained from the results of the current proposal will provide an evidence base for designing future studies identifying risks and mitigating chronic postsurgical pain in children.

Protocol references

- [1] Weiser, T.G., et al., Size and distribution of the global volume of surgery in 2012. *Bull World Health Organ*, 2016. 94(3): p. 201-209F.
- [2] Haroutiunian, S., et al., The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain*, 2013. 154(1): p. 95-102.
- [3] Kehlet, H., T.S. Jensen, and C.J. Woolf, Persistent postsurgical pain: risk factors and prevention. *Lancet*, 2006. 367(9522): p. 1618-25.
- [4] Freeman, R., et al., AAPT Diagnostic Criteria for Peripheral Neuropathic Pain: Focal and Segmental Disorders. *J Pain*, 2018.
- [5] Macrae, W.A. and H.T.O. Davies, Chronic postsurgical pain, in *Epidemiology of Pain*, I.K. Crombie, et al., Editors. 1999, International Association for the Study of Pain: Seattle. p. 125-142.
- [6] Schug, S.A., et al., The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain*, 2019. 160(1): p. 45-52.
- [7] Macrae, W.A., Chronic pain after surgery. *Br J Anaesth*, 2001. 87(1): p. 88-98.
- [8] Gaskin, D.J. and P. Richard, The economic costs of pain in the United States. *J Pain*, 2012. 13(8): p. 715-24.
- [9] Brummett, C.M., et al., New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surg*, 2017. 152(7): p. e170504.
- [10] Clarke, H., et al., Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ*, 2014. 348: p. g1251.
- [11] Gewandter, J.S., et al., Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations. *Pain*, 2015. 156(7): p. 1184-97.
- [12] Haroutounian, S. and T.S. Jensen, Neuropathic Pain Following Surgery, in *Nerves and Nerve Injuries*, T.R.S., Editor. 2015, Elsevier. p. 113-127.
- [13] Hinrichs-Rocker, A., et al., Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - a systematic review. *Eur J Pain*, 2009. 13(7): p. 719-30.
- [14] Mutso, A.A., et al., Reorganization of hippocampal functional connectivity with transition to chronic back pain. *J Neurophysiol*, 2014. 111(5): p. 1065-76.
- [15] Vachon-Preseu, E., et al., Identification of traits and functional connectivity-based neurotraits of chronic pain. *PLoS Biol*, 2019. 17(8): p. e3000349.
- [16] Vachon-Preseu, E., et al., Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain*, 2016. 139(Pt 7): p. 1958-70.
- [17] Willingham, M., et al., The association between postoperative complications and lingering postsurgical pain: an observational cohort study. *Br J Anaesth*, 2019.
- [18] Gaudilliere, B., et al., Clinical recovery from surgery correlates with single-cell immune signatures. *Sci Transl Med*, 2014. 6(255): p. 255ra131.
- [19] Rabbitts, J.A., et al., Longitudinal and Temporal Associations Between Daily Pain and Sleep Patterns After Major Pediatric Surgery. *J Pain*, 2017. 18(6): p. 656-663.
- [20] Gilron, I., et al., Evaluating the Association Between Acute and Chronic Pain After Surgery: Impact of Pain Measurement Methods. *Clin J Pain*, 2017. 33(7): p. 588-594.
- [21] Hah, J.M., et al., Factors Associated With Acute Pain Estimation, Postoperative Pain Resolution, Opioid Cessation, and Recovery: Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open*, 2019. 2(3): p. e190168.

- [22] Kannampalli, T., et al., Characterizing the pain score trajectories of hospitalized adult medical and surgical patients: a retrospective cohort study. *Pain*, 2016. 157(12): p. 2739-2746.
- [23] Singh, J.A., et al., Association of Early Postoperative Pain Trajectories With Longer-term Pain Outcome After Primary Total Knee Arthroplasty. *JAMA Netw Open*, 2019. 2(11): p. e1915105.
- [24] Rolke, R., et al., Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *PAIN®*, 2006. 123(3): p. 231-243.
- [25] Maier, C., 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(3): p. 439-450.
- [26] Baumgärtner, U., et al., Neurogenic hyperalgesia versus painful hypoalgesia: two distinct mechanisms of neuropathic pain. *Pain*, 2002. 96(1-2): p. 141-51.
- [27] Magerl, W., S.H. Wilk, and R.D. Treede, Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain*, 1998. 74(2-3): p. 257-68.
- [28] Price, D.D., et al., Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain*, 1977. 3(1): p. 57-68.
- [29] Nahman-Averbuch, H., et al., Increased pain sensitivity but normal pain modulation in adolescents with migraine. *Pain*, 2019. 160(5): p. 1019-1028.
- [30] Yarnitsky, D., Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol*, 2010. 23(5): p. 611-5.
- [31] Yarnitsky, D., et al., Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain*, 2015. 19(6): p. 805-6.
- [32] Hincker, A., et al., Somatosensory predictors of response to pregabalin in painful chemotherapy-induced peripheral neuropathy: a randomized, placebo-controlled, crossover study. *Pain*, 2019. 160(8): p. 1835-1846.
- [33] Lauria, G., et al., European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol*, 2010. 17(7): p. 903-12, e44-9.
- [34] Wirtz, P.H., et al., Enhanced glucocorticoid sensitivity of cytokine release from circulating leukocytes stimulated with lipopolysaccharide in healthy male smokers. *Brain Behav Immun*, 2004. 18(6): p. 536-43.
- [35] de Craen, A.J., et al., Heritability estimates of innate immunity: an extended twin study. *Genes Immun*, 2005. 6(2): p. 167-70.
- [36] DeRijk, R.H., F. Eskandari, and E.M. Sternberg, Corticosteroid resistance in a subpopulation of multiple sclerosis patients as measured by ex vivo dexamethasone inhibition of LPS induced IL-6 production. *J Neuroimmunol*, 2004. 151(1-2): p. 180-8.
- [37] Ruud, T.E., et al., Effects of infliximab and hydrocortisone on in vitro cytokine responses after stimulation with lipopolysaccharide. *Surg Infect (Larchmt)*, 2013. 14(1): p. 30-4.
- [38] Spijker, S., et al., Stimulated gene expression profiles as a blood marker of major depressive disorder. *Biol Psychiatry*, 2010. 68(2): p. 179-86.
- [39] Vogelzangs, N., et al., Cytokine production capacity in depression and anxiety. *Transl Psychiatry*, 2016. 6(5): p. e825.
- [40] Judah, M.R., et al., Factor structure and validation of the Attentional Control Scale. *Cogn Emot*, 2014. 28(3): p. 433-51.
- [41] DeVito, A.N., et al., Factor Structure of the Attentional Control Scale in Younger and Older Adults: Relationships with Anxiety and Depression. *Journal of Psychopathology and Behavioral Assessment*, 2019. 41(1):

p. 60-68.

- [42] Derryberry, D. and M.A. Reed, Anxiety-related attentional biases and their regulation by attentional control. *J Abnorm Psychol*, 2002. 111(2): p. 225-36.
- [43] Crook, T.H., 3rd, E.P. Feher, and G.J. Larrabee, Assessment of memory complaint in age-associated memory impairment: the MAC-Q. *Int Psychogeriatr*, 1992. 4(2): p. 165-76.
- [44] Crumley, J.J., C.A. Stetler, and M. Horhota, Examining the relationship between subjective and objective memory performance in older adults: a meta-analysis. *Psychol Aging*, 2014. 29(2): p. 250-63.
- [45] Zhang, J., et al., Predicting Post-Operative Complications with Wearables. *Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies*, 2022. 6(2): p. 1-27.
- [46] Cos, H., et al., Predicting Outcomes in Patients Undergoing Pancreatectomy Using Wearable Technology and Machine Learning: Prospective Cohort Study. *J Med Internet Res*, 2021. 23(3): p. e23595.
- [47] Li, D., et al., Feasibility Study of Monitoring Deterioration of Outpatients Using Multimodal Data Collected by Wearables. *ACM Transactions on Computing for Healthcare*, 2020. 1(1): p. 1-22.
- [48] Vollert, J., et al., Stratifying patients with peripheral neuropathic pain based on sensory profiles: algorithm and sample size recommendations. *Pain*, 2017. 158(8): p. 1446-1455.
- [49] Bouhassira, D., et al., Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. *Pain*, 2014. 155(10): p. 2171-9.
- [50] Kalliomäki, J., et al., A randomized, double-blind, placebo-controlled trial of a chemokine receptor 2 (CCR2) antagonist in posttraumatic neuralgia. *Pain*, 2013. 154(5): p. 761-767.
- [51] Demant, D.T., et al., Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: a randomised, double-blind, and placebo-controlled, phenotype panel study. *PAIN*, 2015. 156(11).
- [52] IMI1, C.E., Final Project Report Public Summary. 2015(cited 2023 02/12/2023).
- [53] Baron, R., et al., Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain*, 2017. 158(2): p. 261-272.
- [54] Gierthmühlen, J., et al., Who is healthy? Aspects to consider when including healthy volunteers in QST--based studies-a consensus statement by the EUROPAIN and NEUROPAIN consortia. *Pain*, 2015. 156(11): p. 2203-2211.
- [55] Vollert, J., et al., Symptom profiles in the painDETECT Questionnaire in patients with peripheral neuropathic pain stratified according to sensory loss in quantitative sensory testing. *Pain*, 2016. 157(8): p. 1810-1818.
- [56] Themistocleous, A.C., et al., The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. *Pain*, 2016. 157(5): p. 1132-1145.