INVESTIGATING EXPERIMENTALLY INDUCED PAIN IN ADULT PARTICIPANTS

Please note that applications for ethical review should only be submitted to the Medical Sciences IDREC for use in connection with research undertaken within the UK and the EU, which is not funded by the US National Institutes of Health or another US federal funding agency. Such research that is to be undertaken outside the EU and/or with US funding should be submitted for review to **OxTREC** using OxTREC's full application form.

1. SCOPE

The goal of pain research is to acquire new knowledge on the mechanisms, pathogenesis, diagnosis, and treatment of acute and chronic pain. Pain may also be used, however, as a proxy for the study of something else (e.g. endorphins). This requires research on humans and involves experimentally induced painful stimuli. There are many methods to experimentally activate painful sensations in a safe, controlled and temporary manner. All listed procedures and experimental methods were previously ethically approved and are widely used in pain research and clinical diagnosis. The minimal intensity of noxious stimulus necessary to achieve the goals of the studies is established. Participants are always able to terminate a painful stimulus at will and stimulation intensities will not exceed the individual tolerance level. All researchers involved in data acquisition must undergo safety training for the stimulation device they intend to use. Studies conducted under this Approved Procedure may only include adults aged 18+ years. In case-study samples that include older participants (> 60 years), researchers must be trained to accommodate all procedures to age-related changes (e.g. more delicate skin with age). During research procedures the stimulation device must be supervised by a second researcher who is not involved in other tasks related to the research.

Pain studies can be conducted with or without non-invasive neuroimaging techniques such as Magnetic Resonance Imaging (MRI), Electroencephalography (EEG), and/or Magnetoencephalography (MEG). In studies where neuroimaging techniques are used, such techniques have been approved in CUREC Approved Procedures 17 for MRI, 03 for EEG, and 08 for MEG. When used in an MRI environment, all stimulation devices will first be checked for safety on the specific MRI scanner by a radiographer.

This procedure allows for two different pain methods to be used in tandem (e.g. chemical stimulation followed by pinprick), provided each method is calibrated separately for individual participants prior to use in tandem. Under no circumstances can two pain methods be used simultaneously under this Approved Procedure.

1.1 Sensory stimulation techniques

(i) Touch Pain:
Sensations related to touch that range from light touch to sharp pinprick can be elicited using punctuate probes and von Frey hairs specifically designed to deliver a constant force to the skin surface. Furthermore, a purpose-built pressure device can be used to induce deep tissue pain (e.g.,

joint pain). None of these devices penetrate the skin. The maximum force delivered will be 512 mN for punctate probes and von Frey hair and 250 N for the pressure device. There are no known side effects to any of these stimulations. In studies where neuroimaging techniques are used, these devices are MRI-compatible. These have been approved in earlier NHS ethics applications for use in the Wellcome Centre for Integrative Neuroimaging (WIN) pain laboratory:

- C02.086 "Mapping brain function with fMRI"; PI: Prof. Paul Matthews; COREC
- C03.092 "The effect of gabapentin on the brain response, as measured by functional magnetic resonance imaging (fMRI), to a heat/capsaicin challenge in healthy volunteers"; PI: Dr. Giandomenico Iannetti; OxREC
- C02.327 "FMRI investigations of clinical pain processing mechanisms and their modulation by 'Gold Standard' analgesic compounds"; PI: Prof. Paul Matthews; COREC

(ii) Contact Heat/Cold Thermal Pain:
To induce heat or cold pain, radiant heat, using an infrared laser stimulator, or conductive heat/cold using a contact heat thermode can be applied. These devices are safe, several are CE-approved and all are widely and routinely used for clinical diagnostic purposes. The WIN pain laboratory has many years' experience using these devices.

The limitations for contact heat/cold are:

- minimum temperature: 0°C (Medoc©), 5°C (Somedic©) for a stimulus duration of 3s, max. ramp time: 0.5°C/s)
- maximum temperature: 55°C for a stimulus duration of 3s (max. ramp time: 0.5°C/s)
- maximum size of stimulation site: 12 cm^2 (Somedic©) or 9 cm^2 (Medoc©).

Only laser stimuli that are non-injurious and acceptable to the participant will be used. The laser used to produce painful sensations may cause temporary redness lasting about 20-30 minutes over the skin where it is applied. The main risk is accidental eye damage due to direct or reflected laser beams. To minimise the risk, trained researchers will ensure that all precautions according to University safety guidelines are taken, which includes both the researcher and participant wearing the appropriate safety goggles to protect the eyes whenever the laser is used. All researchers involved in the use of the laser must be trained according to University laser safety guidelines to minimise risk. All procedures currently used in the lab have been amended to adhere to the University laser policy as reviewed by the Health Protection Agency. The Nd:YAP laser (DEKA©; wavelength of 1340 nm) in the WIN pain laboratory has been certified for energy levels between 0.5 and 15 J, a pulse length of 1-20 ms and a spot diameter of up to 15mm.

To define precisely the parameters of thermal stimulation, both skin temperature and skin thickness may be measured using an infrared thermometer, thermal camera and a confocal microscope. These measurement methods are safe and non−invasive. Thermal stimuli have been safely used as part of the WIN pain research programme in other approved pain research.

(iii) Cold Pressor Task:
The cold pressor task (CPT) involves either placing a hand or forearm in cold water, or application of gel ice packs to a hand, forearm or lower leg. This induces a slowly mounting pain that dissipates quickly on withdrawal of the limb from the water or removal of the ice packs. The CPT is considered safe under the following conditions:

The exclusion criteria for this task are:

- history of cardiovascular disorder
- history of fainting or seizures
- history of frostbite

- open cut or sore on limb to be immersed or to which the ice packs will be applied
- fracture of limb to be immersed or to which the ice packs will be applied
- history of Reynaud's Phenomenon (hands get white, then blue, on exposure to cold, then red on warming)

The skin temperature level should not be lower than 1°C. Temperatures between 1°C and 5°C are commonly used with adult participants. Note that lower temperature levels lead to shorter tolerance times and higher drop-out rates.

Water immersion: The unclenched hand is to be immersed up to 5cm above the wrist, in a comfortable position. The participant is free to withdraw the immersed limb from the water at any time.

Gel ice packs: Gel ice packs are attached to the forearm or lower leg using Velcro straps. The participant is free to remove the ice packs at any time.

Reference

Porcelli, A.J. An Alternative to the Traditional Cold Pressor Test: The Cold Pressor Arm Wrap. J. Vis. Exp. (83), e50849, doi:10.3791/50849 (2014).

(iv) Electrical Pain:

For electrical pain, an electrode is applied to the skin surface, after it has been prepared with a cream that enhances conductance. Controlled current is applied only to this prepared surface area, without passing internally into the body. Equipment, such as Digitimer DS7A, Hertfordshire, UK, will be used to elicit a low-level of electrical output that is sufficient to induce a moderate-to-strong pain sensation. Equipment is certified for an output current of 0-100 mA, a source voltage of 100-400 V and stimulus durations between 50 μs to 2ms. Electrical stimulation has been safely used previously in approved studies conducted in the University.

(v) Chemical Stimulation:

Chemical stimulation will be administered by applying low-doses of capsaicin (the active ingredient that gives chilli peppers their hot taste) or menthol (a cooling agent) to the surface of the skin. Capsaicin can produce a moderate burning sensation, which may last for a few hours even after removal of the capsaicin cream. Capsaicin cream has been used safely when applied in accordance with the following parameters:

- Dose: 1% Capsaicin
- Volume: 5 ml
- Surface Area: 2x3 inch
- Exposure: 2 hours [maximum] in any 48-72 hour period

If necessary, capsaicin-evoked burning sensations can be instantly relieved by removing the capsaicin cream and applying a cold stimulus to the site where the cream was applied. Any skin tenderness that is experienced should return to normal after a couple of days and there are no known long-term side effects. Participants will be given contact details to get in touch with a researcher in the event that skin does not return to normal within 48 hours of chemical stimulation.

Menthol may produce a moderate cooling sensation that can last for a few hours, which may remain for a period of time after removal of the menthol cream. Menthol is a well-known cooling agent that on contact would act to cool the skin and/or reduce or eliminate capsaicin-induced burning sensations. When using menthol, a low dose concentration (max: 2%) will be used to cover

the site of the skin being treated. For most participants, the volume of cream needed will approximately be 10 ml spread over a small surface area of the skin. Menthol cream can be removed immediately at any time to stop the sensation.

Chemical stimulation has been safely used as part of the WIN pain research programme in other approved pain research:

Reference

Segerdahl, A. R., Mezue, M., Okell, T. W., Farrar, J. T., & Tracey, I. (2015). The dorsal posterior insula subserves a fundamental role in human pain, Nature Neuroscience 18(4), 499–500. http://doi.org/10.1038/nn.3969

(vi) Others:

In order to investigate different aspects of the pain experience other sensory stimuli (e.g., visual, auditory, olfactory) may be administered using standard experimental equipment. Examples of this may include: word cues, facial cues, auditory tone cues, or flashing checkerboards. These techniques are not harmful and are widely used at WIN/OCMR, and elsewhere in the University.

1.2 Behavioural measures

The behavioural measures listed below are commonly used clinical methods of gauging general physiological measures of a participant's overall health, and allow the researcher to ensure that the participants are healthy and awake throughout the research procedure. The different pain rating scales are essential for collecting perceptual data about how each participant perceives the different stimuli. These data can be useful in terms of explaining the different neurophysiological recordings (e.g. whether the magnitude of Blood Oxygen Level Dependent MRI (BOLD) activation correlates with the intensity of perception).

(i) Physiological monitoring:

a) heart rate and other cardiac measures (MRI-compatible ECG electrodes are available)
b) oxygen saturation (using pulse oximeter)
c) breathing rate (using respiratory bellows)
d) CO_2 via nasal cannulae
e) Galvanic Skin Response using surface electrodes
f) eye-blink conditioning (using surface EMG or non-invasive eyetracker)

(ii) Rating Scales:

a) Visual Analogue Scale (VAS)

The VAS is a measurement instrument that tries to quantify a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain a person feels ranges across a continuum from none to extreme amount of pain. This can be translated by the use of a scale with two anchors of extremes on either side.

b) Numerical Rating Scale (NRS)

Employs the same continuum as the VAS but includes a numerical spectrum. For example, in the case of a painful sensation, no pain/sensation = 0; while an intense pain = 10. The numerical value could vary depending on the resolution required.

c) Graphic Rating Scale (GRS)

The GRS is a commonly used self-report instrument (Jensen and Karoly, 1992). It consists of a scale that is anchored with descriptive adjectives related to the magnitude of a particular subjective experience. For example, a common application of the GRS is to quantify the extent to which a

particular stimulus experienced by the participant was lower or higher than expected. Here, the scale is anchored by -5 on the left side of scale (lower than expected) and +5 on the right side of the scale (higher than expected). The GRS can also be used to gauge how distracted the participant was by a particular stimulus. Here, the scale is anchored with 0 (not at all distracted) and 10 (very strongly distracted).

d) Categorical Rating Scale.

Used in circumstances where either the NRS or VAS are inappropriate. Here, participants are asked to assign an adjective to best explain their pain (e.g. none, mild, moderate, or severe).

e) Quality of perception.

After each stimulus presentation, participants will be asked to qualify the perceived sensation, using a predefined list of descriptors (e.g. 'tingling', 'pricking', 'warm', 'burning', 'touch'…).

(iii) Questionnaires:

Questionnaires are a clinically common, widely used method of accounting for essential psychological factors that are known to affect pain perception. Specific details of each questionnaire will be listed in research-specific applications. Participants will be instructed to complete questionnaires at a designated time either before or after the research procedure(s). Participants will complete the questionnaires and all data must be anonymised and entered into an electronic database that must be stored on a secure server (see Data Management and Protection below). Anonymised paper and pencil versions of questionnaires must be kept confidential, stored in a secured filing cabinet. The data will be available only to the primary researcher conducting the research. Detailed explanation of each questionnaire must be given, as will the participants' rights to confidentiality.

(iv) Other Behavioural Measures:

a) Reaction times

A timer is initiated upon the onset of the sensory stimulus. The participant is asked to press a button upon perception of the stimulus. Pressing the button halts the timer. The reaction time is measured as the delay (in milliseconds) between the onset of the stimulus and the motor response. The average reaction-time measurement, as well as their distribution, will be compared across experimental conditions.

b) Decision

The participant is prompted to select an option (e.g. yes or no) with the use of a button box or a rating scale.

c) Nociceptive reflexes

To assess the nociceptive flexion reflex, EMG activity is recorded from the biceps femoris muscle (using surface electrodes) following electrical stimulation.

1.3 Cognitive-affective modulations of pain

The psychological paradigms listed are commonly used techniques to gauge different aspects of a person's engagement and experience of pain. Each test is designed to study a separate component of this complex experience. The main psychological components of interest are those factors known to be associated with, and affect the experience of, pain. The aim of such research is to see how these factors correlate with and affect pain perception in different participants who have variable personality influences that additionally modify the experience. Each of these measures are commonly used in clinical practice and primarily rely on participants filling out questionnaires or scales during experimentation (see Section: Behavioural Measures), where researchers might have manipulated one component of, for example, their attention or mood state, by classical conditioning task often using visual or auditory inputs, to change their pain experience. Results from each paradigm can be used to explain how each component of pain perception changes the results

acquired with the neurophysiological recordings (e.g. whether a person's emotional state changes the relationship between BOLD activation and the intensity of pain perception).

All measures listed were ethically approved previously for use at WIN and OCMR.

Pain perception is influenced by certain individually specific psychological features such as personality, emotion, attention, anxiety, depression and beliefs. In this way, it is important to measure and control for these aspects of the pain experience. These would be monitored through the use of behavioural measures such as scales and/or questionnaires during testing. All of the above features have been approved previously by NHS ethical review, as follows:

a) Personality
   07/Q1605/4 "Personality and pain perception; PI: Prof. Irene Tracey; NRES
b) Emotion
   C02.086 "Mapping brain function with fMRI"; PI: Prof. Paul Matthews; COREC
   09/H0604/90 "Perceptual decision-making in the context of pain"; PI: Prof. Irene Tracey; NRES
c) Attention
   C02.086 "Mapping brain function with fMRI"; PI: Prof. Paul Matthews; COREC

2. TRAINING OF RESEARCH STAFF

All researchers will complete Research Ethics and Integrity or Good Clinical Practice (GCP – for clinical studies) training in order to be involved in research involving human participants under this procedure. All researchers involved with MRI are required to undergo annual MRI safety training – failure to undergo this training will automatically involve revocation of access to the centres. All researchers involved in data acquisition will undergo safety training for the stimulation device they intend to use.

Where MRI is also used, all scanning will be conducted by a fully trained MRI operator or registered radiographer.

3. METHODS FOR RECRUITING PARTICIPANTS

Potential participants will be identified by one of the methods outlined on the CUREC application. When a potential participant registers interest, further information (prepared using the associated template information sheet) will be sent, together with details as to how to confirm they would like to take part. Contact details of researchers will be detailed in individual adverts and Information Sheets.

This Approved Procedure also covers recruitment of participants from the community (general public) as well as students and staff of the University of Oxford and Oxford Brookes University. It does not cover participants recruited as having particular symptoms (e.g. low mood, chronic pain).

4. INFORMATION PROVIDED TO PARTICIPANTS

The information provided should be appropriate to your specific research and presented in an accessible way. If there is not enough information, potential participants might not be able to make an informed decision. On the other hand, if the information sheet is too long or unclear (e.g. through using overly-technical language) they might not read it properly or it could deter them from taking part. Most word-processing packages provide readability statistics for a document, and one should aim for a 12-year-old (Year 7) reading level for adults.

Please refer to, and use, the template **Information Sheet associated with this Approved Procedure.**

5. CONSENT OF PARTICIPANTS

Written consent will be obtained from all participants using the **Consent Form associated with this Approved Procedure.**

Written consent will be obtained from all participants on the day of the first session, following a suitable (at least 24 hour) period during which they will have had an opportunity to read the Information Sheet and discuss their participation with others and with the researchers. An experienced researcher will answer all and any questions before consent is obtained. Consent will be taken by a member of the research team who has appropriate training, as confirmed by the Principal Investigator. Participants will be reminded that they are able to change their mind and withdraw from the research at any point without penalty. Vulnerable populations or participants who are unable to provide informed consent in English are not covered by this Approved Procedure.

Copies of the signed consent forms will be provided to the participants along with the information sheet. The originals, along with the TMS safety questionnaires administered before every session, will be kept in the files of the researchers.

Please also see CUREC's guidance on the informed consent process.

6. COMPENSATION

Compensation (either financial or in kind) may be offered to participants for their time and inconvenience incurred, as well as reasonable travel expenses. Some studies (for example, those investigating reward processing) may offer a performance-related reward. Individual research proposals will detail the value (if any) of compensation to be offered. The amount may be stated on the Participant Information Sheet, but cannot be disclosed on the advert as this could be coercive.

Consideration should be given to how and when participants are told about any recompense. Participant information sheets and recruitment materials should state that recompense will be made so that potential participants are not discouraged from participating by the associated costs. If reimbursement values are included, advertisements must not emphasise the value of the payment (for example, through the use of formatting). Further guidance is available within CUREC's Best Practice Guidance 05 on Payments and incentives in research.

7. POTENTIAL RISKS TO PARTICIPANTS/RESEARCHERS/OTHERS AND WHAT WILL BE DONE TO MINIMISE

Risks associated with imaging techniques (MRI, EEG, MEG) and methods to meet them are described in Approved Procedures 17 for MRI, 03 for EEG, and 08 for MEG).

All stimuli that are used to experimentally induce pain have been safely used as part of the WIN pain research programme in ethically approved research. The minimal intensity of noxious stimuli necessary to achieve goals of the research is established. The stimulation intensity does not exceed the individual tolerance level. Participants are always able to terminate a painful stimulus at will.

However there are a few possible risks:

Laser. In some cases, application of laser stimuli may produce a slight punctate erythema. On rare occasions, these spots may subsequently become hyper pigmented. They always vanish completely within a few days. The main risk is accidental eye damage due to direct or reflected beams. To minimise this risk, trained researchers must ensure that all precautions according to local safety guidelines are taken, which includes both the researcher and participant wearing the appropriate safety goggles to protect the eyes whenever the laser is used. All researchers involved in the use of the laser must be trained according to University laser safety guidelines to minimise risk. All procedures currently used in the lab must be amended to adhere to the University laser policy as reviewed by the Health Protection Agency.

Contact thermode. Regarding the thermal device, the stimuli used to produce painful sensations may produce temporary redness lasting about 20-30 minutes over the skin where it is applied, when used repeatedly. However, an upper limit must be set to prevent permanent skin damage and calibrated to each participant's tolerable limits. See also Documentation on Pathway Safety and Regulatory Summary for the Medoc® Pathway Device.

Chemical stimulation. Although the risks associated with the use of chemical stimulation – specifically capsaicin and menthol - are low, risk potential increases without appropriate training. Therefore, it is the responsibility of the individual researcher to undergo training and approval for capsaicin use by a member of the WIN pain group and to adhere fully to standard operating procedures set out for capsaicin use. The main risk when using chemical stimulation is the accidental irritation of non-target areas of skin of either the researcher or participant when applying the creams. To minimise this risk, trained researchers must adhere to all precautions according to local standard operating procedures, including wearing disposable gloves and protective eye-wear when applying or removing creams. To reduce chance of eye exposure during the clean up stage, it is advisable when removing cream that participants also wear protective eyewear, or that they are asked to look away.

8. MONITORING AND REPORTING OF ADVERSE OR UNFORESEEN EVENTS

Adverse or unforeseen events associated with MRI scanning are covered in CUREC_AP_IDREC_17 and for MEG in CUREC_AP_IDREC_08.

In the unlikely event that noxious stimulation produces an adverse event, the participant should immediately be referred to an appropriate clinician.

9. COMMUNICATION OF RESULTS

Research results may be written up for publication in peer-reviewed scientific journals, presented at scientific conferences (in abstract or presentation formats), entered into anonymised repositories of imaging data, submitted as part of course degrees and may form part of grant applications. In all cases, results will be anonymised and not contain any data that could be linked to the participants.

10. DUTY OF CARE ISSUES / CONFIDENTIALITY

Personal data (such as date of birth, and personal questions relating to MRI safety) as well as questionnaire responses may be necessary for individual studies. Information Sheets will detail this and explain that any personal information will be anonymised wherever possible, and information about participants maintained in strict confidentiality.

Some studies may use validated questionnaires asking participants about state and trait anxiety and/or depression to interpret how these factors influence processing and perception of research

stimuli. These questionnaires are not to be used for recruitment or screening purposes. However, if a researcher, as a result of these questionnaires, has concerns that a participant may have an undiagnosed psychiatric condition that is causing distress, CUREC guidance (BPG 08) will be followed. The researcher must seek advice from the Principal Investigator who may discuss the symptoms in greater detail with the participant and/or offer the opportunity to speak with a senior clinical researcher if they are not clinically trained themselves.

11. DATA MANAGEMENT AND PROTECTION

Participants' informed consent must be obtained for participation in the research, which includes the collection, storage and retention of all data related to the research. Directly identifiable personal information held by the research team (such as contact details, consent forms and screening forms, which include name or other identifiers) must be held securely - either in paper format in lockable filing cabinets with access only by the University researchers, or in a password-protected database, on an encrypted machine or on a protected server. These should be servers provided by the University where the risks and access have been professionally managed. Other servers will require security assessment by University Information Security. Other research data (e.g., EEG files, behavioural reaction time files, questionnaires) must be labelled with a code number rather than a name or initials, and accessed via a password- and firewall-protected server.

The keys linking personal details to the codes used to label other research data may be kept in paper format in lockable filing cabinets with access only by the researchers, or in a password protected spreadsheet on University approved servers. The keys should be kept separately from other research data. Such keys should be destroyed as soon as no longer needed, as should other personal data (with due regard to University and other guidelines on data retention, e.g. of consent forms).

Contact details may be retained after the end of the research where the participant agrees to be contacted for future studies. These should be held separately from the research data, and a copy of the consent form retained as evidence of agreement to be contacted. For participants who do not wish to be contacted in the future, contact details will be destroyed as soon as possible after completion of their research participation. Personal and research data may be viewed by regulatory bodies and designated individuals within the University of Oxford for the purposes of monitoring and auditing the research with the written consent of the participant.

Anonymised data may be shared with other research institutions, including researchers outside of the UK and the EU, for use in other and future research studies. For detail on anonymisation, please refer to the Information Commissioner's Office (ICO) Code of Practice –'Anonymisation: managing data protection risk', especially Appendix 2 and Annex 1.

Where data has been anonymised (all identifying information removed, including any linkage document), there is no limit as to how long this may be retained by the researchers. However, the period of retention should be stated on participant information.

Sharing of Data

Research teams will be encouraged to make their data available for reuse and validation. In all cases, the data will be shared as openly as possible and as closed as necessary in order to protect the privacy of participants. Online repositories will be assessed by research teams for their appropriateness with regard to:

- the required treatment and de-identification of unique brain and biometric data in line with UK GDPR;

- control of how the data are accessed and re-used, including terms to protect the ongoing privacy of participants;
- required attribution of the data to the originating research team, the University and funding bodies;
- management of data withdrawal requests made by participants.

Authorised scanning centre personnel and investigators listed as being on the research team will have access to any MRI data. MRI data is automatically coded at source and stored with a unique key in a secure database within the scanning system. Such data thus retains a link to direct identifiers within the scanning sytem, even after destruction of research personal data. Imaging data held by scanning facilities will be stored on archive tapes indefinitely, even if the participant withdraws from the research they are enrolled in, and this must be explained to participants when obtaining their informed consent for data collection and retention.

12. FURTHER INFORMATION

Template consent form, participant information sheet and poster adverts exist for this Approved Procedure and should be used.

13. CHANGE HISTORY

Version No.	Significant Changes	Previous Version No.
2.0	Incorporates reference to the University Safeguarding Code of Practice and related requirements. Retitled `Approved Procedure' (previously `Protocol'). Approved by CUREC, 19 November 2015	N/A
3.0	Incorporates the use of chemical stimulation - namely capsaicin and menthol – and possible risks Incorporates the use of MEG as a measurement tool Removed protocol for the outcome of the identification of a brain abnormality during scanning as this is covered by the approved procedure on MRI scanning in healthy volunteers. Re-wording of information sheet section for clarity and guidance.	2.0
4.0	Removed requirement of study documents to be reviewed by CTRG prior to submission to the relevant IDREC. Updated document references for CUREC guidance.	3.0
5.0	Addition of pain induced by the cold-pressor method	4.0
5.1	Updated hyperlinks for new CUREC website	5.0
5.2	Changed references of Functional Magnetic Resonance Imaging of the Brain (FMRIB) to Wellcome Centre for Integrative Neuroimaging (WIN)	5.1
5.3	Addition of the option of ice packs for the cold pressor task	5.2
5.4	Updated to improve accessibility	5.3

Version No.	Significant Changes	Previous Version No.
5.5	Administrative revisions. Complete update of data management section – text approved by CUREC Nov 2021	5.4
6.0	Quinquennial Review, resulting in minor changes to text	5.5