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Evaluating the efficacy of intranasal oxytocin on pain and function among individuals who experience chronic pain: A multisite, placebo-controlled, blinded, sequential, within-subjects crossover trial.

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Abstract

Introduction: Current treatments for chronic pain (e.g. opioids) can have adverse side effects and rarely result in resolution of pain. As such, there is a need for adjuvant analgesics that are non-addictive, have few adverse side effects, and are effective for pain management across several chronic pain conditions. Oxytocin is a naturally occurring hormone that has gained attention for its potential analgesic properties. The objective of this trial is to evaluate the efficacy of intranasal oxytocin on pain and function among adults with chronic pain.

Methods and Analysis: This is a placebo-controlled, triple-blind, sequential, within-subject crossover trial. Adults with chronic neuropathic, pelvic, and musculoskeletal pain will be recruited from three Canadian provinces (BC, AB, and NL, respectively). Enrolled patients will provide one saliva sample pre-treatment to evaluate basal oxytocin levels and polymorphisms of the oxytocin receptor gene before being randomized to one of two trial arms. Patients will self-administer three different oxytocin nasal sprays twice daily for a period of 2-weeks (i.e. 24 IU, 48 IU, and placebo). Patients will complete daily diaries including standardized measures on days 1, 7 and 14. Primary outcomes include pain and pain-related interference. Secondary outcomes include emotional function, sleep disturbance, and global impression of change. Intention-to-treat analyses will be performed to evaluate whether improvement in pain and physical function will be observed post-treatment.

Ethics and dissemination: Trial protocols were reviewed by the Newfoundland and Labrador Health Research Ethics Board (HREB #20227), University of British Columbia Clinical Research Ethics Board (CREB #H20-00729), the University of Calgary Conjoint Health Research Ethics Board (REB20 #0359), and Health Canada (Control # 252780). Results will be disseminated through publication in in peer-reviewed journals and presentations at scientific conferences.

Registration: This trial is registered on ClinicalTrials.gov (Registration # NCT04903002)

Strengths and limitations of this study:

- The effect of oxytocin will be evaluated across different chronic pain presentations (i.e. musculoskeletal, pelvic and neuropathic pain), and clinically-relevant outcomes will be measured as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)
- Two doses of oxytocin will be administered, to evaluate a dose-response relationship.
- The effect of oxytocin will only be evaluated over a 2-week period, precluding longer-term assessment.

- The 48-IU dosing is the last course of treatment in both trial arms which may introduce expectancy effects due to incomplete blinding at this dose.
- Saliva samples will be collected to measure basal oxytocin levels and polymorphisms of the oxytocin receptor gene as potential moderators of treatment effect.

1.0 Introduction:

In 2011 the Institute of Medicine concluded that chronic pain, defined as pain that persists longer than 3-months or beyond the expected duration of healing,[1] is a public health concern and should be treated as a disease itself.[2] Nationally representative data indicates that 20% of Canadians over 18 years of age[3] and 15% of children[4] suffer with chronic pain. The prevalence of chronic pain increases with age. Approximately 65% of community dwelling seniors and 80% of older adults living in care facilities experience chronic pain.[5]

Currently available treatments for chronic pain rarely result in complete resolution of symptoms,[6] and often do not produce concomitant improvements in physical and emotional functioning.[7] For example, a 2018 meta-analysis reported that 1 in 8 patients respond to opioid medication with a mean 6.9mm (on a 100mm visual analogue scale) reduction in pain, small improvement in physical function and no improvement in mental function.[8] Moreover, current pharmacological treatments for pain, including opiates, are often addictive, associated with adverse effects,[9,10] and have limited effectiveness in areas such as neuropathic pain. Given the gap between suffering and adequate pain management, there is a need for analgesics that are safe, non-addictive, have low adverse effect profiles, and offer effective relief for a variety of painful conditions.

Intranasal oxytocin has gained increasing attention in recent years and has demonstrated promising results for pain management.[11-13] Oxytocin is a neuropeptide that is produced naturally in the supraoptic and paraventricular nuclei of the hypothalamus.[14] It is released peripherally into the bloodstream via the posterior pituitary, and into the central nervous system via paraventricular neurons.[15] New evidence from several sources, including our team, suggests that oxytocin is a safe method for decreasing sensitivity to pain with a low risk of adverse effects.[12,13] There are three mechanisms through which oxytocin may decrease pain sensitivity.[12] First, a hypothalamic-spinal

projection originating from the paraventricular nucleus transports oxytocin to the dorsal horn (Lamina-I, II, and IV),[15] an area involved in pain modulation. A subset of neurons in the dorsal horn (~35%) contain oxytocin receptors that influence glutamatergic neurons which, in turn, activate GABAergic neurons, resulting in an inhibition of pain-carrying Aδ- and C-fibers.[16-18] Second, evidence suggests that oxytocin binds to opioid receptors and may stimulate endogenous opioid release in the brain. An opioid system located in the periaqueductal gray activates a series of descending controls that prevent spinal cord transmission regarding injury.[19] Oxytocin administered to the periaqueductal gray results in antinociception that can be blocked by the administration of an opioid antagonist.[20,21] Further, analgesic effects of endogenous and exogenous oxytocin can be blocked by the opioid antagonist naloxone.[22] The final mechanism involves improving mood, decreasing anxiety, and mitigating the stress response. In an informative controlled trial, intranasal administration of oxytocin in men resulted in greater calmness, less anxiety, and a trend toward lower cortisol during the Trier Social Stress Test.[23] Given that negative emotion inductions (e.g., anxiety, sadness, anger) are associated with increased reports of pain,[24-26] along with concomitant heightened autonomic responses,[25] oxytocin may decrease pain sensitivity by improving mood and anxiety, and buffering the stress response.

Preliminary evidence suggests that oxytocin may be a safe and effective adjuvant analgesic that is applicable to a broad patient population. Our team published a systematic review of the effect of oxytocin on pain in animals and humans.[12] Oxytocin had a reliable effect as defined by increasing pain tolerance in 29 out of 33 animal studies reviewed. This effect was large (standard mean difference = 2.28), and persisted across central and peripheral modes of administration, and various noxious stimuli (e.g., heat, electric, chemical).[12] Results from research into the association between oxytocin and pain in humans has been more variable and is associated with considerable methodological heterogeneity and quality. For example, two studies have assessed associations between oxytocin and pain using experimental pain procedures in healthy adults, reporting a decrease in pain sensitivity to finger prick,[27]

and no difference in pain-unpleasantness to electric shock.[28] While interesting, interpreting the results is difficult due to methodological concerns including insufficient sample size, one-dimensional pain measurement,[28] and use of a poorly described finger prick pain procedure.[27] Our team conducted the first methodologically rigorous placebo-controlled, blinded, within-subjects crossover trial evaluating the effect of intranasal oxytocin on acute pain.[29] We observed clinically meaningful effects of oxytocin on pain, particularly neuropathic indicators. With regard to chronic pain, oxytocin administration has been reported to lower pain sensitivity among patients experiencing chronic back pain,[30] headache,[31] constipation,[32] and colon pain.[33] It has been difficult to draw firm conclusions about the association between oxytocin and chronic pain in humans from these trials, however, due to design issues, including the lack of an adequate control condition,[31] use of a delivery method with a high likelihood of confounding pain assessment (e.g., intrathecal punch),[30] peripheral administration,[33] or the recruitment of a sample size that was inadequately powered to detect meaningful effects.[32,34] Further, no trial to date has assessed all clinically relevant outcomes endorsed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) - an international group of experts that develop recommendations to improve the design, execution, and interpretation of clinical trials of treatments for pain.[35]

Given the heterogeneity of extant trials, we propose a methodologically rigorous trial evaluating the efficacy of intranasal oxytocin on pain and function among men and women with chronic pain that evaluates clinically relevant outcomes endorsed by the IMMPACT.[35] Potential mediators and moderator of treatment effects will be assessed using basal oxytocin levels and polymorphisms of the oxytocin receptor gene measured using salivary assays given that: 1) chronic pain patients exhibit low basal oxytocin levels relative to controls,[30,36,37] and may reflect underlying abnormality in the oxytocinergic system;[12] and 2) relative to those with an rs53576 A allele, individuals with a rs53576G/G oxytocin receptor genotype show reduced amygdala,[38] neuroendocrine,[23] and stress

reactivity across a range of contexts,[39,40] and report greater benefit from social support[41] following oxytocin administration. This represents a movement towards precision medicine.

1.2 Research Questions: We will evaluate the efficacy of intranasal oxytocin when used as an adjuvant treatment (i.e., in addition to usual therapies) for improving pain and function (physical and emotional) among men and women with chronic neuropathic, musculoskeletal or pelvic pain.

Primary Hypotheses: Relative to placebo, patients will report greater improvement in: 1) pain intensity; and 2) physical function measured using the Brief Pain Inventory (BPI-SF) following a 2-week course of twice-daily 24-IU or 48-IU intranasal oxytocin administration.

Secondary Hypotheses: Patients will report improvement in emotional function, sleep, and global impression of change following intranasal oxytocin administration relative to placebo.

Exploratory Questions: Potential mediators and moderator of treatment effects will be assessed using basal oxytocin levels and polymorphisms of the oxytocin receptor gene measured using salivary assays. This represents a movement towards precision medicine.

2 The Proposed Trial

2.1 Design and Trial Registration.

A multi-site, placebo-controlled, triple-blind, sequential, within-subject crossover trial evaluating the efficacy of intranasal oxytocin on pain and function among patients with chronic pain. This is a basket trial consisting of heterogenous populations of chronic pain conditions from multi-sites across Canada. This trial will be conducted in compliance with the trial protocol, good clinical practice, institutional ethics boards and applicable regulatory requirements, and is registered on ClinicalTrials.gov # NCT04903002.

2.2 Study Settings.

There is increasing recognition that most common chronic pain conditions are heterogeneous with a high degree of overlap and that most patients enrolled in clinical trials are not representative of community dwelling chronic pain patients.[42] As such, there will be four participating sites across three provinces, each province recruiting a different primary neuromusculoskeletal (NMSK) pain population. Adults with chronic neuropathic pain be recruited from the Jim Pattison Outpatient Care & Surgical Centre Pain Clinic (JPOCSC-PC; Surrey, BC) and the Initium Centre for Pain Management (ICPM; Abbotsford, BC). The JPOCSC-PC is a multi-disciplinary centre that accepts referrals from a catchment area of 2-million people. 2,000 patients are seen per month, of which approximately 20% present with chronic neuropathic pain. Consecutive women with chronic pelvic pain will be recruited from the Calgary Chronic Pain Centre (Calgary, AB) and directly from the gynecology clinics of MR and MN. The waitlist for an assessment of chronic pelvic pain is approximately 500 patients. Consecutive adults with chronic musculoskeletal pain will be recruited from the Carbonear General Hospital (Carbonear, NL). Approximately, 40 patients with chronic pain are seen each week, of which approximately 60% present with primary shoulder, neck, or back pain.

2.3 Patient Eligibility.

2.3.1 Inter-Site Inclusion Criteria: 1) Adult (> 18 years) men and premenopausal women; 2) On stable medication for pain management for 3 months or more with no anticipated changes during the 10-weeks of this trial; 3) Moderate pain at baseline (i.e., a score of 4-8 on a 10-point numeric rating scale) to prevent floor and ceiling effects; and 4) Can commit the use of two forms of effective contraception (e.g., barrier methods), or one highly effective method, including abstinence, intrauterine device, intrauterine system (IUS), vasectomy, tubal ligation, or hormonal contraceptive (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants).

2.3.2 Inter-Site Exclusion Criteria: 1) Positive urine pregnancy test or contemplating pregnancy; 2) Concurrent use of another nasal spray; 3) Nasal pathology (e.g., ears, nose, and throat diagnosis); 4) Diabetes insipidus; 5) Current diagnosis or history of cancer; 6) Significant unmanaged psychopathology (e.g., severe depression as indicated by a score ≥ 15 on the Patient Health Questionnaire -9[43]) due to its inverse association with patient adherence to procedures;[44] 7) receiving hormone treatment for gender-related motivations; 8) documented cardiovascular event (e.g., myocardial infarction); 9) known prolongation of the QTc interval; 10) known hypersensitivity to oxytocin; 10) known latex allergy; or 11) known or suspected renal impairment. Exclusion criteria will be vetted through a review of patient medical records and self-report given the concordance between self-report and medical diagnosis.[45]

2.3.3 Intra-Site Criteria:

***Surrey & Abbotsford, BC*:** Men and women with primary neuropathic pain - pain arising as a direct consequence of a lesion or disease affecting the central or peripheral nervous system[46] - will be eligible. Neuropathic pain will be screened for using a score of 3+ on the Douleur Neuropathique 4 Interview,[47]and confirmed on clinical assessment.

Calgary, AB: Women with chronic (intermittent or constant) pelvic musculoskeletal pain (i.e., located primarily in the pelvic region and reproducible on palpation of the pelvic floor) who have not received a hysterectomy will be eligible. Women with a primary diagnosis of endometriosis, dysmenorrhea, functional bowel disorder, interstitial cystitis, fibromyalgia or sacroiliac instability as defined by European Guidelines,[48] will be excluded.

***Carbonear NL*:** Men and women with primary musculoskeletal pain of back, neck, or shoulder origin will be eligible. Pain will be assessed using the BPI-SF and confirmed through physical examination.[49,50]

***Across Sites*:** Adults with multiple chronic pain conditions will be eligible to participate so long as their primary pain complaint meets eligibility criteria. Recruiting different primary NMSK presentations will allow us to evaluate the generalizability of intranasal oxytocin across common chronic pain presentations typically observed within the community and may allow for improved optimization of treatment in future work.

2.4 Procedure

2.4.1 Patient recruitment, screening and enrollment. Potentially eligible patients will be approached by a member of our study team during their regularly scheduled appointment at the clinic, and receive information about the objectives of the trial. Interested patients will undergo screening, including: 1) completion of a urine pregnancy test; blood work to evaluate renal impairment (as defined by an eGFR <45 by the Cockcroft-Gault equation) if the history suggests any stage or renal insufficiency, including history of diabetes, inflammatory diseases, hypertension and no Creatinine has been drawn in the last 2 years; and 3) ECG to evaluate prolongation of the QTc interval among anyone who may be at risk, including those prescribed antidepressant medication. Patients who meet all eligibility criteria will be randomized to study arm before completing a baseline assessment.

2.4.2 Randomization, Allocation and Concealment.

The commercially available software, https://app.studyrandomizer.com/ will be used to generate a list of randomly sequenced numbers for assigning patients to condition in a manner outlined in CONSORT reporting guidelines.[51,52] As depicted in Figure 1, patients will be randomized to one of two sequences: 1) 24-IU oxytocin, placebo, 48-IU oxytocin; or 2) placebo, 24-IU oxytocin, 48-IU oxytocin. Central randomization stratified by province (BC, AB, NL) and performed using a 1:1 allocation schedule with permuted blocks of 4 and 6. Sex will be added as an additional stratification factor for sites in BC and NL. The lists will be uploaded on a web-based password protected randomization system. When an

eligible participant consents to the study, randomization website will be contacted through a closed system and randomization code will be assigned to the participant. Automated audit trails will document the patient allocation number and treatment sequence, and the date and time of transaction.

2.4.3 Blinding.

This is a triple-blind study. In order to protect against expectation effects and biases, neither site investigators nor patients will know which nasal spray contains oxytocin or which sequence of conditions patients are assigned. The allocation sequence will be concealed from researchers using automated randomization. The bottles containing 24-IU oxytocin, 48-IU oxytocin, and placebo will be identical in appearance, smell, texture and taste, and only identifiable through a color labeling system known to the site pharmacists and study sponsor. Each provinces randomization sequence will be accessed by the site pharmacist and bottles prepared accordingly. Neither the RA assessing outcomes nor the statistician performing analyses will be unaware of condition. Patient blinding can be broken in the case of an adverse event (e.g., emergency department attendance). Patients will be provided a study card with a number to call to reach the central administrator who can de-identify condition in the unlikely case of an adverse drug reaction. The decision to unmask will be made on a case-by-case basis and will depend on potential risk.

2.4.4 Baseline Assessment.

Baseline assessments will involve: 1) completion of study measures, refer to Table 1; 2) collection of approximately 4mL of saliva into Cryovials using a standard unstimulated passive drool technique. Saliva samples will be frozen until shipped to Salimetrics for analysis of salivary oxytocin concentration and genetic polymorphism in the oxytocin receptor gene OXTR rs53576; and 3) training on procedures for nasal spray administration. Patients will be provided with the option of completing baseline assessments immediately following randomization, or scheduling a convenient time within 2-

weeks. Baseline assessments for women will be scheduled to occur within close proximity to the start of the luteal phase of the menstrual cycle (i.e., days 14-28) as this is the stage during which women report greatest pain.[53] Due to the impact of the global pandemic, patients will have the option of completing study measures virtually. Patients will attend clinic to provide a saliva sample, undergo nasal spray training, and receive their assigned nasal spray. Clinic attendance will be scheduled in the afternoon to avoid diurnal fluctuation in saliva oxytocin. Patients will be asked to avoid foods with high sugar, acidity, or caffeine 1-hour prior to visiting the clinic as these can confound saliva assays.

Table 1.

Schedule of assessments

		Randomization		2-week diaries			
Testing Variables	**Phone Screen**	**Baseline**		**Daily Diary**	**Day 7 of Diary**	**Day 14 of Diary**	**Follow-up**
Inclusion Criteria	X						
Sociodemographics		X					
Medical History		X					
Vitals		X					X
Pain NRS	X			X			X
BPI-SF Intensity		X			X	X	
BPI-SF Interference		X			X	X	
Emotional Function							
Mood		X		X			
DASS		X			X	X	
Sleep		X			X	X	
Global Impression of Change						X	
Expectancy		X					
Side Effects						X	X

BPI-SF = Brief Pain Inventory - Short Form; DASS = Depression, Anxiety and Stress Scale

2.4.5 Trial Interventions.

The intervention will span three 2-week conditions (24-IU, 48-IU and placebo) and two 2-week wash-out periods for a total duration of 10-weeks.

Experimental Condition.

There will be two experimental conditions. *Experimental Condition 1*: Patients will self-administer a 2-week course of 24-IU intranasal oxytocin [4-IU per puff (12-IU delivered to each nostril); Syntocinon,

Novartis, Switzerland], twice per day (once in the morning and once in the evening). *Experimental Condition 2*: Patients will self-administer a 2-week course of 48-IU intranasal oxytocin [4-IU per puff (24-IU delivered to each nostril)], twice per day. Given that treatment adherence is crucial to treatment success, we will ensure standardization of nasal spray administration by training patients in the self-administration of intranasal oxytocin in accordance with published recommendations.[54] Intranasal administration of oxytocin is an effective method of administering the neuropeptide across the blood brain barrier.[55] Twice daily dosing will ensure elevated central concentration of oxytocin throughout the day given that salivary concentration of oxytocin remains elevated for 7-hours following intranasal administration.[56] Patients will be instructed to store nasal spray at room temperature (between 15-25°C) after first use. The inclusion of 2-doses will allow us to determine the lowest effective dose (i.e., 24-IU or 48-IU) which will inform future trials assessing long-term treatment optimization. Doses of 24-IU and 48-IU were chosen because these are the most frequently used doses in studies with humans and have proven safe for long-term study.[49,50]

Control Condition.

Patients will receive an intranasal placebo containing the same ingredients as the oxytocin nasal spray with the exception of active oxytocin. Administration schedule and procedure will be identical to that described in the experimental condition.

Wash-Out Periods.

Conditions will be separated by a wash-out period of approximately two-weeks to ensure that oxytocin has fully cleared the system. This time frame is sufficient given that the half-life of oxytocin administered centrally using nasal spray is 2 to 7 hours and 7 half-lives will be achieved for clearance in 14 to 49 hours. A 2-week wash-out will also allow each course of intranasal administration to

coincide with the same phase of womens' menstrual cycle (i.e., the luteal phase). This is relevant given that estrogen has a priming effect on oxytocin synthesis, release, and receptor expression.[57]

2.4.6 Follow-up.

Patients will be contacted over the phone 2-weeks following completion of the trial (12-weeks following randomization) to assess for potential adverse events.

2.7 Measures.

Refer to Table 1 for Schedule of Assessments.

Primary Outcome.

The primary outcomes will be the between condition (24-IU vs. placebo; 48-IU vs. placebo) change in pain intensity and physical function from Day 1 to Day 14 measured using the Brief Pain Inventory - Short Form (BPI-SF).[58] The BPI-SF measures pain intensity, the impact of pain on seven daily activities (e.g., activity, work, sleep), and analgesic use. It has been recommended for use in trials measuring pain across multiple chronic pain conditions.[35] The BPI-SF was originally designed to measure cancer pain, but has been shown to be a reliable and valid instrument for measuring non-cancer pain.[59-62] 2-week and 1-month test-retest values for pain and function typically range between .72 and .98.[63]

Secondary Outcomes.

Secondary outcomes include emotional function, sleep disturbance, and global impression of change. *Emotional Function* will be measured weekly using the 21-item Depression Anxiety Stress Scale (DASS-21 [64]). Scales for depression, anxiety and stress are considered to approximate facets of diagnostic categories, including Depression scale for mood disorders, Anxiety scale for panic disorder, and Stress scale for generalized anxiety disorder.[65] *Sleep Disturbance* will be assessed weekly with the

Medical Outcomes Study Sleep Scale (MOS-S [66]). The MOS-S is a 12-item self-report measure designed to assess the important dimensions of sleep, including initiation, maintenance, respiratory problems, quantity, quality, and somnolence. *Global Change* across the course of study will be measured at the end of each 2-week course of nasal spray using the *Patients'* Global Impression of Change scale (PGIC [67]). There has been wide use of the PGIC in chronic pain trials [68,69], and data provide a responsive and readily interpretable measure of participants' assessment of clinical importance of treatment.

Daily Diaries.

Ambulatory assessments will be administered by way of REDCap. Patients will complete electronic diaries throughout each 2-week course of nasal spray administration. Patients will make daily recording of: 1) time of nasal spray administration; 2) average pain using a 0 "No pain" to 10 "Pain as bad as you can imagine" scale; 3) the degree to which pain has interfered with enjoyment in life and general activity using scales with anchors at 0 "Does not interfere" and 10 "Interferes completely." Validated measures will be completed during days 1, 7, and 14, refer to Table 1. Patients will be asked to guess whether the nasal spray administered contained oxytocin or placebo following each 14-day course of nasal spray administration.

Demographics and Covariates.

A d*emographic* questionnaire will collect age, ethnicity, medical comorbidities, medications taken, employment status, marital status, obstetrical history, menstrual history, urinary symptoms, headaches, substance use, and smoking status. Concern over pain will be assessed using the 13-item *Pain Catastrophizing Scale* (PCS [70]). Treatment expectations will be measured with the *Credibility / Expectancy Questionnaire* (CEQ [71]). Allodynia/hyperalgesia will be assessed using the *Central Sensitization Inventory* (CSI[72,73]) and confirmed with Q-tip testing.[74]

Side Effects and Safety Monitoring.

As recommended for trials of chronic pain,[75] side effects will be assessed using open ended prompts (i.e., have you experienced any unwanted symptoms in the past 24-hours?) and the *Symptom Assessment Schedule*[76] supplemented with additional symptoms (e.g., euphoria, nasal irritation, dizziness) identified in a recent trial evaluating the effect of intranasal oxytocin on pain in a sample of 14 women with fibromyalgia.[34]

3.1 Sample Size Calculation:

We based our sample size calculation on the number of patients needed to evaluate a clinically significant reduction in pain intensity and improvement in physical function of the primary outcomes: change in pain intensity and physical function from day 1 to day 14 that occurs between conditions (24-IU oxytocin vs. placebo; 48-IU oxytocin vs. placebo). The hypothesis tests are one-sided and the trial is powered using a sequential, repeated-measures crossover design with one interim analysis to monitor the preliminary activity of the 24-IU and 48-IU doses of oxytocin relative to placebo (refer to section 3.2.1 for greater detail on the interim analysis).

The overall type I error rate will be 0.05 and the O'Brien Fleming method[77] will be used to control for the inflation of type I error due to the interim analysis. The interim analysis will be conducted when primary outcomes are available for half of the proposed sample. The Sidak method[78] will be used to adjust for multiple comparisons (i.e., $\alpha = .0127$ after adjusting for 4-comparisons: 24-IU & 48-IU doses of oxytocin compared to placebo for pain intensity and physical function). Based on previous research with chronic pain populations,[58] we assume a standard deviation of 2.0 for pain intensity and physical function and a block-based symmetric correlation matrix under which the 2-week correlation within the same arm is assumed to be 0.8;[63] and the sub-correlation matrix of Day1 and Day14 pain intensity and physical function across two arms is comparable for any two arms; and

the correlation of Day1 and Day 1 on two arm equals that of Day14 and Day 14. We anticipate that the correlation of Day1 and Day14 cross-arms will be lower than the correlation of the same day pain intensity/physical function. As a conservative measure, we assume the correlation of Day1 and Day14 is comparable to the same day correlation cross two arms and a better power will be achieved if the correlation between Day1 and Day14 is lower. The sample size is determined as the largest for two scenarios on whether the sub-correlation matrix of Day1 and Day14 is stable over phases or not.

For the scenario of stable sub-correlation matrix of Day1 and Day14, all phase data will be included in the analysis. Target power is 0.9 to detect a 0.5 standard deviation difference in pain intensity/physical function, which corresponds to an effect size of 0.56 for the outcomes of change between Day1 and Day14 under the aforementioned assumptions on the covariance matrix. The required sample size is 41 per province to accommodate one interim analysis. If the sub-correlation matrix of Day1 and Day14 is unstable cross phases, only the first two phases data will be included in the analysis and the size for evaluating the efficacy of the 24-IU and 48-IU over the placebo is reduced to 2/3, where the two samples are independent ($\alpha = .0127$ using Sidak). Under this scenario, the power is set as 0.8 for the same effect size and the required sample size is 54, which is increased to 81 accounting for abandoning the phase-III data due to instability of the correlation. Therefore, the sample size of 81 per province will be used and this is the robust size to guarantee at least 80% power and an overall type I error of 0.05 with an interim analysis for different scenarios of the correlation matrix of pain intensity/physical function. The covariates of sex and province will be adjusted and the rule of 8 additional cases per covariate will be followed for the combined analysis on the efficacy of 24-IU and 48-IU oxytocin relative to placebo. Accounting for a potential attrition rate of 20% and the balance among the 2 sequences per province, a total sample of 336 patients (112 per province) is required.

3.2 Data Analysis.

An intention-to-treat (ITT) analysis will be performed,[79] in accordance with recommendations by CONSORT.[51,52] ITT analyses provide an assessment of the practical impact of the treatment. *Primary Analyses*: The hypotheses that improvement in pain and physical function will be observed following 2-week administration of oxytocin nasal spray relative to placebo will be assessed using BPI-SF average 24-hour pain-intensity scores. Using linear mixed models in SAS, the analytic strategy will be a mixed models Analysis of Covariance with fixed effects [time (Day 1, Day 14) and condition (24-IU oxytocin, 48-IU oxytocin, placebo)] and random effect (individual), and sex (male, female) as between-subject factor after adjusting for relevant covariates (i.e., province, basal oxytocin at baseline, expectation, pain catastrophizing, medical comorbidity). One interim analysis will be performed (see 2.17 for details). Based on previous literature, BPI-SF assessed pain is a relatively "well-behaved" variable with respect to the assumptions of a general linear model.[80] Even so, prior to conducting any analyses, preliminary examination of the assumptions of the GLM will be conducted.[80] Should the data indicate violation of assumption, we will perform appropriate transformations and/or consider the appropriate interaction term(s).[80] Missing data will be handled using multiple imputation[81] in accordance to Harrell's guidelines.[82] *Secondary Analyses*: The effects of the intervention on change in emotional function, sleep disturbance, and global impression of change between conditions will be evaluated in a manner analogous to that described above. *Exploratory analyses* will be performed to evaluate whether basal oxytocin concentration or polymorphism of the oxytocin gene receptor moderate or mediate treatment outcomes.

3.2.1 Frequency of Analysis: An ***interim analysis*** will be conducted when complete data is available from half of the desired sample size. The interim analysis will be used to decide: 1) stop the trial for efficacy if overwhelming evidence indicates that the 48-IU dose of intranasal oxytocin is efficacious relative to placebo (p-value < 0.0083); 2) drop the 24-IU dose for inefficacy if evidence supports a conservative test of the null hypothesis that 24-IU oxytocin is equivalent to placebo if the conditional

power is less than 0.2 if continuing the stage 2 data collection; or 3) continue the trial as planned. The O'Brien Fleming method will control the overall type I rate at 0.0127 with 0.0083 alpha spending at the interim, and the overall type II error rate at 0.1 with 0.029 spending at the interim for each of the 24-IU and 48-IU doses and primary outcome. ***Final analyses*** will be conducted at trial completion.

3.2.2 Subgroup Analyses: Sub-group analyses (e.g., dose of oxytocin, province, sex) are built into the analytic plan. Secondary analyses include interactions between dose, pain type, sex, and gender.

3.3 Risk Management and Safety Monitoring Board.

A Data and Safety Monitoring Board (DSMB) has been established to perform (unblinded) analyses according to the DSMB charter. The DSMB is composed of three independent clinical experts, and a statistician with expertise in RCTs. The DSMB will advise on any serious adverse event (SAE) reported during the conduct of the trial. Moreover, safety and efficacy will be evaluated during the interim analysis. Early termination will only occur if the DSMB is unanimous in their conclusion of an unfavorable benefit-to-risk ratio.[83] Strict termination criteria were not established a-priori given that: 1) Rescue medication is not needed for intranasal oxytocin. The best method to resolve side-effects is to discontinue use of the drug, which is our recommended course of action; 2) chronic neuromusculoskeletal pain is not a life-threatening condition; 3) study duration is brief; and 4) intranasal oxytocin has been extensively studied and side effects are rare and benign.[84] The advice of the DSMB will be sent to the study sponsor of the. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing medical research ethics committee, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

3.4 Ethics and dissemination.

Results from this feasibility trial will be disseminated to the academic community through conference presentations and the publication of peer-reviewed manuscripts. Results will be posted to our website www.munbehaviourmedicine.ca and made available to patients, providers and the general public.

3.5 Patient and public involvement.

Patients with lived experience were consulted in the design of this project and assisted in preparation of study materials. Engagement will continue throughout trial conduction and be emphasised when preparing materials for dissemination.

3.6 Data management.

Data will be collected, de-identified and stored. Electronic data will be stored on password-protected servers in encrypted files. De-identified data will be retained for 25-years and made available to members of the investigative team. De-identified data will be made available on reasonable request where such requests are compliant with receipt of ethical approval from the sending and receiving hosts institutional ethics review boards.

4.1 Patient Adherence: We will use a multi-pronged approach to encourage patient engagement. First, the timeline and demands of the trial will be explicitly discussed at the outset with patients, who will be

asked to sign a behavioural contract to commit to trying to meet the requirements. Second, patients will receive telephone reminders prior to each laboratory visit and again if they miss one visit. Third, expectations will be developed for attendance. Patients will know our research staff by name and made aware that their research associate has an appointment scheduled with them and will be awaiting their arrival. Fourth, patients who have difficulties attending sessions will be provided with a motivational conversation during which ambivalence towards attending sessions will be openly discussed with the goal of securing commitment to attend sessions. We have successfully employed these strategies with some very challenging patient groups (e.g., patients with cancer related fatigue, obese patients attending exercise sessions). These strategies have been identified by Cochrane reviews as methods for improving patient recruitment[85] and retention.[86]

Author's contributions: All authors (JAR, TSC, LC, DF, AM, AAM, MN-R, PAP, MR, YY) were involved in the conceptualization and design of the trial. All authors (JAR, TSC, LC, DF, AM, AAM, MN-R, PAP, MR, YY) made significant intellectual contributions to the written protocol and have approved the submitted version.

Conflicts of Interest: None declared.

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Data Availability: Deidentified data will be made available upon reasonable request where such requests are compliant with receipt of ethical approval from the sending and receiving hosts institutional ethics review boards.

Ethical Approval Statement: Trial protocols were reviewed and approved by the Newfoundland and Labrador Health Research Ethics Board (HREB #20227), University of British Columbia Clinical Research Ethics Board (CREB #H20-00729), University of Calgary Conjoint Health Research Ethics Board (REB20 #0359), and Health Canada (Control # 252780).

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Figure Caption

Figure 1. Flow chart of RCT design

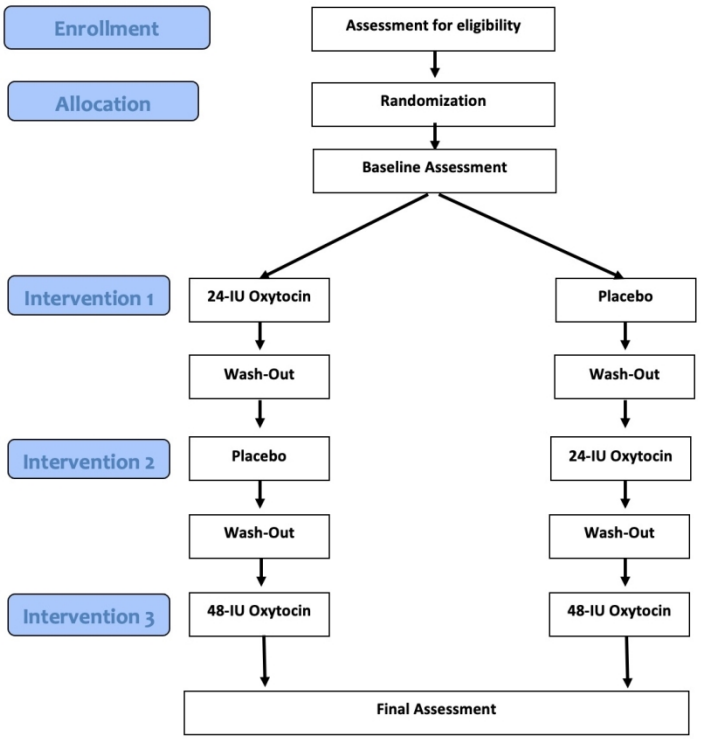

Figure 1. Flow chart of RCT design

276x210mm (144 x 144 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Section 2.1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A (b/c this is for publication)
Funding	4	Sources and types of financial, material, and other support	Funding Statement
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title Page
	5b	Name and contact information for the trial sponsor	Title Page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Author Contributions
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Section 3.3
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Sections 1.1 and 1.2
	6b	Explanation for choice of comparators	Section 2.7
Objectives	7	Specific objectives or hypotheses	Section 1.2

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Section 2.1
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Section 2.2
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Section 2.3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Section 2.4.5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Section 3.3
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Section 4.1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Sections 2.3.1 and 2.3.2
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Section 2.7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Section 3.1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Section 2.2
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Section 2.4.2
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Section 2.4.3
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Section 2.4.2
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Section 2.4.3
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Section 2.4.3
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Sections 2.4.4- 2.4.7 and Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Section 4.1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Section 2.7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Section 3.2
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Section 3.2
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Section 3.2
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Section 3.3
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Section 3.1
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Section 2.7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Abstract and section 2.1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Section 2.4.1
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Conflicts of Interest
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Section 3.6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Abstract

	31b	Authorship eligibility guidelines and any intended use of professional writers	Author Contributions
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Section 3.6
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Section 2.4.4

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Evaluating the efficacy of intranasal oxytocin on pain and function among individuals who experience chronic pain: Protocol for a multisite, placebo-controlled, blinded, sequential, within-subjects crossover trial.

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Evaluating the efficacy of intranasal oxytocin on pain and function among individuals who experience chronic pain: Protocol for a multisite, placebo-controlled, blinded, sequential, within-subjects crossover trial.

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Abstract

Introduction: Current treatments for chronic pain (e.g. opioids) can have adverse side effects and rarely result in resolution of pain. As such, there is a need for adjuvant analgesics that are non-addictive, have few adverse side effects, and are effective for pain management across several chronic pain conditions. Oxytocin is a naturally occurring hormone that has gained attention for its potential analgesic properties. The objective of this trial is to evaluate the efficacy of intranasal oxytocin on pain and function among adults with chronic pain.

Methods and Analysis: This is a placebo-controlled, triple-blind, sequential, within-subject crossover trial. Adults with chronic neuropathic, pelvic, and musculoskeletal pain will be recruited from three Canadian provinces (BC, AB, and NL, respectively). Enrolled patients will provide one saliva sample pre-treatment to evaluate basal oxytocin levels and polymorphisms of the oxytocin receptor gene before being randomized to one of two trial arms. Patients will self-administer three different oxytocin nasal sprays twice daily for a period of 2-weeks (i.e. 24 IU, 48 IU, and placebo). Patients will complete daily diaries including standardized measures on days 1, 7 and 14. Primary outcomes include pain and pain-related interference. Secondary outcomes include emotional function, sleep disturbance, and global impression of change. Intention-to-treat analyses will be performed to evaluate whether improvement in pain and physical function will be observed post-treatment.

Ethics and dissemination: Trial protocols were approved by the Newfoundland and Labrador Health Research Ethics Board (HREB #20227), University of British Columbia Clinical Research Ethics Board (CREB #H20-00729), University of Calgary Conjoint Health Research Ethics Board (REB20 #0359), and Health Canada (Control # 252780). Results will be disseminated through publication in in peer-reviewed journals and presentations at scientific conferences.

Registration: This trial is registered on ClinicalTrials.gov (Registration # NCT04903002)

Strengths and limitations of this study:

- The effect of oxytocin will be evaluated across different chronic pain presentations (i.e. musculoskeletal, pelvic and neuropathic pain), and clinically-relevant outcomes will be measured as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)
- Two doses of oxytocin will be administered, to evaluate a dose-response relationship.
- The effect of oxytocin will only be evaluated over a 2-week period, precluding longer-term assessment.
- The 48-IU dosing is the last course of treatment in both trial arms which may introduce expectancy effects due to incomplete blinding at this dose.
- Saliva samples will be collected to measure basal oxytocin levels and polymorphisms of the oxytocin receptor gene as potential moderators of treatment effect.

1.0 Introduction:

In 2011 the Institute of Medicine concluded that chronic pain, defined as pain that persists longer than 3-months or beyond the expected duration of healing,[1] is a public health concern and should be treated as a disease itself.[2] Nationally representative data indicates that 20% of Canadians over 18 years of age[3] and 15% of children[4] suffer with chronic pain. The prevalence of chronic pain increases with age. Approximately 65% of community dwelling seniors and 80% of older adults living in care facilities experience chronic pain.[5]

Currently available treatments for chronic pain rarely result in complete resolution of symptoms,[6] and often do not produce concomitant improvements in physical and emotional functioning.[7] For example, a 2018 meta-analysis reported that 1 in 8 patients respond to opioid medication with a mean 6.9mm (on a 100mm visual analogue scale) reduction in pain, small improvement in physical function and no improvement in mental function.[8] Moreover, current pharmacological treatments for pain, including opiates, are often addictive, associated with adverse effects,[9,10] and have limited effectiveness in areas such as neuropathic pain. Given the gap between suffering and adequate pain management, there is a need for analgesics that are safe, non-addictive, have low adverse effect profiles, and offer effective relief for a variety of painful conditions.

Intranasal oxytocin has gained increasing attention in recent years as a promising analgesic.[11-14] Oxytocin is a neuropeptide that is produced in the hypothalamus,[15] and released into the peripheral and central nervous system through independent pathways.[16] Evidence from several sources, including our team, suggests that oxytocin may be a safe and effective method for pain management.[12,13] Oxytocin may decrease pain sensitivity through three mechanisms:[12] 1) oxytocin is transported to an area involved in pain modulation, Lamina-I, II, and IV of the dorsal horn, through a hypothalamic-spinal projection.[16] Approximately 35% of neurons in the dorsal horn contain oxytocin receptors that act to

inhibit pain-carrying Aδ- and C-fibers;[17-19] 2) oxytocin binds to opioid receptors, and results in analgesic effects when administered to the periaqueductal gray, and effect that can be blocked with an opioid antagonist.[20,21] Further, analgesic effects of endogenous and exogenous oxytocin can be blocked by the opioid antagonist naloxone;[22] and 3) oxytocin may decrease pain sensitivity by improving mood, reducing anxiety, and buffering stress given that the induction of negative emotions are associated with heightened pain[23-25] and autonomic arousal.[24] In an informative controlled trial, intranasal administration of oxytocin in men resulted in greater calmness, less anxiety, and a trend toward lower cortisol during the Trier Social Stress Test.[26]

Preliminary evidence suggests that oxytocin may be an effective adjuvant analgesic that is applicable to a broad patient population. Our team published a systematic review of the effect of oxytocin on pain in animals and humans.[12] Oxytocin had a reliable effect as defined by increasing pain tolerance in 29 out of 33 animal studies reviewed. This effect was large (standard mean difference = 2.28), and persisted across central and peripheral modes of administration, and various noxious stimuli (e.g., heat, electric, chemical).[12] Results from research into the association between oxytocin and pain in humans has been variable due to methodological heterogeneity. For example, two studies have assessed associations between oxytocin and pain using experimental pain procedures in healthy adults, reporting a decrease in pain sensitivity to finger prick,[27] and no difference in pain-unpleasantness to electric shock.[28] Interpreting these results is difficult due to methodological concerns including insufficient sample size, one-dimensional pain measurement,[28] and use of a poorly described finger prick pain procedure.[27] Our team conducted the first methodologically rigorous placebo-controlled, blinded, within-subjects crossover trial evaluating the effect of intranasal oxytocin on acute pain.[29] We observed clinically meaningful effects of oxytocin on pain, particularly neuropathic indicators. With regard to chronic pain, individuals experiencing chronic back pain,[30] headache,[31] constipation,[32] and colon pain[33] have reported lower sensitivity to pain following the administration of oxytocin.

Confidence in the association between oxytocin and chronic pain has been difficult to discern due to limitations in study designs, including selection of an insufficient control condition,[31] use of an intrathecal punch delivery method that likely confounded pain assessment,[30] administration of oxytocin peripherally without verification of influence in the central nervous system,[33] or inadequate statistical power to detect meaningful effects.[32,34] Further, no trial to date has assessed all clinically relevant outcomes endorsed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) - an international group of experts that develop recommendations to improve the design, execution, and interpretation of clinical trials of treatments for pain.[35]

Given the heterogeneity of extant trials, we propose a methodologically rigorous trial evaluating the efficacy of intranasal oxytocin on pain and function among men and women with chronic pain that evaluates clinically relevant outcomes endorsed by the IMMPACT.[35] Potential mediators and moderator of treatment effects will be assessed using basal oxytocin levels and polymorphisms of the oxytocin receptor gene measured using salivary assays given that: 1) chronic pain patients exhibit low basal oxytocin levels relative to controls,[30,36,37] and may reflect underlying abnormality in the oxytocinergic system;[12] and 2) relative to those with an rs53576 A allele, individuals with a rs53576G/G oxytocin receptor genotype show reduced amygdala,[38] neuroendocrine,[26] and stress reactivity across a range of contexts,[39,40] and report greater benefit from social support[41] following oxytocin administration. This represents a movement towards precision medicine.

1.2 Research Questions: We will evaluate the efficacy of intranasal oxytocin when used as an adjuvant treatment (i.e., in addition to usual therapies) for improving pain and function (physical and emotional) among men and women with chronic neuropathic, musculoskeletal or pelvic pain.

Primary Hypotheses: Relative to placebo, patients will report greater improvement in: 1) pain intensity; and 2) physical function measured using the Brief Pain Inventory (BPI-SF) following a 2-week course of twice-daily 24-IU or 48-IU intranasal oxytocin administration.

Secondary Hypotheses: Patients will report improvement in emotional function, sleep, and global impression of change following intranasal oxytocin administration relative to placebo.

Exploratory Questions: Potential mediators and moderator of treatment effects will be assessed using basal oxytocin levels and polymorphisms of the oxytocin receptor gene measured using salivary assays. This represents a movement towards precision medicine.

2 Methods and Analysis

2.1 Design and Trial Registration.

A multi-site, placebo-controlled, triple-blind, sequential, within-subject crossover trial evaluating the efficacy of intranasal oxytocin on pain and function among patients with chronic pain. This is a basket trial consisting of heterogenous populations of chronic pain conditions from multi-sites across Canada. This trial will be conducted in compliance with the trial protocol, good clinical practice, institutional ethics boards and applicable regulatory requirements, and is registered on ClinicalTrials.gov # NCT04903002. A sample informed consent form can be located in the supplementary file "OT and Pain – Consent MUN V1.2"

2.2 Study Settings.

There is increasing recognition that most common chronic pain conditions are heterogeneous with a high degree of overlap and that most patients enrolled in clinical trials are not representative of community dwelling chronic pain patients.[42] As such, there will be four participating sites across three provinces, each province recruiting a different primary neuromusculoskeletal (NMSK) pain population.

Adults with chronic neuropathic pain be recruited from the Jim Pattison Outpatient Care & Surgical Centre Pain Clinic (JPOCSC-PC; Surrey, BC) and the Initium Centre for Pain Management (ICPM; Abbotsford, BC). The JPOCSC-PC is a multi-disciplinary centre that accepts referrals from a catchment area of 2-million people. 2,000 patients are seen per month, of which approximately 20% present with chronic neuropathic pain. Consecutive women with chronic pelvic pain will be recruited from the Calgary Chronic Pain Centre (Calgary, AB) and directly from the gynecology clinics of MR and MN. The waitlist for an assessment of chronic pelvic pain is approximately 500 patients. Consecutive adults with chronic musculoskeletal pain will be recruited from the Carbonear General Hospital (Carbonear, NL). Approximately, 40 patients with chronic pain are seen each week, of which approximately 60% present with primary shoulder, neck, or back pain.

2.3 Patient Eligibility.

2.3.1 Inter-Site Inclusion Criteria: 1) Adult (> 18 years) men and premenopausal women; 2) On stable medication for pain management for 3 months or more with no anticipated changes during the 10-weeks of this trial; 3) Moderate pain at baseline (i.e., a score of 4-8 on a 10-point numeric rating scale) to prevent floor and ceiling effects; and 4) Can commit the use of two forms of effective contraception (e.g., barrier methods), or one highly effective method, including abstinence, intrauterine device, intrauterine system (IUS), vasectomy, tubal ligation, or hormonal contraceptive (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants).

2.3.2 Inter-Site Exclusion Criteria: 1) Positive urine pregnancy test or contemplating pregnancy; 2) Concurrent use of another nasal spray; 3) Nasal pathology (e.g., ears, nose, and throat diagnosis); 4) Diabetes insipidus; 5) Current diagnosis or history of cancer; 6) Significant unmanaged psychopathology (e.g., severe depression as indicated by a score ≥ 15 on the Patient Health Questionnaire -9[43]) due to its inverse association with patient adherence to procedures;[44] 7) receiving

hormone treatment for gender-related motivations; 8) documented cardiovascular event (e.g., myocardial infarction); 9) known prolongation of the QTc interval; 10) known hypersensitivity to oxytocin; 10) known latex allergy; or 11) known or suspected renal impairment. Exclusion criteria will be vetted through a review of patient medical records and self-report given the concordance between self-report and medical diagnosis.[45]

2.3.3 Intra-Site Criteria:

***Surrey & Abbotsford, BC*:** Men and women with primary neuropathic pain - pain arising as a direct consequence of a lesion or disease affecting the central or peripheral nervous system[46] - will be eligible. Neuropathic pain will be screened for using a score of 3+ on the Douleur Neuropathique 4 Interview,[47] and confirmed on clinical assessment.

Calgary, AB: Women with chronic (intermittent or constant) pelvic musculoskeletal pain (i.e., located primarily in the pelvic region and reproducible on palpation of the pelvic floor) who have not received a hysterectomy will be eligible. Women with a primary diagnosis of endometriosis, dysmenorrhea, functional bowel disorder, interstitial cystitis, fibromyalgia or sacroiliac instability as defined by European Guidelines,[48] will be excluded.

***Carbonear NL*:** Men and women with primary musculoskeletal pain of back, neck, or shoulder origin will be eligible. Pain will be assessed using the BPI-SF and confirmed through physical examination.[49,50]

***Across Sites*:** Adults with multiple chronic pain conditions will be eligible to participate so long as their primary pain complaint meets eligibility criteria. Recruiting different primary NMSK presentations will allow us to evaluate the generalizability of intranasal oxytocin across common chronic pain presentations typically observed within the community and may allow for improved optimization of treatment in future work.

2.4 Procedure

2.4.1 Patient recruitment, screening and enrollment. Potentially eligible patients will be approached by a member of our study team during their regularly scheduled appointment at the clinic, and receive information about the objectives of the trial. Interested patients will undergo screening, including: 1) completion of a urine pregnancy test; blood work to evaluate renal impairment (as defined by an eGFR <45 by the Cockcroft-Gault equation) if the history suggests any stage or renal insufficiency, including history of diabetes, inflammatory diseases, hypertension and no Creatinine has been drawn in the last 2 years; and 3) ECG to evaluate prolongation of the QTc interval among anyone who may be at risk, including those prescribed antidepressant medication. Patients who meet all eligibility criteria will be randomized to study arm before completing a baseline assessment. Recruitment will begin in September 2021 until the target sample size is recruited, or March 2024.

2.4.2 Randomization, Allocation and Concealment.

The commercially available software, https://app.studyrandomizer.com/ will be used to generate a list of randomly sequenced numbers for assigning patients to condition in a manner outlined in CONSORT reporting guidelines.[51,52] As depicted in Figure 1, patients will be randomized to one of two sequences: 1) 24-IU oxytocin, placebo, 48-IU oxytocin; or 2) placebo, 24-IU oxytocin, 48-IU oxytocin. Central randomization stratified by province (BC, AB, NL) and performed using a 1:1 allocation schedule with permuted blocks of 4 and 6. Sex will be added as an additional stratification factor for sites in BC and NL. The lists will be uploaded on a web-based password protected randomization system. When an eligible participant consents to the study, randomization website will be contacted through a closed system and randomization code will be assigned to the participant. Automated audit trails will document the patient allocation number and treatment sequence, and the date and time of transaction.

2.4.3 Blinding.

This is a triple-blind study. In order to protect against expectation effects and biases, neither site investigators nor patients will know which nasal spray contains oxytocin or which sequence of conditions patients are assigned. The allocation sequence will be concealed from researchers using automated randomization. The bottles containing 24-IU oxytocin, 48-IU oxytocin, and placebo will be identical in appearance, smell, texture and taste, and only identifiable through a color labeling system known to the site pharmacists and study sponsor. Each provinces randomization sequence will be accessed by the site pharmacist and bottles prepared accordingly. Neither the RA assessing outcomes nor the statistician performing analyses will be unaware of condition. Patient blinding can be broken in the case of an adverse event (e.g., emergency department attendance). Patients will be provided a study card with a number to call to reach the central administrator who can de-identify condition in the unlikely case of an adverse drug reaction. The decision to unmask will be made on a case-by-case basis and will depend on potential risk.

2.4.4 Baseline Assessment.

Baseline assessments will involve: 1) completion of study measures, refer to Table 1; 2) collection of approximately 4mL of saliva into Cryovials using a standard unstimulated passive drool technique. Saliva samples will be frozen until shipped to Salimetrics for analysis of salivary oxytocin concentration and genetic polymorphism in the oxytocin receptor gene OXTR rs53576; and 3) training on procedures for nasal spray administration. Patients will be provided with the option of completing baseline assessments immediately following randomization, or scheduling a convenient time within 2-weeks. Baseline assessments for women will be scheduled to occur within close proximity to the start of the luteal phase of the menstrual cycle (i.e., days 14-28) as this is the stage during which women report greatest pain.[53] Due to the impact of the global pandemic, patients will have the option of completing study measures virtually. Patients will attend clinic to provide a saliva sample, undergo nasal spray training, and receive their assigned nasal spray. Clinic attendance will be scheduled in the

afternoon to avoid diurnal fluctuation in saliva oxytocin. Patients will be asked to avoid foods with high sugar, acidity, or caffeine 1-hour prior to visiting the clinic as these can confound saliva assays.

Table 1.

Schedule of assessments

			Randomization			
			2-week diaries			
Testing Variables	**Phone Screen**	**Baseline**	**Daily Diary**	**Day 7 of Diary**	**Day 14 of Diary**	**Follow-up**
Inclusion Criteria	X					
Sociodemographics		X				
Medical History		X				
Vitals		X				X
Pain NRS	X		X			X
BPI-SF Intensity		X		X	X	
BPI-SF Interference		X		X	X	
Emotional Function						
Mood		X	X			
DASS		X		X	X	
Sleep		X		X	X	
Global Impression of Change					X	
Expectancy		X				
Side Effects					X	X

BPI-SF = Brief Pain Inventory - Short Form; DASS = Depression, Anxiety and Stress Scale

2.4.5 Trial Interventions.

The intervention will span three 2-week conditions (24-IU, 48-IU and placebo) and two 2-week wash-out periods for a total duration of 10-weeks.

Experimental Condition.

There will be two experimental conditions. *Experimental Condition 1*: Patients will self-administer a 2-week course of 24-IU intranasal oxytocin [4-IU per puff (12-IU delivered to each nostril); Syntocinon, Novartis, Switzerland], twice per day (once in the morning and once in the evening). *Experimental Condition 2*: Patients will self-administer a 2-week course of 48-IU intranasal oxytocin [4-IU per puff (24-IU delivered to each nostril)], twice per day. Given that treatment adherence is crucial to treatment success, we will ensure standardization of nasal spray administration by training patients in the self-administration of intranasal oxytocin in accordance with published recommendations.[54] Intranasal

administration of oxytocin is an effective method of administering the neuropeptide across the blood brain barrier.[55] Twice daily dosing will ensure elevated central concentration of oxytocin throughout the day given that salivary concentration of oxytocin remains elevated for 7-hours following intranasal administration.[56] Patients will be instructed to store nasal spray at room temperature (between 15-25°C) after first use. The inclusion of 2-doses will allow us to determine the lowest effective dose (i.e., 24-IU or 48-IU) which will inform future trials assessing long-term treatment optimization. Doses of 24-IU and 48-IU were chosen because these are the most frequently used doses in studies with humans and have proven safe for long-term study.[49,50]

Control Condition.

Patients will receive an intranasal placebo containing the same ingredients as the oxytocin nasal spray with the exception of active oxytocin. Administration schedule and procedure will be identical to that described in the experimental condition.

Wash-Out Periods.

Conditions will be separated by a wash-out period of approximately two-weeks to ensure that oxytocin has fully cleared the system. This time frame is sufficient given that the half-life of oxytocin administered centrally using nasal spray is 2 to 7 hours and 7 half-lives will be achieved for clearance in 14 to 49 hours. A 2-week wash-out will also allow each course of intranasal administration to coincide with the same phase of womens' menstrual cycle (i.e., the luteal phase). This is relevant given that estrogen has a priming effect on oxytocin synthesis, release, and receptor expression.[57]

2.4.6 Follow-up.

Patients will be contacted over the phone 2-weeks following completion of the trial (12-weeks following randomization) to assess for potential adverse events.

2.5 Patient and public involvement.

Patients with lived experience were consulted in the design of this project and assisted in preparation of study materials. Engagement will continue throughout trial conduction and be emphasised when preparing materials for dissemination.

2.6 Measures.

Refer to Table 1 for Schedule of Assessments.

Primary Outcome.

The primary outcomes will be the between condition (24-IU vs. placebo; 48-IU vs. placebo) change in pain intensity and physical function from Day 1 to Day 14 measured using the Brief Pain Inventory - Short Form (BPI-SF).[58] The BPI-SF measures pain intensity, the impact of pain on seven daily activities (e.g., activity, work, sleep), and analgesic use. It has been recommended for use in trials measuring pain across multiple chronic pain conditions.[35] The BPI-SF was originally designed to measure cancer pain, but has been shown to be a reliable and valid instrument for measuring non-cancer pain.[59-62] 2-week and 1-month test-retest values for pain and function typically range between .72 and .98.[63]

Secondary Outcomes.

Secondary outcomes include emotional function, sleep disturbance, and global impression of change. *Emotional Function* will be measured weekly using the 21-item Depression Anxiety Stress Scale (DASS-21 [64]). Scales for depression, anxiety and stress are considered to approximate facets of diagnostic categories, including Depression scale for mood disorders, Anxiety scale for panic disorder, and Stress scale for generalized anxiety disorder.[65] *Sleep Disturbance* will be assessed weekly with the Medical Outcomes Study Sleep Scale (MOS-S [66]). The MOS-S is a 12-item self-report measure designed to assess the important dimensions of sleep, including initiation, maintenance, respiratory

problems, quantity, quality, and somnolence. *Global Change* across the course of study will be measured at the end of each 2-week course of nasal spray using the *Patients'* Global Impression of Change scale (PGIC [67]). There has been wide use of the PGIC in chronic pain trials [68,69], and data provide a responsive and readily interpretable measure of participants' assessment of clinical importance of treatment.

Daily Diaries.

Ambulatory assessments will be administered by way of REDCap. Patients will complete electronic diaries throughout each 2-week course of nasal spray administration. Patients will make daily recording of: 1) time of nasal spray administration; 2) average pain using a 0 "No pain" to 10 "Pain as bad as you can imagine" scale; 3) the degree to which pain has interfered with enjoyment in life and general activity using scales with anchors at 0 "Does not interfere" and 10 "Interferes completely." Validated measures will be completed during days 1, 7, and 14, refer to Table 1. Patients will be asked to guess whether the nasal spray administered contained oxytocin or placebo following each 14-day course of nasal spray administration.

Demographics and Covariates.

A d*emographic* questionnaire will collect age, ethnicity, medical comorbidities, medications taken, employment status, marital status, obstetrical history, menstrual history, urinary symptoms, headaches, substance use, and smoking status. Concern over pain will be assessed using the 13-item *Pain Catastrophizing Scale* (PCS [70]). Treatment expectations will be measured with the *Credibility / Expectancy Questionnaire* (CEQ [71]). Allodynia/hyperalgesia will be assessed using the *Central Sensitization Inventory* (CSI[72,73]) and confirmed with Q-tip testing.[74]

Side Effects and Safety Monitoring.

As recommended for trials of chronic pain,[75] side effects will be assessed using open ended prompts (i.e., have you experienced any unwanted symptoms in the past 24-hours?) and the *Symptom Assessment Schedule*[76] supplemented with additional symptoms (e.g., euphoria, nasal irritation, dizziness) identified in a recent trial evaluating the effect of intranasal oxytocin on pain in a sample of 14 women with fibromyalgia.[34]

3.1 Sample Size Calculation:

We based our sample size calculation on the number of patients needed to evaluate a clinically significant reduction in pain intensity and improvement in physical function of the primary outcomes: change in pain intensity and physical function from day 1 to day 14 that occurs between conditions (24-IU oxytocin vs. placebo; 48-IU oxytocin vs. placebo). The hypothesis tests are one-sided and the trial is powered using a sequential, repeated-measures crossover design with one interim analysis to monitor the preliminary activity of the 24-IU and 48-IU doses of oxytocin relative to placebo (refer to section 3.2.1 for greater detail on the interim analysis).

The overall type I error rate will be 0.05 and the O'Brien Fleming method[77] will be used to control for the inflation of type I error due to the interim analysis. The interim analysis will be conducted when primary outcomes are available for half of the proposed sample. The Sidak method[78] will be used to adjust for multiple comparisons (i.e., $\alpha = .0127$ after adjusting for 4-comparisons: 24-IU & 48-IU doses of oxytocin compared to placebo for pain intensity and physical function). Based on previous research with chronic pain populations,[58] we assume a standard deviation of 2.0 for pain intensity and physical function and a block-based symmetric correlation matrix under which the 2-week correlation within the same arm is assumed to be 0.8;[63] and the sub-correlation matrix of Day1 and Day14 pain intensity and physical function across two arms is comparable for any two arms; and the correlation of Day1 and Day 1 on two arm equals that of Day14 and Day 14. We anticipate that the

correlation of Day1 and Day14 cross-arms will be lower than the correlation of the same day pain intensity/physical function. As a conservative measure, we assume the correlation of Day1 and Day14 is comparable to the same day correlation cross two arms and a better power will be achieved if the correlation between Day1 and Day14 is lower. The sample size is determined as the largest for two scenarios on whether the sub-correlation matrix of Day1 and Day14 is stable over phases or not.

For the scenario of stable sub-correlation matrix of Day1 and Day14, all phase data will be included in the analysis. Target power is 0.9 to detect a 0.5 standard deviation difference in pain intensity/physical function, which corresponds to an effect size of 0.56 for the outcomes of change between Day1 and Day14 under the aforementioned assumptions on the covariance matrix. The required sample size is 41 per province to accommodate one interim analysis. If the sub-correlation matrix of Day1 and Day14 is unstable cross phases, only the first two phases data will be included in the analysis and the size for evaluating the efficacy of the 24-IU and 48-IU over the placebo is reduced to 2/3, where the two samples are independent ($\alpha = .0127$ using Sidak). Under this scenario, the power is set as 0.8 for the same effect size and the required sample size is 54, which is increased to 81 accounting for abandoning the phase-III data due to instability of the correlation. Therefore, the sample size of 81 per province will be used and this is the robust size to guarantee at least 80% power and an overall type I error of 0.05 with an interim analysis for different scenarios of the correlation matrix of pain intensity/physical function. The covariates of sex and province will be adjusted and the rule of 8 additional cases per covariate will be followed for the combined analysis on the efficacy of 24-IU and 48-IU oxytocin relative to placebo. Accounting for a potential attrition rate of 20% and the balance among the 2 sequences per province, a total sample of 336 patients (112 per province) is required.

3.2 Data Analysis.

An intention-to-treat (ITT) analysis will be performed,[79] in accordance with recommendations by CONSORT.[51,52] ITT analyses provide an assessment of the practical impact of the treatment. *Primary Analyses*: The hypotheses that improvement in pain and physical function will be observed following 2-week administration of oxytocin nasal spray relative to placebo will be assessed using BPI-SF average 24-hour pain-intensity scores. Using linear mixed models in SAS, the analytic strategy will be a mixed models Analysis of Covariance with fixed effects [time (Day 1, Day 14) and condition (24-IU oxytocin, 48-IU oxytocin, placebo)] and random effect (individual), and sex (male, female) as between-subject factor after adjusting for relevant covariates (i.e., province, basal oxytocin at baseline, expectation, pain catastrophizing, medical comorbidity). One interim analysis will be performed (see 2.17 for details). Based on previous literature, BPI-SF assessed pain is a relatively "well-behaved" variable with respect to the assumptions of a general linear model.[80] Even so, prior to conducting any analyses, preliminary examination of the assumptions of the GLM will be conducted.[80] Should the data indicate violation of assumption, we will perform appropriate transformations and/or consider the appropriate interaction term(s).[80] Missing data will be handled using multiple imputation[81] in accordance to Harrell's guidelines.[82] *Secondary Analyses*: The effects of the intervention on change in emotional function, sleep disturbance, and global impression of change between conditions will be evaluated in a manner analogous to that described above. *Exploratory analyses* will be performed to evaluate whether basal oxytocin concentration or polymorphism of the oxytocin gene receptor moderate or mediate treatment outcomes.

3.2.1 Frequency of Analysis: An ***interim analysis*** will be conducted when complete data is available from half of the desired sample size. The interim analysis will be used to decide: 1) stop the trial for efficacy if overwhelming evidence indicates that the 48-IU dose of intranasal oxytocin is efficacious relative to placebo (p-value < 0.0083); 2) drop the 24-IU dose for inefficacy if evidence supports a conservative test of the null hypothesis that 24-IU oxytocin is equivalent to placebo if the conditional

power is less than 0.2 if continuing the stage 2 data collection; or 3) continue the trial as planned. The O'Brien Fleming method will control the overall type I rate at 0.0127 with 0.0083 alpha spending at the interim, and the overall type II error rate at 0.1 with 0.029 spending at the interim for each of the 24-IU and 48-IU doses and primary outcome. ***Final analyses*** will commence after the follow-up has been completed for the final participant enrolled (e.g., May 2024) and span 3-months in duration.

3.2.2 Subgroup Analyses: Sub-group analyses (e.g., dose of oxytocin, province, sex) are built into the analytic plan. Secondary analyses include interactions between dose, pain type, sex, and gender.

3.3 Risk Management and Safety Monitoring Board.

A Data and Safety Monitoring Board (DSMB) has been established to perform (unblinded) analyses according to the DSMB charter. The DSMB is composed of three independent clinical experts, and a statistician with expertise in RCTs. The DSMB will advise on any serious adverse event (SAE) reported during the conduct of the trial. Moreover, safety and efficacy will be evaluated during the interim analysis. Early termination will only occur if the DSMB is unanimous in their conclusion of an unfavorable benefit-to-risk ratio.[83] Strict termination criteria were not established a-priori given that: 1) Rescue medication is not needed for intranasal oxytocin. The best method to resolve side-effects is to discontinue use of the drug, which is our recommended course of action; 2) chronic neuromusculoskeletal pain is not a life-threatening condition; 3) study duration is brief; and 4) intranasal oxytocin has been extensively studied and side effects are rare and benign.[84] The advice of the DSMB will be sent to the study sponsor of the. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing medical research ethics committee, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

3.4 Ethics and dissemination.

Results from this feasibility trial will be disseminated to the academic community through conference presentations and the publication of peer-reviewed manuscripts. Results will be posted to our website www.munbehaviourmedicine.ca and made available to patients, providers and the general public. Trial protocols were approval by the Newfoundland and Labrador Health Research Ethics Board (HREB #20227), University of Calgary Conjoint Health Research Ethics Board (REB20 #0359), University of British Columbia Clinical Research Ethics Board (CREB #H20-00729), and Health Canada (Control # 252780).

3.6 Data management.

Data will be collected, de-identified and stored. Electronic data will be stored on password-protected servers in encrypted files. De-identified data will be retained for 25-years and made available to members of the investigative team. Individual participant de-identified data (including data dictionaries) will be made available beginning 3-months after final follow-up data has been collected (anticipated September 2024) to researchers who provide a methodologically sound proposal for the purpose of achieving the aims of the approved proposal. Data sharing will be enacted with a data-transfer agreement between the sending and receiving institutions. Proposals should be directed to the corresponding author (JAR).

4.1 Patient Adherence: We will use a multi-pronged approach to encourage patient engagement. First, the timeline and demands of the trial will be explicitly discussed at the outset with patients, who will be asked to sign a behavioural contract to commit to trying to meet the requirements. Second, patients will receive telephone reminders prior to each laboratory visit and again if they miss one visit. Third, expectations will be developed for attendance. Patients will know our research staff by name and made aware that their research associate has an appointment scheduled with them and will be awaiting their arrival. Fourth, patients who have difficulties attending sessions will be provided with a motivational

conversation during which ambivalence towards attending sessions will be openly discussed with the goal of securing commitment to attend sessions. We have successfully employed these strategies with some very challenging patient groups (e.g., patients with cancer related fatigue, obese patients attending exercise sessions). These strategies have been identified by Cochrane reviews as methods for improving patient recruitment[85] and retention.[86]

Author's contributions: All authors (JAR, TSC, LC, DF, AM, AAM, MN-E, PAP, MR, YY) were involved in the conceptualization and design of the trial. All authors (JAR, TSC, LC, DF, AM, AAM, MN-R, PAP, MR, YY) made significant intellectual contributions to the written protocol and have approved the submitted version.

Conflicts of Interest: None declared.

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Data Availability: Deidentified data will be made available upon reasonable request where such requests are compliant with receipt of ethical approval from the sending and receiving hosts institutional ethics review boards.

Ethical Approval Statement: Trial protocols were reviewed and approved by the Newfoundland and Labrador Health Research Ethics Board (HREB #20227), University of British Columbia Clinical Research Ethics Board (CREB #H20-00729), University of Calgary Conjoint Health Research Ethics Board (REB20 #0359), and Health Canada (Control # 252780).

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Figure Caption

Figure 1. Flow chart of RCT design

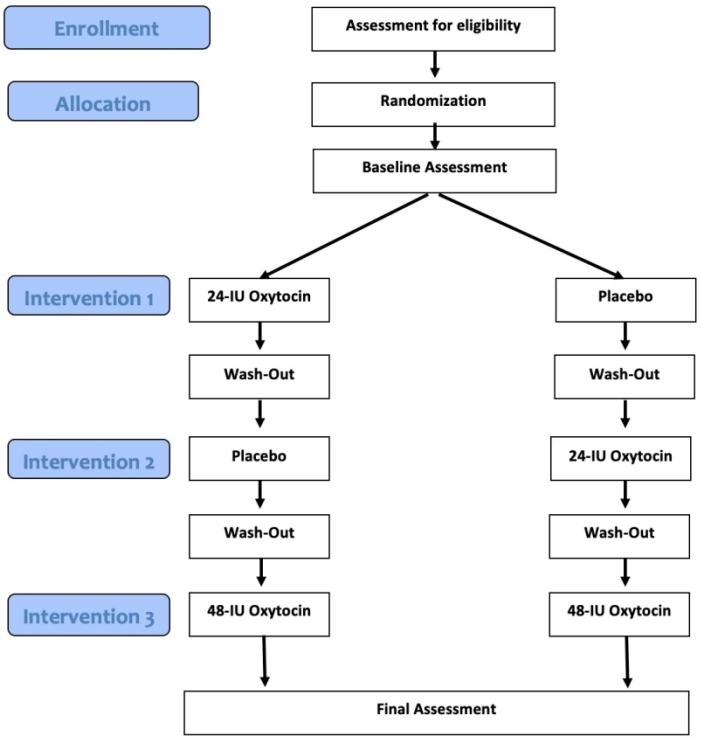

Figure 1. Flow chart of RCT design

276x210mm (144 x 144 DPI)

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Title:	Evaluating the efficacy of intranasal oxytocin on pain and function among individuals who experience chronic pain: A multisite, placebo-controlled, blinded, sequential, within-subjects crossover trial.
Short Title:	Evaluating the efficacy of intranasal oxytocin on chronic pain.
Trial Sponsor:	Dr. Joshua A. Rash, PhD Memorial University of Newfoundland Phone: 709-864-7687 Email:jarash@mun.ca
Physician Lead:	Dr. David Flusk, MD
Research Coordinators:	Ms. Anastasia Mekhael & Ms. Laura Harris-Lane Memorial University of Newfoundland – Behavioural Medicine Centre Phone: 709-864-7686 Email: munbmc@mun.ca
Protocol Number	CIHR-PG#426528

Consent to Take Part in a Clinical Trial

This form is part of the process of informed consent. It should give you the basic idea of what this research is about and what your participation will involve. It also describes your right to withdraw from the study. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. Take your time to read this form carefully and to understand the information given to you. Please contact the researcher, Dr. Joshua Rash, if you have any questions about the study or would like more information before you consent.

Your participation in this study is completely voluntary. If you choose not to take part in this research or if you decide to withdraw from the research once it has started, there will be no negative consequences for you or change to your current care, now or in the future.

1. Why am I being asked to take part in this study?

We are inviting you to take part in this research because you experience chronic pain.

This research is being done to learn whether the use of a nasal spray that contains oxytocin improves pain and function when compared to a placebo (a nasal spray that looks like the study drug, but does not contain oxytocin). Participants will be asked to undergo three 2-week courses where they will use a nasal spray two times each day. Two courses of nasal spray contain oxytocin of different concentration while the third course of nasal spray is a placebo. The placebo is used to make the results more reliable and is not intended to have any effect on you. By taking part in this study you will help expand the body of knowledge towards improving the way that chronic pain is managed.

2. Can I participate in the study?

Individuals may be eligible to participate if:

1. Are 18 years of age or older
2. On stable medication for pain management with no anticipated changes during the 10 weeks of this trial
3. Generally have a moderate level of pain (i.e. a score if 4-8 on a 10-point scale)
4. For woman, are premenopausal and can commit to a method of effective contraceptive (e.g., abstinence, IUD) during the 10-weeks of this trial.
5. Experience persistent muscle or skeletal pain (e.g., in back, neck or shoulders).

In addition, individuals may not be eligible to participate if the following apply:

1. Are pregnant or contemplating pregnancy during the next 10 weeks
2. Are using another nasal spray
3. Have an ear, nose or throat diagnosis
4. Have been diagnosed with cancer or have a history of cancer
5. Have recently used or are using illicit drugs or narcotics delivered intranasally (e.g. cocaine)
6. Have significant, unmanaged mental health concerns
8. Are receiving hormone treatment for gender-related motivations

2b. What if I experience multiple chronic pain conditions?

If you experience multiple chronic pain conditions, you are still eligible so long as your primary pain complaint originates in the back, neck or shoulders.

3. What is being tested?

Oxytocin is a naturally occurring hormone that is released during skin-to-skin contact and massage. Synthetic oxytocin can be administered using a nasal spray to enhance natural levels. While originally administered using needle injections in very high doses to stimulate labor and delivery during childbirth, low doses of oxytocin delivered by a nasal

spray can have a calming effect that lowers stress, reduces anxiety, and enhances trust. Research suggests that low doses of oxytocin delivered using a nasal spray reduces the experience of pain.

We would like to learn whether the use of oxytocin nasal spray helps to improve your pain and function.

This study involves the self-administration of a nasal sprays that contain a 24 international unit or 48 international unit doses of the hormone oxytocin. This is a commonly used dose and method of administration that is well tolerated in humans.

4. How many people will take part in this study?

We plan to have 336 people from three Canadian provinces will take part in this study, including 112 people from Newfoundland and Labrador.

5. How long will I be in this study?

This study will span 10-weeks in duration.

6. What are the study groups?

Each participant will complete three study conditions that are assigned in a random order.

Condition 1:
This condition involves the administration of a nasal spray containing a dose of 24 international units of oxytocin twice daily over a period of 2-weeks.

Condition 2:
This condition involves the administration of a nasal spray containing a dose of 48 international units of oxytocin twice daily over a period of 2-weeks.

Condition 3:
This condition involves the administration of a placebo nasal spray twice daily over a period of 2-weeks.

All nasal sprays contain a water-based, sterile solution with a preservative.

7. Are there risks to taking part in this study?

This study involves the self-administration of nasal sprays that contain doses of 24 international units and 48 international units of the hormone oxytocin. These are commonly used doses and method of administration that are well tolerated in humans. While the risks are minimal, there is a possibility that you could experience side effects. Between 1/100 and 1/1,000 people who use intranasal oxytocin report experiencing headache, nausea, or nasal irritation. Further, between 1/1,000 and 1/10,000 people report experiencing lowered blood pressure or abdominal contractions. While rate of occurrence is unknown, there is potential cardiac risk in the form of QTc prolongation. Contact the study investigator if you experience adverse effects that may be related to the study medication (phone numbers provided below). In the event of a medical emergency call 911. In addition, some of the questionnaires may be sensitive in nature, as they

pertain to your mood; these might cause emotional discomfort to participants, in which case they may choose to skip over them. Contact the Mental Health Crisis Line at **1-888-737-4668** if you experience significant psychological distress.

- **Reproductive risks**
  a. **Women:** Risks associated with pregnancy and breastfeeding are unknown and women should not become pregnant or breast-feed while taking part in this study.
  b. **Men:** There are no known reproductive risks for men.

8. What will happen if I take part in this study?

In order to participate in this study you must commit to not altering your pain medication within the following 10-weeks. If you agree to participate, the following procedures will be done in addition to your usual care:

A) Completion of a urine pregnancy test (for women) before beginning participation.
B) Complete a pain rating questionnaire and undergo a screening to evaluate suitability to participate.
C) Provide one sample of your saliva at the beginning of the study. Your saliva is being collected so that we can assess your level of naturally occurring oxytocin.
D) Complete questionnaires about your pain, daily function, and emotional well-being 3 times during each 2-week course of nasal spray. The purpose of these questionnaires is to understand whether your pain, mood, and daily function is influenced by the administration of nasal spray. Questionnaires will take **approximately 15- 20-minutes to complete.** Some of the questions are personal; you may choose not to answer these if you wish. Some of these questions pertain to your mood and may be sensitive in nature. If you wish to skip over these questions, you may.
E) Answer four questions each day about timing of nasal spray administration, pain, mood, and daily function.
F) Self-administer a 2-week course of nasal spray on three occasions over a 10-week period.

9. What are the possible benefits of taking part in this study?

You may not experience direct benefit from participating in this study. Participation will allow you to engage in the scientific process and contribute to knowledge that may improve pain management in the future.

10. Are there other choices?

You will continue to receive the usual standard of care that you have been receiving if you elect not to participate in this study.

11. What happens at the end of the trial?

Intranasal oxytocin will be available through the study but only until your participation ends.

12. If I decide to take part in this study can I stop later?

It is your choice to take part in this study, participation is voluntary. You can change your mind at any time during the research study. The study team may ask why you are withdrawing for reporting purposes, but you do not need to give a reason to withdraw from the study if you do not want to. Withdrawal from the study will not have any effect on the care you will receive. If you decide to leave the study, you can contact the study doctor or investigator.

You have the right to request the destruction of your information or samples collected during the study, or you may choose to leave the study and allow the investigators to keep the information already collected about you until that point.

13. What about new information?

It is possible that during the study we will get new information about a more effective treatment or other information that may affect your willingness to remain in the study. If this happens, you will be notified about the new information in a timely manner. You will be asked whether you want to continue taking part in this study and you may be invited to sign a new consent form, if you decide to continue in the research study.

A description of this clinical trial will be available on clinicaltrials.gov as required by local and international laws and regulations. This website will not include information that can identify you. You can search this website at any time.

14. Are there other reasons why I might stop being in the study?

The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- Your study doctor feels that you are experience a side effect that is likely related to the use of the study drug.
- New information becomes available and the study is no longer in your best interest.
- You need treatment not allowed in the study
- If you plan to or become pregnant
- If the study is stopped by (sponsor), the Health Research Ethics Board (HREB), Health Canada.

If you are asked to leave the study, the reasons for this will be explained to you and you will have the opportunity to ask questions about this decision. If your participation in the study is stopped, your study doctor will provide information about how to stop safely. If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form. Your study doctor will arrange for you to continue your care outside of the study.

15. Will it cost me anything?

You will not have to pay for any part of this study. Individuals will be given an honorarium of $20.00 per clinic visit (4 visits) totaling $80.00 for the duration of the study.

16. What about my privacy and confidentiality?

Protecting your privacy is one of our top priorities. Every effort will be made to protect your privacy, including: 1) removing any personal identifying information once your data

has been received (i.e., name, email address); 2) storing data in a locked and secured office; 3) securing online data with password encryption software; 4) **being contacted through your choice of phone or a secure platform that is compliant with the Public Health Information Act (PHIA; e.g. Zoom)**; 5) ensuring that all members of the study team undergo periodic training in best practices for data management; and 6) using a commercially available survey software with industry standard security features, **Qualtrics**, to collect survey responses.

Despite our best efforts, privacy cannot always be guaranteed. For example, we may be required by law to allow access to research records under exceptional circumstances. These circumstances usually involve random audits of health records where the focus is on appropriate record keeping by the investigators listed. Such audits may be conducted by Health Canada who is under legal obligation to respect your privacy.

When you give consent below you give us permission to

- Collect information from you and use de-identified information in the analysis of study data.
- Collect and store one saliva sample from you, for the purpose of this study. Saliva samples will be collected and stored in Newfoundland and Labrador until trial completion. They will then be shipped to Salimetrics located in California where they will reside under the care of Dr. Steve Granger and be analyzed for resting salivary levels and genetic structure of the oxytocin receptor gene. Please note that the saliva samples are collected in cryovials and are labeled only with a barcode (and no other participant-identifying information). As such, Salimetrics does not have access to identifying information about participants.

Access to records

We will not have access to your medical records.

Use of your study information

The research team will collect and use only the information they need for this research study. This information will include:

- Information from conversations had over telephone and video conference
- Information from study questionnaires
- Information from saliva sample

Your name and contact information will be kept secure by the research team at Memorial University in **Newfoundland and Labrador and only shared with Dr. Joshua Rash as required by Health Canada.**

As required by Health Canada, data obtained throughout the process of this trial will be retained for 25-years.

Information collected and used by the research team will be stored in a locked office in the Department of Psychology at Memorial University of Newfoundland. The security of this information will be safeguarded by Dr. Rash.

17. Who will see my medical information?

Representatives from the following organizations may come to the hospital/clinic and look at your personal health information under the supervision of the study staff to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines:

- Representatives of the Health Research Ethics Board
- Representatives of Health Canada, group of people who oversee the use of drugs in research in Canada.

Your access to records

You have the right to know what information is collected and may ask the study investigator to see the information that has been collected about you. This is a 'triple-blinded' study, which means that neither the research team members, nor the study doctor are aware of which nasal spray you are taking at any given time. Blinding will be broken in the case of a serious adverse event. You will be provided with a study card with a number to call to reach the central administrator, who can de-identify the condition that you are assigned to in the case of an emergency.

18. Reporting and the sharing of results with participants:

Please contact the researcher **after January 2024** if you are interested in the outcome of this study. Please note that we will be unable to provide you with your individual results because identifying information is not stored with your data. Individual participant results will not be reported in academic publications or presentations arising from this research – averages of responses across groups of participants will be reported instead. Results of this project will be presented on our website (www.munbehaviourmedicine.ca/).

19. What are my rights when participating in a research study?

You have the right to receive all information that could help you make a decision about participating in this study, in a timely manner. You have the right to ask questions about this study at any time and to have them answered to your satisfaction. You also have the right to withdraw from the study at any point in time.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

Signing this form gives us your consent to be in this study. It tells us that you understand the information about the research study. When you sign this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

20. Questions or problems:

If you have any questions about taking part in this study, you can meet with the investigator who is in charge of the study. That person is:

Dr. Josh Rash at 709 864 7687
jarash@mun.ca

Or you can talk to someone who is not involved with the study at all, but can advise you on your rights as a participant in a research study. This person can be reached through:

Ethics Office at 709-777-6974
info@hrea.ca

This study has been reviewed and given ethics approval by the Newfoundland and Labrador Health Research Ethics Board.

Please proceed to the next page.

SIGNATURE PAGE

	Please check as appropriate	
I have read the consent.	☐ Yes	☐ No
I have had the opportunity to ask questions/to discuss this study	☐ Yes	☐ No
I have received enough information about the study.	☐ Yes	☐ No
I understand that I am free to withdraw from the study • at any time • without having to give a reason • without affecting my future care	☐ Yes	☐ No
I understand that it is my choice to be in the study and that I may not benefit.	☐ Yes	☐ No
I understand how my privacy is protected and my records kept confidential.	☐ Yes	☐ No
I agree that the study doctor or investigator may read the parts of my hospital records which are relevant to the study.	☐ Yes	☐ No
I agree to take part in this study.	☐ Yes	☐ No

Signature of participant	Printed name	Day Month Year

Signature of person conducting the consent discussion	Name printed	Day Month Year

To be signed by the investigator:

I have explained this study to the best of my ability. I invited questions and gave answers. I believe that the participant fully understands what is involved in being in the study, any potential risks of the study and that he or she has freely chosen to be in the study.

Signature of investigator	Name Printed	Day Month Year

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Section 2.1 (pg. 6)
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A (b/c this is for publication)
Funding	4	Sources and types of financial, material, and other support	Funding Statement (pg. 21)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title Page
	5b	Name and contact information for the trial sponsor	Title Page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Author Contributions (pg. 21)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Section 3.3 (pg. 18)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Sections 1.1 and 1.2 (pg. 5-6)
	6b	Explanation for choice of comparators	Section 2.7 (pg. 13)
Objectives	7	Specific objectives or hypotheses	Section 1.2 (pg. 6)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Section 2.1 (pg. 6)
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Section 2.2 (pg. 7)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Section 2.3 (pg. 7-9)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Section 2.4.5 (pg. 11-13)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Section 3.3 (pg. 18)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Section 4.1 (pg. 19-20)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Sections 2.3.1 and 2.3.2 (pg. 7-8)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Section 2.7 (pg. 13-15)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Section 3.1 (pg. 15-16)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Section 2.2 (pg. 7)
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Section 2.4.2 (pg. 9-10)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Section 2.4.3 (pg. 10)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Section 2.4.2 (pg. 9-10)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Section 2.4.3 (pg. 10)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Section 2.4.3 (pg. 10)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Sections 2.4.4- 2.4.7 and Table 1 (pg. 10, 13-14 and 11)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Section 4.1 (pg. 19-20)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Section 2.7 (pg. 14)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Section 3.2 (pg. 17-18)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Section 3.2 (pg. 17-18)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Section 3.2 (pg. 17)

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Section 3.3 (pg.18)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Section 3.2.1 and 3.3 (pg. 17 and 18)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Section 2.7 (pg. 15)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Abstract and section 2.1 (pg. 2 and 6)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Section 2.4.1 (pg. 9)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Conflicts of Interest (pg. 21)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Section 3.6 (pg. 19)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Abstract (pg. 2)
	31b	Authorship eligibility guidelines and any intended use of professional writers	Author Contributions (pg. 21)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Section 3.6 (pg. 19)
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Section 2.4.4 (pg. 11)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.