Impact of vitamin C on the reduction of opioid consumption after an emergency department visit for acute musculoskeletal pain: a double-blind randomised control trial protocol

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ABSTRACT

Introduction Recent evidence has shown that vitamin C has some analgesic properties in addition to its antioxidant effect and can, therefore, reduce opioid use during recovery time. Vitamin C analgesic effect has been explored mostly during short-term postoperative context or in disease-specific chronic pain prevention, but never after acute musculoskeletal injuries, which are often seen in the emergency department (ED). The protocol’s primary aim is to compare the total morphine 5 mg pills consumed during a 2-week follow-up between patients receiving vitamin C or a placebo after ED discharge for an acute musculoskeletal pain complaint.

Methods and analysis We will conduct a two-centre double-blind randomised placebo-controlled trial with 464 participants distributed in two arms, one group receiving 1000 mg of vitamin C two times a day for 14 days and another one receiving a placebo. Participants will be ≥18 years of age, treated in ED for acute musculoskeletal pain present for less than 2 weeks and discharged with an opioid prescription for home pain management. Total morphine 5 mg pills consumed during the 2-week follow-up will be assessed via an electronic (or paper) diary. In addition, participants will report their daily pain intensity, pain relief, side effects and other types of pain medication or other non-pharmacological approach used. Three months after the injury, participants will be also contacted to evaluate chronic pain development. We hypothesised that vitamin C, compared with a placebo, will reduce opioid consumption during a 14-day follow-up for ED discharged patients treated for acute musculoskeletal pain.

Ethics and dissemination This study has received approval from the Ethics Review Committee from the ‘Comité d’éthique de la recherche du CIUSSS du Nord-de-l’ile-de-Montréal (No 2023–2442)’. Findings will be disseminated through scientific conferences and peer-reviewed journal publication. The data sets generated during the study will be available from the corresponding author on reasonable request.

Trial registration number NCT05555576 ClinicalTrials. Gov PRS.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This randomised controlled trial evaluating the effects of vitamin C on short-term opioid consumption in emergency department discharge patients with acute musculoskeletal injuries is novel.
⇒ The advantages of using vitamin C as treatment remains its low toxicity and low side effects.
⇒ This study is performed only on acute musculoskeletal injuries in two academic centres and may not generalise to other types of painful conditions or centres.
⇒ This study excludes patients already using opioids or vitamin C, patients treated for cancer, chronic pain or opioid use disorder.
⇒ There might be confounding factors not addressed by the randomisation and the compliance may be inconsistent.

INTRODUCTION

Opioids remain an important part of the treatment for moderate to severe acute pain in the emergency department (ED) and are frequently prescribed for home pain management after ED discharge.1, 2 However, even short-term opioids’ use after an ED visit can cause undesirable side effects like constipation, nausea/vomiting, drowsiness, weakness3 and can also produce more severe adverse events like respiratory depression.4 It can also lead to long-term use,16 opioid use disorders,7 overdose and death.8, 9 Furthermore, larger quantity of opioid consumed is associated with a higher prevalence of opioid-related adverse events.10 Therefore, reducing opioid consumption for acute pain without compromising the patients’ home pain management is a constant challenge for clinicians.11

Currently, the main strategy employed to reduce opioid consumption is to limit the
rate and/or the quantity of opioids prescribed for acute pain.\textsuperscript{12-15} The efficacy of this approach to reduce the quantity of opioid prescribed remains low and studies rarely report patient-centred outcomes such as pain relief or patients’ satisfaction.\textsuperscript{16} Yet, using adjunct analgesia was associated with less pain and opioid use.\textsuperscript{17} Non-steroid anti-inflammatory drugs (NSAIDs) are frequently suggested as adjutants to reduce opioid consumption but are known to contribute to gastrointestinal, cardiovascular, musculoskeletal (MSK) and renal adverse effects.\textsuperscript{18,19} Recent evidence showed that vitamin C (ascorbic acid) has analgesic properties by adding, through an unknown mechanism, an antinoceptive action to its antioxidant effect.\textsuperscript{20-22} One potential mechanism is to reduce free radicals’ production, which helps protect tissues (including nerves) from irreversible damage.\textsuperscript{23,24} The advantages of using vitamin C as an adjunct to opioids in acute pain management remain its low toxicity and low side effects, also in addition to performing well in different types of pain disorders.\textsuperscript{25}

Two meta-analysis reported the effects of vitamin C for immediate postoperative pain. One found a moderate-level evidence supporting the use of a 2 g oral preoperative dose of vitamin C as an adjunct for reducing postoperative morphine consumption.\textsuperscript{26} The other showed significant reductions in pain scores and opioid requirements up to 24 hours postoperative, suggesting the effectiveness of perioperative (on the day of the surgery or up to 30 min after the surgery’s beginning) vitamin C use.\textsuperscript{27} One study using 500 mg intravenously two times a day up to the third day after surgery also demonstrated less pain intensity and opioid consumption with vitamin C.\textsuperscript{28} Taking 200 mg orally of vitamin C three times a day, for 10 days after tooth extraction, was associated with reduced postoperative pain. However, this small study did not find any difference between 600 mg and 1500 mg per day of vitamin C.\textsuperscript{29} The only study performed in a non-postoperative acute pain context showed that intravenous administration of vitamin C was effective in reducing the incidence of post-herpetic neuralgia.\textsuperscript{30}

The efficacy of vitamin C to prevent specific types of chronic pain, notably in complex regional pain syndromes (CRPS), has been reported in a meta-analysis.\textsuperscript{31} Using a daily regimen of at least 500 mg of oral vitamin C initiated immediately after extremity surgery or injury and continued for 45 to 50 days, all studies showed a significant decrease of CRPS incidence up to 90 days after the event. Two other meta-analyses showed that daily supplementation with 500 mg of vitamin C for 50 days decreased the 1-year risk of CRPS after wrist fracture or limb extremity fractures.\textsuperscript{32,33} Taking 1 g per day of vitamin C for 40 days after a total knee arthroplasty also reduces CRPS risk.\textsuperscript{34} Yet, a literature synthesis on the effect of vitamin C on CRPS after distal radius fracture found a decrease in efficacy in recent studies.\textsuperscript{35}

**Study rationale**

The literature suggests that administration of vitamin C has an effect in reducing pain and opioid consumption in the context of immediate postoperative acute pain (24 to 72 hours), which is similar to pain caused by trauma seen in ED. However, we could not find evidence on the effectiveness of vitamin C administration after an ED visit in the context of acute pain, notably in trauma injuries like fractures, bruises, sprains, strains, etc. Therefore, we propose to evaluate the efficacy of a 14-day regimen of vitamin C given to ED patients discharged with an opioid prescription for acute MSK pain on total opioid consumption after 2 weeks. The 2-week period was chosen because it defines the usual acute pain timeframe,\textsuperscript{36} during which the need for analgesics including opioids is essentially resolved in most patients (88% of our previous study cohort).\textsuperscript{37} Since vitamin C is also associated with less postherpetic neuralgia and CRPS, we also propose to evaluate its impact on the incidence of chronic pain and CRPS at 3 months.

**Study objectives**

The primary aim of this protocol is to evaluate the effectiveness of vitamin C, compared with placebo (lactose), in reducing the total morphine 5 mg pills consumed during a 2-week period following ED discharge for an acute MSK pain complaint.

The secondary aims are to compare the following between patients receiving vitamin C and patients receiving a placebo: pain intensity trajectories, average pain relief during the 2 week, side effects, total morphine 5 mg pills consumed after a 2-week follow-up for each type of MSK pain (fracture, contusion, cervical pain, lower back pain, MSK pain at other sites), global chronic pain incidence (including CRPS) at 3 months and for each type of MSK pain specifically, CRPS incidence for limb fractures and for wrist fracture at 3 months, and prevalence of opioid use at 3 months.

**METHODS AND ANALYSES**

**Study design**

We will conduct a double-blind, randomised, placebo-controlled trial performed in two tertiary trauma care university-affiliated hospitals located in Montreal and Quebec City (Québec, Canada) with an annual census of 60 000 and 67 000 visits, respectively. This parallel group randomised trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT 2010) statement for reporting parallel-group randomised trial.\textsuperscript{38} This protocol has been reported according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (online supplemental file online 1).\textsuperscript{39}

**Participants and recruitment**

Consecutive patients (from 8 hours to 20 hours every day) diagnosed with an acute MSK pain complaint ongoing for less than 2 weeks and discharged from the ED with an opioid prescription will be approached by the treating clinician to participate in the study and obtain their verbal consent to participate in the study.
consent to be seen by a research assistant. The decision to prescribe opioids will be at the treating physician’s discretion. Based on our previous work, all included patients will receive an identical 20 pills of 5 mg morphine prescription. The research assistant will then verify the patient’s inclusion and exclusion criteria, explain the research protocol and obtain informed written consent.

**Eligibility criteria**
Patients will be included in the study when they satisfy all following criteria: (1) aged 18 and over, (2) treated in ED for acute MSK pain present for less than 2 weeks, (3) discharged with an opioid prescription, (4) French or English speaking.

Patients will be excluded from the study if any of the following criteria apply: (1) opioid use 1 month prior to ED visit; (2) already taking vitamin C supplement; (3) active cancer; (4) treated for chronic pain; (5) treated for opioid use disorder; (6) unable to fill out diary or unavailable for follow-up; (7) any allergy, intolerance or sensitivity to milk or morphine; (8) treated with cyclosporine or warfarin; (9) pre-existing oxalate nephropathy or hemochromatosis; (10) pregnant or lactating (dosage >1800 mg not recommended). For women of childbearing age and sexually active in the past 3 months, urine pregnancy test will be performed.

**Randomisation method and blinding**
Eligible patients will be block randomised at the initial visit (via 1:1 ratio) to either 1000 mg vitamin C taken orally two times a day or matching placebo (lactose) using a centralised randomisation web system. Allocation concealment will be in place to ensure that the investigator and the individual enrolling the subject into the study have no prior knowledge of group assignment. Since fractures are associated with more opioid consumption, randomisation will be a stratified by fracture (yes or no) and by centre. According to the centralised

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**Figure 1** Flowchart of patients’ enrolment in the study.
web system, an independent pharmacist will dispense prepacked numbered bottles of either vitamin C or placebo capsules for each patient. Both will be dispensed in identical capsule and the pharmacist will be unaware of the trial-group assignments. Each participant will be assigned a number and received the capsules in the corresponding prepacked bottle. Group allocation will be disclosed only after final analysis or at the request of the patient’s treating clinician.

**Early withdrawal of subjects**
At the time of consent, participants will be informed that their participation in this research is voluntary and that they may discontinue participation at any time.

**Withdrawal of subject as the result of investigator decision**
1. If an investigator terminates a subject’s participation in the trial, the investigator will explain to the subject the reasons for this action and, as appropriate, other treatment options.
2. If subjects were to have a serious adverse reaction to the medication, the investigator will recommend discontinuation of medication and provide aid for treatment.

**Data collection and follow-up for withdrawn subjects**
Data collected prior to participant withdrawal may be retained and used including Protected Personally Identifiable Information in a manner that is consistent with the study purpose and procedures as noted in this protocol and supplemental documents, unless a study participant notifies the primary investigator to remove all its information from the study.

**Study drug**
Vitamin C (ascorbic acid) is a vital nutrient; it helps form and maintain bones, skin and blood vessels and has antioxidant properties. It is not produced by the human body but occurs naturally in fruits, vegetables and other foods. It is also available as supplement over the counter in pharmacies, supermarkets, health supplement stores, and online.

**Previous vitamin C dosage used for pain management**
Our study will evaluate the impact of vitamin C in addition to an opioid prescribed for acute pain after an ED discharge. The current recommended dietary allowances of vitamin C are 90 and 75 mg/day for adult men and women, respectively. For anaesthetic or opioid sparing effects, recommended daily doses of vitamin C are larger. Levine and coworkers have shown that oral vitamin C uptake becomes less efficient as the dose increases due to transporter saturation. Although an oral dose of 200 mg vitamin C is completely absorbed, doses of 500 mg and 1250 mg vitamin C are only absorbed at <75% and 50%, respectively. Therefore, to maximise uptake and plasma concentrations of vitamin C, the chosen oral dose should ideally be administered in several smaller doses over the day. Vitamin C has low toxicity and is not believed to cause serious adverse effects at high intakes. The most common complaints are diarrhoea, nausea, abdominal cramps and other gastrointestinal disturbances due to the osmotic effect of unabsorbed vitamin C in the gastrointestinal tract. A tolerable upper limit of 2000 mg per day of vitamin C has been established, and adverse events, including oxalate nephropathy or haemolysis in glucose-6-phosphate dehydrogenase-deficient patients, are reported for short course of vitamin C only with very high dosage (up to 60 g intravenous over 2 days) or solely for studies using lower dosages during to many months.

Considering dosages used in studies performed in acute postoperative and chronic pain context, adverse events reported with different dosages, and the absorption of vitamin C given orally, we will compare the effect of 1000 mg vitamin C taken orally two times a day (one in the morning and one in the evening) for a 14-day period after ED discharge for the treatment arm to a placebo for the control arm.

**Subject compliance monitoring**
All participants will be asked to complete a 14-day electronic or paper diary. Each day, participants will be asked whether they took both their study-Products, other non-pharmacological approach (ice, heat, heat, and found them easy to complete.

**Study procedures**
After verifying all eligibility criteria, the research assistant will document the following initial data in REDCap: unique patient identifier, demographic variables (sex, gender, age and ethnicity), phone numbers, email address, complaint and pain location at triage, pain duration before ED visit, ED length of stay, final diagnosis (injury type and severity), history of opioid use or substance use disorder, analgesics received during ED stay, pain intensity at triage and discharge, pain medication prescribed at discharge, usual medication, vitamins and natural products, other non-pharmacological approach (ice, heat,
immobilisation, etc), and if it was a work or motor vehicle-related incident. A pharmacist will dispense either active or placebo capsules and patients will be informed not to start consuming any other vitamin or natural products. All participating patients will be granted online access to an already validated 14-day electronic diary and questionnaire. An identical paper version (also previously tested) of the 14-day diary and questionnaire will be provided to patients without internet access or less familiar with smartphones. Patients will be instructed in person on how to use the electronic or paper diary and to start with acetaminophen and NSAID (if prescribed) before consuming opioids. Patients will also have phone access to research assistants should they require assistance.

Electronic questionnaires are generally favoured over phone interviews because they may be less affected by social desirability bias. This diary is used daily for real-time recording of quantity, date and names of all pain medications consumed, including vitamin C, related to the patient’s ED visit. At the end of each day, pain intensity will be assessed by one question: ‘What was your pain level throughout the day?’ measured on an 11-point numerical rating scale (NRS) from 0 to 10 (0 is no pain and 10 is worst pain imaginable) and, in general, if their pain had been relieved during the day (yes or no). Participants will be asked at the end of each day if they took their two study capsules (see paper version of the diary example in online supplemental file 1).

At the end of 2 weeks, patients will have a scheduled visit (in person or virtual depending on the patient’s preference), where they will bring all their medications. A series of questions will be asked regarding their actual pain intensity level as measured on an 11-point NRS from 0 to 10 (0 is no pain and 10 is worst pain imaginable), the frequency of their pain during a typical week, if they still consumed opioids in the last 2 weeks, medication used for pain, pain frequency during a typical week and to answer the Pain Disability Index (PDI) questionnaire. The PDI is made up of seven categories that are measured on a scale from 0 (no disability) to 10 (all of the individual’s normal activities have been totally disrupted or impossible because of pain). Family and household responsibilities, recreation, social activities, occupation, sexual activities, independence and life support activities make up the seven areas of the PDI. Subsequently, a total score is calculated by adding the responses to the seven items to give a PDI score, which can be between 0 and 70. The percentage obtained can correspond to five diagnose: 0%–20% (minimal disability), 21%–40% (moderate disability), 41%–60% (severe disability), 61%–80% (infirm) and 81%–100% (bedridden). Chronic pain will be defined as at least as moderate disability on the PDI. The 3-month follow-up period was chosen because pain is usually considered chronic when it persists or recurs for more than 3 months. Patients will also be asked whether their medications were adequate for their overall pain management. For patients with limb fractures who are still in pain, an in-person visit will be scheduled to evaluate the presence of CRPS defined by the Budapest criteria, which includes a physical examination (see box 1).

Patients who had filled their initial opioid prescription will be contacted by phone 1 year after their initial visit and asked whether they consumed opioids in the previous 2 weeks. For patients who still consumed opioids, they will be asked to answer questions on opioid dependence using the rapid opioid dependence screen (RODS) as well as their reasons for consuming opioids. The RODS questionnaire is a newly validated measure of opioid dependence. This tool, composed of eight ‘yes/no’ questions, is designed to evaluate opioid dependence in clinical and research settings and is based on the Diagnostic and Statistical Manual of Mental Disorders V.IV. It takes 2 min to complete, and patients are considered as possibly opioid dependent if they answered positively to three or more of the eight items. This questionnaire has shown good internal consistency (α=0.92), fair inter-item correlations (0.66 to 0.87) and strong sensitivity (0.97) and specificity (0.76) when compared with a neuropsychiatric interview. Patients who meet the criteria for possible opioid dependency will be referred to an opioid use disorder clinic near their location.

The effect of vitamin C on 24-hour postoperative opioid consumption was used to compute treatment effect size for our primary outcome (total morphine 5 mg pills consumed after a 2-week follow-up). Two studies using oral route of vitamin C were reported, one by Kanazi et al.\textsuperscript{57} and one by Tunay et al.\textsuperscript{58} To be more conservative, we used the study with the smallest treatment effect (Tunay) and calculated an effect size of $d=0.32$. Anticipating a similar treatment effect, 190 participants in each arm are necessary to achieve a power of 0.90 with an alpha of 0.05 (PASS, V.11.0). Given the 18% lost to follow-up observed during a previous study using the same diary,\textsuperscript{37} a total of 464 patients will be recruited.

Previous studies made on the same population have shown an average recruitment rate of two participants per day at our study site.\textsuperscript{37} Therefore, an 8-month period will be necessary to enrol the initial sample. Accounting for the 3-month follow-up period and another 12 months for safety follow-up, a total of approximately 24 months will be required for recruitment and follow-up.

### Statistical analysis

#### Sample size determination

The effect of vitamin C on 24-hour postoperative opioid consumption was used to compute treatment effect size for our primary outcome (total morphine 5 mg pills consumed after a 2-week follow-up). Two studies using oral route of vitamin C were reported, one by Kanazi et al.\textsuperscript{57} and one by Tunay et al.\textsuperscript{58} To be more conservative, we used the study with the smallest treatment effect (Tunay) and calculated an effect size of $d=0.32$. Anticipating a similar treatment effect, 190 participants in each arm are necessary to achieve a power of 0.90 with an alpha of 0.05 (PASS, V.11.0). Given the 18% lost to follow-up observed during a previous study using the same diary,\textsuperscript{37} a total of 464 patients will be recruited.

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#### Analysis plan and statistical methods

We propose an intention to treat analysis with an additional per-protocol analysis. Mann-Whitney U test or t-test, depending on data distributions, will be used to compare the total morphine 5 mg pills consumed after a 2-week follow-up between both arms. Although participants will be stratified by type of painful condition and randomised into the two arms, we will compare their distributions for potential confounding variables by calculating group-specific means and proportions, as appropriate.\textsuperscript{59} As a sensitivity analysis, we will use a multiple regression analysis to evaluate the effect of vitamin C on total 5 mg pills consumed controlling for coanalgesic use, sex/gender, age, and ethnicity.

To compare pain intensity trajectories between both groups, group-based trajectory modelling (GBTM) will be used. GBTM is a statistical tool that identifies groups of patients with similar behavioural evolution over time without assuming the existence of a specific trend or number of groups.\textsuperscript{60} This new tool offers a more flexible approach of identifying linear or non-linear trajectories of pain evolution.\textsuperscript{61} Complete description of the modelling
was reported in a previous work. A χ² test will be used to compare the proportion of patients within each trajectory between each arm.

Proportion of participants with pain relief, and side effect during the 14-day follow-up, opioid use, chronic pain and CRPS at 3 months will be tested using χ² tests. Multiple comparison adjustments using false discovery rate are planned to control for inflated alpha error rate. Results will be presented using effect size with their 95% CIs. No interim analysis is planned and consequently the study will not be terminated earlier.

Missing outcome data
Missing data and dropouts will be assessed monthly by the data manager. Remedial measures, including staff retraining, will be used as needed to minimise missing data and patients lost to follow-up. For statistical analysis, potential missing data will be estimated using multiple imputation approach based on previous identified predictors if data are missing at random. It creates several different plausible imputed data sets and appropriately combining results obtained from each of them.

Patient and public involvement
A patient partner was involved in the study design and in the paper and electronic version of the pain medication diary that will be used in this study.

**ETHICS AND DISSEMINATION**

**Ethics approval**
This study has been granted ethics approval from the local Ethics Review Committee. Any protocol deviations will be submitted to the Ethics Review Committee for review.

**Data management**
Confidential and informed consent will occur in a private room. Every precaution will be taken to ensure data confidentiality. Only research team members will have access to both the paper and electronic data. Subjects will be assigned a unique study ID that will be used on all case report forms and database reporting. The database will be REDCap, which is HIPAA compliant, encrypted and password protected. Electronic data files will be accessible only on password-protected computers. Any hard copies will be maintained in a locked cabinet in a locked office by a member of the research team. There will be strict adherance to data management protocols. All source documents and trial documentation will be kept in a secure location by the investigators for 15 years.

The study investigators will have full access to and ownership of all data. Deidentified data will be made available to other interested investigators for additional analyses, on reasonable request, following reports of primary outcomes and with appropriate data use agreement.

The trial steering committee, who will also act as the data safety committee and will be composed of six members: principal investigator, project manager, research coordinator, biostatistician, clinical pharmacist and one ED clinician. It will oversee all study progress aspects and ensure participants safety, monitor recruitment, data collection and quality. Monitoring will be done monthly while any serious adverse events will be reported immediately to the committee, which will notify the REB and the Natural Health Products Directorate.

**Dissemination plan**
We plan to use the study data to write a manuscript for publication in a respected peer-reviewed journal in a timely fashion. Journal choice will be dependent on study findings but will likely be related to the fields of pain and emergency medicine. The principal author is a member of national/regional committees on pain management/opioid use, and part of a Canadian research network which will facilitate knowledge transfer. Results will likely be presented at national and international conferences.

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**Box 1 Budapest clinical diagnostic criteria for complex regional pain syndrome**

1. Continuing pain, which is disproportionate to any inciting event.
2. Must report at least one symptom in three of the four following categories.
   - **Sensory**: reports of hyperesthesia and/or allodynia.
   - **Vasomotor**: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
   - **Sudomotor/oedema**: reports of oedema and/or sweating changes and/or sweating asymmetry.
   - **Motor/trophic**: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

3. Must display at least one sign at time of evaluation in two or more of the following categories:
   - **Sensory**: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement).
   - **Vasomotor**: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry.
   - **Sudomotor/oedema**: evidence of oedema and/or sweating changes and/or sweating asymmetry.
   - **Motor/trophic**: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

4. There is no other diagnosis that better explains the signs and symptoms.
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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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INFORMATION AND CONSENT FORM

RESEARCH PROJECT: 2022-2442

Impact of vitamin C on pain relief after an emergency department visit for acute musculoskeletal pain

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PREAMBLE

We are requesting your participation in a research project because you have visited the Hospital’s Emergency Department and have been prescribed pain medication. Before agreeing to participate in this project and signing this information and consent form, please take the time to read, understand, and carefully consider the following information.

This form may contain words that you do not understand. We encourage you to ask any questions you may have to the researcher in charge of the project or other staff assigned to the research project and ask them to explain any words or information that is not clear.

Participating in multiple research projects at the same time could be detrimental to you. If you are already involved in other research projects, please let us know.

NATURE AND OBJECTIVES OF THE RESEARCH PROJECT

Recent data has shown that vitamin C has some analgesic properties in addition to its antioxidant effect, that it can relieve pain during healing and even prevent chronic pain. Our study is being conducted to evaluate the effectiveness of a 14-day course of oral vitamin C administered to emergency department patients prescribed pain medication for musculoskeletal pain. Up to 464 people treated for acute pain and prescribed pain medication will participate in this study which will be carried out in two Quebec hospitals. If you agree to participate in the study, the total duration of your participation will be 3 months (including the inscription of your pain relief medication in a 14-day diary and follow-ups at 14 and 90 days). Some participants may be contacted by phone at 12months.

Vitamin C is authorized by Health Canada. It has already been used for the treatment of pain in post-operative and chronic pain studies.
STUDY PROCESS AND METHODS USED

If you are eligible and agree to participate in this study, you will be randomized (assigned by chance) to receive either vitamin C or a placebo.

A placebo is a product that looks like the drug being studied but does not contain any active drug in its components. The placebo is used to provide a comparison with vitamin C to ensure that changes to your health, good or bad, are not due to chance alone.

The treatment groups in this study are:

- Group taking 1000 mg of oral vitamin C twice a day
- Group taking a placebo twice a day

This is a randomized double-blind study, which means that you will be assigned to one of the treatment group. Your assignment to either treatment group is random. For example, 232 people (50%) will receive vitamin C and 232 (50%) will receive a placebo. Neither you, the physician in charge of the project, nor the study staff will know which treatment group you will be assigned to and you will not be able to choose your group. However, in case of an emergency, the physician in charge of the project will be able to obtain this information.

Before you leave the emergency room, you will meet a research assistant who will explain the project, answer your questions, and give you a bottle containing the daily doses of vitamin C or placebo to take. You will be asked to take 1 tablet orally, twice a day for 14 days.

While taking the vitamin C/placebo, you will be asked to fill out a daily diary to tell us about all the medications you will be taking to relieve your pain. You may choose to complete this diary electronically or on paper, based on your preference.

Before leaving the emergency department, and at 14 and 90 days, you will be asked to complete a 10-minute questionnaire, including demographic information, your quality of life, and your pain medication prescription. You will also be asked to participate in a follow-up on day 14 in person or via video conference, depending on your preference. If you suffered a fracture and still have pain at 3 months, you will be required to attend an in-person assessment including a physical examination with a physician and research staff. You may receive a phone call at 12 months for a 2 minutes questionnaire.

For participants who choose the electronic diary, you will need to download the free MyCap app on your iPhone or Android smartphone. You will then need to scan the QR code provided and follow the instructions in the app to allow you to enter your daily data.

By agreeing to participate in this study, you authorize us to contact your pharmacy or consult your medication record to obtain the list of medications consumed during your participation in the study.

You also authorize us to contact you in the future to propose another research project arising from this one.
PARTICIPANT EXPECTED COLLABORATION

Your participation in this research project involves that:

- You complete a 10-minute questionnaire before leaving the emergency department
- You take the vitamin C that was provided to you according to the instructions given
- You record your pain relief medication in the diary for a period of 14 days
- You participate in a 10 minutes follow-up visit on day 14, in person or by video conference
- You complete a 10 minutes telephone questionnaire on day 90
- If you had a fracture and are still experiencing pain after 90 days, you will have to participate to a 15 minutes meeting with a physician and research staff
- For some participants only, you may complete a 2 minutes telephone questionnaire at 12 months
- You don’t take any vitamin C supplements purchased over the counter or prescribed by a physician during the 90-day study

BENEFITS ASSOCIATED WITH THE RESEARCH PROJECT

You may benefit personally from participating in this research project, but we cannot assure you of this. The results obtained in this study will contribute to the advancement of scientific knowledge in the field.

RISKS ASSOCIATED WITH THE RESEARCH PROJECT

Vitamin C has low toxicity, even at very high doses. The side effects most often experienced are diarrhea, nausea, abdominal cramps, and other gastrointestinal disorders. The dosage used in this project makes the risk of side effects rare.

Taking the placebo will not have any adverse effect on you.

However, there may be unknown risks and potential side effects (allergies and others) associated with the use of an investigational product.

DISADVANTAGES ASSOCIATED WITH THE RESEARCH PROJECT

There are few disadvantages for your participation in the project other than the time you will take to complete the questionnaires as well as the follow-up meeting in person or via video conference at 14 days. Patients with a fracture who are still in pain at 90 days should allow time for an additional visit.

CONFIDENTIALITY

During your participation in this research project, the physician in charge of the project and the research team will collect, in a research file, information about you needed to meet the scientific objectives of the research project.
The study file may include information from your medical file such as your identity, name, gender and date of birth.

All study data collected during this research will remain confidential to the extent permitted by law. You will be identified by a code number only. The code key linking your name to your research file will be kept by the physician in charge of this research project.

To ensure your safety, a copy of this consent form will be added to your medical file. As a result, any person or company to whom you give access to your medical records will be able to obtain this information.

This research data will be kept for at least 15 years after the end of the study by the physician in charge of this research project. The research data may be published or discussed at scientific meetings; however, it will not be possible to identify you.

For purposes of surveillance, monitoring, protection, safety and authorization of the drug under study by regulatory agencies, your research file and your medical file may be consulted by a person mandated by regulatory agencies, in Canada or abroad, such as Health Canada, as well as by authorized representatives of the sponsor, the institution or the Research Ethics Board. These individuals and organizations will have access to your personal data, but they adhere to a strict confidentiality policy.

You have the right to consult your research file to verify the information collected and have it corrected if necessary.

In addition, access to certain information before the end of the research project may require that you be removed from the project in order to preserve its integrity.

**SHOULD YOU SUFFER ANY HARM**

Should you suffer any injury as a result of the administration of the study drug or any procedure related to this research project, you will receive the care and services required by your medical condition.

By agreeing to participate in this research project, you do not waive any of your rights and you do not release the physician in charge of the research project, the sponsor, and the institution from their civil and professional liability.

**FUNDING OF THE RESEARCH PROJECT**

The research project is funded by (Fonds des Urgentistes de l'Hôpital du Sacré-Cœur de Montréal). In the context of the project, the CIUSSS NIM, Hôpital du Sacré-Cœur de Montréal emergency department research team, which acts as a clinical research organization, is receiving funding to carry out this research project. However, the research team has no financial interest in the study and will not receive any money personally for conducting this study.

**VOLUNTARY PARTICIPATION AND RIGHT OF WITHDRAWAL**

Your participation in this research project is voluntary. You are therefore free to refuse to participate. You may also withdraw from this research project at any time by informing the physician in charge of the research project or a member of the research team, without having to give any reasons.
Your decision not to participate or to withdraw from this research project will not affect the quality of care and services to which you are entitled or your relationship with the teams providing them. The physician in charge of this research project or the research ethics board may terminate your participation without your consent. This can happen if new findings or information indicate that your participation in the research project is no longer in your best interest, if you do not comply with the research project's guidelines, or if there are administrative reasons to withdraw from the project.

If you decide to withdraw from the research project or are withdrawn from the project, no further data will be collected. The information previously collected in this study will still be retained, analyzed, or used to ensure the integrity of the research project, as specified in this document.

Any new knowledge gained during the course of the research project that may affect your decision to continue to participate will be communicated to you promptly.

**COMPENSATION**

You will be entitled to 2 financial compensations of $25 each for your participation in this project:

- The first payment when the diary, the day 1 and 14 questionnaires are completed
- The second payment when the 90-day questionnaire is completed (and if applicable, the follow-up visit)

Patients with a fracture who are still experiencing pain at 90 days will receive free parking tickets for their follow-up visit.

**CONTACT INFORMATION**

If you have any questions or problems related to the research project, or if you wish to withdraw from the project, you may contact the physician in charge or a member of the research team at the following number: 514-338-2222, ext. 13318.

If you have any questions about your rights as a participant in this research project or if you have any complaints or comments, you can contact The Office of the Complaints and Service Quality Commissioner of the Centre intégré universitaire de santé et des services sociaux du Nord-de-l'Île-de-Montréal (CIUSSS NÎM) at (514) 384-2000 ext. 3316 or at commissaireplaintes.cnmtl@ssss.gouv.qc.ca.

If you have any questions for a professional or a researcher who is not involved in this study, you can contact Dr. Justine Lessard, emergency physician, at 514-335-1252.

The CIUSSS du Nord-de-l'Île-de-Montréal's research ethics committee has given its ethical approval to the research project and will ensure its follow-up.
CONSENT

Impact of vitamin C on pain relief after an emergency department visit for acute musculoskeletal pain

I read the information and consent form. The research project, this information and consent form were explained to me. My questions have been answered, and I was given time to make a decision. After consideration, I consent to participate in this research project under the conditions stated, including the use of my personal information.

I authorize the research team to access my medical records.

_____________________________________________________________________
Name of the participant                                    Signature                                  Date

Signature of person obtaining consent

I have explained the research project, this information and consent form to the participant and have answered the questions asked.

_____________________________________________________________________
Name of the person obtaining consent                          Signature                                  Date

Principal Investigator's commitment

I certify that this information and consent form have been explained to the participant and that any question he/she had was answered. I, along with the research team, agree to abide by what has been agreed upon in the Information and Consent Form and to provide a signed and dated copy to the participant.

Raoul Daoust

_____________________________________________________________________
Name of the Principal Investigator                                 Signature                                  Date
Example of the paper version of the medication and pain diary for Day 1 to Day 7

<table>
<thead>
<tr>
<th>MEDICATION NAME</th>
<th>DOSE (mg) PER TABLET</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>DAY 4</th>
<th>DAY 5</th>
<th>DAY 6</th>
<th>DAY 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study capsule</td>
<td>500 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For each pain medication, enter the total number of tablets taken per day. If you don’t take a specific medication on a given day, enter 0 in the box.

Each day, answer both questions below:

<table>
<thead>
<tr>
<th>In general, has your pain been relieved today?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What was your average pain today?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0=no pain</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Day 2</td>
</tr>
<tr>
<td>Day 3</td>
</tr>
<tr>
<td>Day 4</td>
</tr>
<tr>
<td>Day 5</td>
</tr>
<tr>
<td>Day 6</td>
</tr>
<tr>
<td>Day 7</td>
</tr>
</tbody>
</table>
Example of paper version of the medication and pain diary for Day 8 to Day 14

<table>
<thead>
<tr>
<th>WEEK 2</th>
<th>MEDICATION NAME</th>
<th>DOSE (mg) PER TABLET</th>
<th>DAY 8</th>
<th>DAY 9</th>
<th>DAY 10</th>
<th>DAY 11</th>
<th>DAY 12</th>
<th>DAY 13</th>
<th>DAY 14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vitamin C</td>
<td>500 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For each pain medication, enter the total number of tablets taken per day. If you don’t take a specific medication on a given day, enter 0 in the box.

Each day, answer both questions below.

<table>
<thead>
<tr>
<th></th>
<th>DAY 8</th>
<th>DAY 9</th>
<th>DAY 10</th>
<th>DAY 11</th>
<th>DAY 12</th>
<th>DAY 13</th>
<th>DAY 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>In general, has your pain been relieved today?</td>
<td>□ Yes</td>
<td>□ Yes</td>
<td>□ Yes</td>
<td>□ Yes</td>
<td>□ Yes</td>
<td>□ Yes</td>
<td>□ Yes</td>
</tr>
<tr>
<td>What was your average pain today?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 = no pain</td>
<td>10 = the worst pain imaginable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>__ /10</td>
<td>__ /10</td>
<td>__ /10</td>
<td>__ /10</td>
<td>__ /10</td>
<td>__ /10</td>
<td>__ /10</td>
</tr>
</tbody>
</table>
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>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)</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background and rationale</td>
<td>6a</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
</tr>
</tbody>
</table>

Version of 2022-10-03
Vitamin C acute pain # 2022-2442

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<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial design</td>
<td>8</td>
</tr>
<tr>
<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
<td>6-7</td>
</tr>
</tbody>
</table>

**Methods: Participants, interventions, and outcomes**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study setting</td>
<td>9</td>
</tr>
<tr>
<td>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</td>
<td>6</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>10</td>
</tr>
<tr>
<td>Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)</td>
<td>7</td>
</tr>
<tr>
<td>Interventions</td>
<td>11a</td>
</tr>
<tr>
<td>Interventions for each group with sufficient detail to allow replication, including how and when they will be administered</td>
<td>10</td>
</tr>
<tr>
<td>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)</td>
<td>8</td>
</tr>
<tr>
<td>11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)</td>
<td>10</td>
</tr>
<tr>
<td>11d Relevant concomitant care and interventions that are permitted or prohibited during the trial</td>
<td>10</td>
</tr>
<tr>
<td>Outcomes</td>
<td>12</td>
</tr>
<tr>
<td>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</td>
<td>16</td>
</tr>
<tr>
<td>Participant timeline</td>
<td>13</td>
</tr>
<tr>
<td>Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)</td>
<td>12</td>
</tr>
<tr>
<td>Sample size</td>
<td>14</td>
</tr>
<tr>
<td>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</td>
<td>15</td>
</tr>
<tr>
<td>Recruitment</td>
<td>15</td>
</tr>
<tr>
<td>Strategies for achieving adequate participant enrolment to reach target sample size</td>
<td>15</td>
</tr>
</tbody>
</table>

Version of 2022-10-03
Vitamin C acute pain # 2022-2442
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  7

Allocation concealment mechanism  16b  Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  7

Implementation  16c  Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  7

Blinding (masking)  17a  Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  8

17b  If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial  8

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  10-13

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  10

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  17

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  15-16
<table>
<thead>
<tr>
<th>Section</th>
<th>20b</th>
<th>20c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods for any additional analyses (eg, subgroup and adjusted analyses)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

### Methods: Monitoring

<table>
<thead>
<tr>
<th>Data monitoring</th>
<th>21a</th>
<th>21b</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

### Harms

<table>
<thead>
<tr>
<th>Harms</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct</td>
<td>11</td>
</tr>
</tbody>
</table>

### Auditing

<table>
<thead>
<tr>
<th>Auditing</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Ethics and dissemination

<table>
<thead>
<tr>
<th>Research ethics approval</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol amendments</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consent or assent</th>
<th>26a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consent or assent</th>
<th>26b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confidentiality</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>17</td>
</tr>
<tr>
<td>Item</td>
<td>Page</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Declaration of interests</td>
<td>28</td>
</tr>
<tr>
<td>Access to data</td>
<td>29</td>
</tr>
<tr>
<td>Ancillary and post-trial care</td>
<td>30</td>
</tr>
<tr>
<td>Dissemination policy</td>
<td>31a</td>
</tr>
<tr>
<td></td>
<td>31b</td>
</tr>
<tr>
<td></td>
<td>31c</td>
</tr>
<tr>
<td>Appendices</td>
<td></td>
</tr>
<tr>
<td>Informed consent materials</td>
<td>32</td>
</tr>
<tr>
<td>Biological specimens</td>
<td>33</td>
</tr>
</tbody>
</table>

Financial and other competing interests for principal investigators for the overall trial and each study site

Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

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

Authorship eligibility guidelines and any intended use of professional writers

Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Model consent form and other related documentation given to participants and authorised surrogates

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

*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.