Supplemental Material

Study protocol for a double-blind, randomised trial in British Columbia of low-dose naltrexone for post-COVID fatigue syndrome

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Box S1: Withdrawal criteria

Withdrawal criteria
Participants can withdraw from the study at any time without giving reasons. If a participant withdraws from the study, they may still be asked to attend a final safety visit to ensure their safety. There will be no additional follow-up for a withdrawn participant, except in the event of an adverse event (AE) or serious adverse event (SAE), where they will be followed until the AE or SAE fully resolves. Participants should be withdrawn from the study if: 1. The study investigator judges it is not in the participant's best interest to continue. 2. The participant experiences serious side effects due to the study treatment. The study doctor will assess the participants symptoms from the AE/SAE and the participant will be withdrawn if determined appropriate by the investigator. If withdrawn for an AE/SAE, the participant will still be followed by the study team until the AE/SAE resolves. 3. The participant needs to begin take long-term opioid medication. Participants who take opioid medication over a short time during the study to manage acute pain, will be allowed to continue in the study. The protocol deviation will be recorded. The study doctor and team will reinforce guidance on taking alternative medication for pain and ensure the participant is aware that taking opioids for pain relief may not work well due to the naltrexone's opioid blocking effects. 4. The participant becomes pregnant during the study. The study treatment will be stopped, and they be withdrawn from the study. 5. The participant is unable to fulfill the requirements for the study. For example, if the participant misses or does not complete the 1) baseline assessments or 2) assessments at more than one consecutive time point (does not complete 6-week and 12-week assessments). Participants withdrawn from the study will not be replaced.
Data collection from participants who withdraw
No new data/information will be collected from participants after they withdraw, except for: 1. Reason for withdrawal (if by participant choice: reason will not be collected unless participant provides a reason for their withdrawal). 2. Any information that is required to be collected related to an AE/SAE that the withdrawn participant is being followed for. The withdrawn participant will be followed until the AE/SAE has fully resolved. All data that has been collected prior to withdrawal will be retained for analysis.

Box S2: Trial oversight

Trial Steering Committee
A Trial Steering Committee (TSC) will be formed with patient partners, the investigators, and other team members. The TSC will meet virtually at least monthly in the first two months and then every 2 months for the remaining study period. The goals of the Steering Committee will include: 1. Ensuring adherence to the study timeline. 2. Reviewing protocol, reporting, discussing, and resolving challenges. 3. Providing a regular environment for the presentation of study data (including recruitment and final trial data). 4. Fostering patient and knowledge user engagement. 5. Planning for knowledge translation activities.
Data Safety and Monitoring Board
The Data Safety and Monitoring Board (DSMB) will be comprised of peer researchers with expertise in clinical trials and ethics, who are once removed from the study team. The frequency of scheduled meetings depends on patient enrollment and safety event rates. For the DSMB, a research assistant from the study team will coordinate meetings, draft agendas, take meeting minutes and log discussions. In instances where closed DSMB meetings are called, a research assistant independent of the study team will perform the tasks noted above. Before the study starts, the DSMB will: 1. Review the study protocol, overall data collection methods and safety monitoring procedures. 2. Define safety and related parameters to be monitored, including methods for review and frequency of monitoring. 3. Provide letter of review/approval of study initiation to the PI/Trial Steering Committee. During the study period, the DSMB will: 1. Review data generated by the study, particularly adverse events, unexpected and serious adverse events on a periodic basis and as advised by the study team and recommend one of the following actions to the Trial Steering Committee – continue as is, continue with modification, discontinue part of study, or discontinue completely. 2. Provide letter of review/approval at pre-determined intervals.
Study Monitor
The role of the study monitor is to verify: 1. That the rights and wellbeing of the participants are protected. 2. That reported trial data is accurate, compete and verifiable from source documents. 3. The conduct of the trial is compliance with the currently approved protocol, good clinical practices (GCP) and any applicable regulatory requirements.

Table S1: Exploratory outcomes

Laboratory measures (peripheral blood serum)	
Inflammatory markers	Comprised of IL-6 (measured in pg/mL) and hsCRP (measured in mg/L).
Cytokine profile	Comprised of GM-CSF, IFNγ, IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-12p40, IL-12p70, IL-13, MCP-1, TNFα. These are measured in pg/mL using the Human Cytokine Proinflammatory Focused 15-plex Discovery Assay® Array (Eve Technologies).
Creatine kinase (CK)[1]	An assessment of disease severity,[1] measured in units/L.
Thyroid profile[2]	An indirect measure of disease severity,[2] comprised of rT3 (measured in ng/dL), fT3 (measured in pmmol/L), fT4 (measured in pmmol/L) and TSH (measured in mIU/L).
AM cortisol*	Measured between 800h and 1000h, in nmol/L.
Adrenocorticotropic hormone (ACTH)*	Measured between 800h and 1000h, in pmol/L.
Patient reported outcome measures	
Fatigue VAS [3]	1 item, scored from 0 (least fatigue) to 10 (most fatigue).
Sleep Questionnaire (SQ-2)[4]	4 items, scored from 0 (no sleep problems) to 24 (most sleep problems)
Sleep VAS[4]	1 item Scored from 0 (no sleep problems) to 10 (worst quality of sleep imaginable)
Patient Health Questionnaire-9 (PHQ-9)[5]	Scored from 0 (no depression symptoms) to 27 (most depression symptoms).
Generalized Anxiety Disorder-2 (GAD-7)[6]	Scored from 0 (no anxiety symptoms) to 21 (most anxiety symptoms).
Self-reported health EQ-5D VAS[7]	Scored from 0 (worst imaginable health) to 100 (best imaginable health).
Post-COVID-19 Functional Status Scale[8]	Scored from 0 (no functional limitations) to 4 (severe functional limitations).
Physical measurements^	
Hand grip strength[9]	Measured in kg using a digital hand dynamometer. The highest value over 3 attempts will be for each time point will be used.
Sit to stand test[10]	To test leg strength and endurance, measured in number of repetitions in 30 seconds.
Postural blood pressure and heart rate	Measurements are taken in supine position and then three times over 5 minutes following passive standing (i.e. at 1, 3, and 5 minutes)

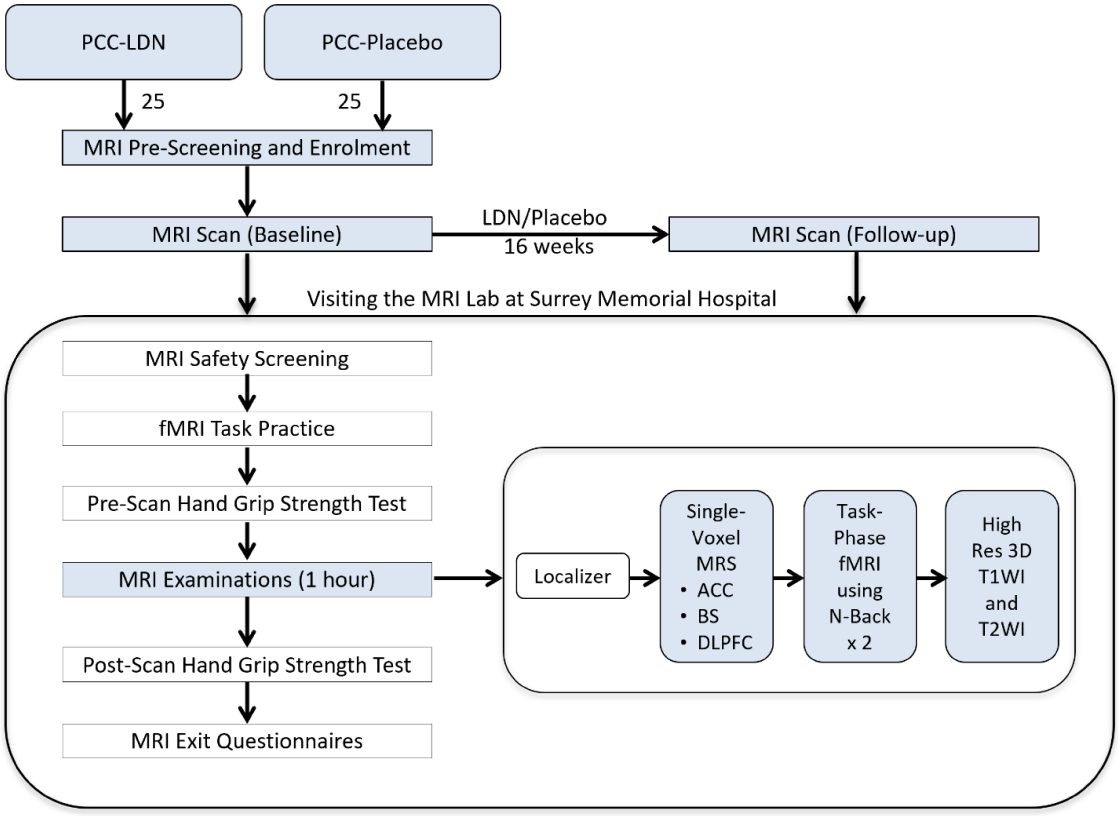
Legend. This table outlines the exploratory outcome measures. Details regarding primary and secondary outcomes are detailed in the main text. For all exploratory outcomes, we will evaluate changes in the measure between baseline and 16 weeks. Abbreviations: EQ-5D- Euroqol 5-dimensions; fT3- free triiodothyronine; fT4- free thyroxine; GM-CSF-granulocyte-macrophage colony-stimulating factor; hsCRP-high sensitivity CRP; IL-interleukin; MCP-1- monocyte chemoattractant protein 1; p40- subunit p40; POTS- postural orthostatic tachycardia syndrome; rT3- reverse triiodothyronine; TNF- tumor necrosis factor; TSH- thyroid stimulating hormone; VAS-visual analogue scale. *Optional for participants who choose to have bloodwork done in AM; ^optional for participants who choose in-person assessments.

Table S2: Laboratory tests

Test	Type	Purpose	Participants	Timing
ACTH	Serum	Exploratory outcome	Optional	Baseline, 16 weeks
Albumin	Serum	Eligibility	All	Baseline
ALP	Serum	Eligibility	All	Baseline
AM Cortisol	Serum	Exploratory outcome	Optional	Baseline, 16 weeks
ALT	Serum	Eligibility	All	Baseline
AST	Serum	Eligibility	All	Baseline, 16 weeks
Bilirubin	Serum	Eligibility	All	Baseline
Calcium	Serum	Eligibility	All	Baseline
CBC with differential	Serum	Eligibility	All	Baseline
Creatinine	Serum	Eligibility	All	Baseline
CK	Serum	Eligibility, exploratory outcome	All	Baseline, 16 weeks
CRP	Serum	Eligibility, exploratory outcome	All	Baseline, 16 weeks
fT3	Serum	Eligibility, exploratory outcome	All	Baseline, 16 weeks
fT4	Serum	Eligibility, exploratory outcome	All	Baseline, 16 weeks
GM-CSF	Serum	Exploratory outcome	All	Baseline, 16 weeks
IFNγ	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-1β	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-1RA	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-2	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-4	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-5	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-6	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-8	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-10	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-12	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-12p40	Serum	Exploratory outcome	All	Baseline, 16 weeks
IL-13	Serum	Exploratory outcome	All	Baseline, 16 weeks
LDH	Serum	Eligibility	All	Baseline
MCP-1	Serum	Exploratory outcome	All	Baseline, 16 weeks
Potassium	Serum	Eligibility	All	Baseline
rT3	Serum	Exploratory outcome	All	Baseline, 16 weeks
Sodium	Serum	Eligibility	All	Baseline
TNFα	Serum	Exploratory outcome	All	Baseline, 16 weeks
TSH	Serum	Eligibility, exploratory outcome	All	Baseline, 16 weeks
Urine opioid screen	Urine	Eligibility	First 16	Baseline

Legend. This is a complete list of laboratory tests completed during the study. Blood samples will be taken at a LifeLabs of the participants' choice, which will usually be local to the participant's location. Abbreviations: ACTH- adrenocorticotropic hormone; ALP- alkaline phosphatase; ALT- alanine aminotransferase; AST- aspartate aminotransferase; CBC- complete blood count; CK- creatine kinase; CRP- c-reactive protein; fT3- free triiodothyronine; fT4- free thyroxine; GM-CSF-granulocyte-macrophage colony-stimulating factor; IL-interleukin; LDH- lactate dehydrogenase; MCP-1- monocyte chemoattractant protein 1; p40- subunit p40; rT3- reverse triiodothyronine; TSH- thyroid stimulating hormone; TNFα- tumour necrosis factor alpha.

Figure S1: Protocol for MRI Study



Legend. As part of a sub-study of this clinical trial, 25 consenting participants in each study arm will undergo functional MRI testing. Participants will complete a hand grip assessment before and after imaging, and complete cognitive tasks during the fMRI testing. Abbreviations: ACC-agenesis of corpus collosum; BS-brainstem; DLPFC-dorsolateral pre-frontal cortex; fMRI- functional magnetic resonance imaging; MRI-magnetic resonance imaging; T1WI- T1 weighted imaging; T2WI- T2 weighted imaging.

Appendix 1: Batch testing protocol

The following plan is for batch testing the first batch of compounded study drug for the clinical trial, as requested by Heath Canada during the approval process. This study has Health Canada authorization. The batch testing must be completed, and the results reported to Health Canada, before dosing the first patient in the trial.

Naltrexone capsules in 1mg or 4.5mg size are to be analysed by ultra-high pressure liquid chromatograph-tandem mass spectrometer (UHPLC-MSMS) for confirmation of concentration in each capsule. This process will require a deuterium labelled standard (Sigma N-047 naltrexone-d3 solution. Certified reference material)

We will use a multiple reaction monitoring (MRM) approach for naltrexone with a transition of 342 -- 324 for unlabelled naltrexone and 345 – 327 for the deuterium labelled standard. The MRM approach uses a tandem mass spectrometer (two mass spectrometers in line one after the other) The first mass (342 for naltrexone) is isolated by the first mass spectrometer, the naltrexone will then be fragmented by collision with gas molecules and the fragment, or second ion (324 for naltrexone) will be isolated by the second mass spectrometer. The fragment ion will then be detected, and the intensity of the signal is equivalent to the concentration of the naltrexone.

Appropriate standard curves will be created using a 2.1 X 50mm Accucore phenyl-hexyl column (Thermo Scientific 17926-052130) and water/methanol as mobile phases. Standard curves will be created using dilutions of a European Pharmacopoeia standard from Sigma: Naltrexone Hydrochloride #Y0000400 with n=10 standards ranging in concentration from 10 nanogram per millilitre (ng/ml) through 500ng/ml. Standard curves will be included in the report to demonstrate linearity and range. The UHPLC-MSMS utilized is a Waters H-class UHPLC and Xevo TQS tandem mass spectrometer and will be run in positive ion mode.

Naltrexone impurity C (Sigma nomenclature or USP naltrexone related compound A), a European Pharmacopoeia reference standard from Sigma Y-0000410, will be analysed as a system suitability test as impurity C has the same molecular weight as Naltrexone and has the same MRM transitions of 342 – 327. Consequently, impurity C and naltrexone must be separated by UHPLC prior to entering the mass spectrometer. System suitability testing will be done to ensure the chromatographic separation of these two compounds prior to sample analysis.

Other known impurities of naltrexone will not be detected with a 345 -- 327 MRM as they have different molecular weights.

Analytical accuracy will be determined by spiking capsules with analytical standards of naltrexone. 1mg capsules will be cut open with a scalpel and the contents added to 1000milliliters (ml) water. 100microliters (ul) of this solution will be added to 900ul water for a dilution of 1/10 and an approximate concentration of 100 nanograms/millilitre (ng/ml).

4.5mg capsules will be treated in the same manner as the 1mg capsules except the final dilution will be 20ul into 980ul water providing an expected concentration of 90ng/ml.

5ul of deuterium labelled internal standard (naltrexone-d3 diluted to 1ug/ml concentration) will be added to all samples to allow for quantitation of the naltrexone. Results will be determined and expressed as a percentage of the expected dose.

To determine analytical accuracy, solutions from the 1mg and 4.5mg capsules (diluted to the equivalent of 100ng/ml and 90ng/ml) will be spiked and recovery determined.

Naltrexone standard will be spiked into the diluted capsule contents using the scheme in the following tables.

Placebo capsule:

	expected	measured	% recovery
no spike	0		
50ng/ml	50		
100ng/ml	100		
150ng/ml	150		
200ng/ml	200		

1mg capsule diluted to 100ng/ml:

	spiked	measured	expected	% recovery
no spike	0		100	
50ng/ml	50		150	
100ng/ml	100		200	
150ng/ml	150		250	
200ng/ml	200		300	

4.5 mg capsule diluted to 90ng/ml:

	spiked	measured	expected	% recovery
no spike	0		90	
50ng/ml	50		140	
100ng/ml	100		190	
150ng/ml	150		240	

Analytical precision will be determined using 8 capsules of 1mg and 4.5mg quantity. Capsules will be treated as described above.All 8 replicates at each concentration will be analysed by HPLC-MS and the mean, standard deviation and %RSD will be determined for each.

Confirmation of capsule dose and content uniformity will be combined.

A total of 10 capsules of 1mg and 4.5mg will be treated as described above. Samples will be analysed by HPLC-MS and results expressed as a percentage of the expected dose (1mg or 4.5mg). This will confirm the accuracy of the expected doses.

These results will also be used to calculate an acceptance criterion for content uniformity. If the results of the 10 capsules do not meet the USP definition of acceptance criteria, then an additional 20 capsules will be analysed and acceptance criteria calculated.

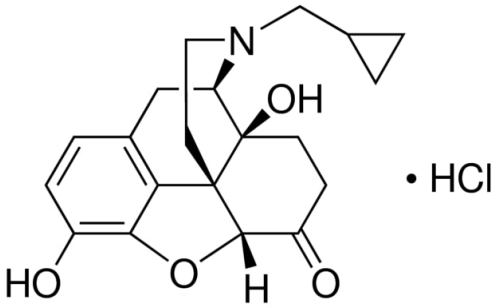
The compounding pharmacy has criteria for dose variability stating results should be between 90% and 110% of the expected value.

Purity determination will utilize aThermo Scientific Q-exactif Orbitrap. The Orbitrap has a mass accuracy of about 1part per million error. A 2.1 X 50mm C18 column will be used and all 10 of the final solutions for both 1mg and 4.5mg capsules, used for content uniformity will be analysed by Orbitrap mass spectrometry in positive ion mode.

The placebo capsule will also be analysed by Orbitrap.

We will actively search for each of the 10 known contaminants and breakdown products of naltrexone shown in the list below, based on accurate mass. Percent purity will be calculated based on area counts of naltrexone and any known contaminants/breakdown products found in each chromatogram.

Additionally, chromatograms of naltrexone capsules and placebo capsule will be compared to identify peaks found only in the naltrexone capsules. Any such peaks will have accurate mass recorded and be included in the percent purity calculation.



naltrexone		341.1627	C20H23NO4
impurity	a	315.1107	C17H17NO5
	b	287.1158	C16H17NO4
	c	341.1627	C20H23NO4
	d	680.3170	C40H44N2O8
	e	395.2097	C24H29NO4
	f	357.1576	C20H23NO5
	g	357.1576	C20H23NO5
	h	343.1784	C20H25NO4
	i	355.1420	C20H21NO5
	j	355.1784	C21H25NO4

Appendix 2: Sensitivity analysis for sample size calculation

For this trial, the sample size was calculated using data from the CCDP registry,[11] and based on effect size (d)=0.5.

As a sensitivity analysis, we also performed a sample size calculation through an alternative approach of using a minimal clinically important difference (MCID). As there are no published MCIDs for ME/CFS or PCC that we could identify in the literature, we used a published MCID ascertained from patients with systemic lupus erythematous (SLE).[12] This study included 80 participants and reported a MCID (95%CI) of 0.6 (0.3-0.9), or 5.4 (2.7-8.1) on the 7 to 54 scale for FSS.

After assuming a standard normal confidence interval was derived using all 80 patients, we calculated a standard deviation of 1.36, which corresponds to an effect size of 0.6/1.36 = 0.44. This results in a sample size of 81 per group, or 101 accounting for 20% loss to follow up.

Appendix 3: Side effects and adverse events

Trials with LDN for conditions other than PCFS have shown that LDN is safe and well-tolerated.[13–16] In our clinical experience, minor side effects were observed in <10% of patients. These include sleep dysfunction, in particular vivid dreams, and minor gastro-intestinal upset.

Hepatotoxicity
Naltrexone has been identified as a hepatotoxin. This was identified using doses five times the recommended dose and no cases of hepatic failure due to naltrexone have ever been reported. The doses in this study are significantly less (4.5 mg) than the recommended doses for opiate blockade or treatment for opioid or alcohol dependence (50 mg). Even though the risk of this is very low, participants will be informed of the potential, told to call the study team, and seek emergency medical attention if they experience any symptoms of hepatitis or liver dysfunction.

Other Adverse Events
Adverse reactions that have been reported both at baseline and during clinical trials with naltrexone are as follows (note the maximum dose used in this study is over 10 times lower than those used for listed uses)[17]:

- More than 10%: Difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.
- Less than 10%: Loss of appetite, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills.
- Less than 1% of subjects:
    - Respiratory: nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath;
    - Cardiovascular: nose bleeds, phlebitis, edema, increased blood pressure, non-specific EGG changes, palpitations, tachycardia;
    - Gastrointestinal: excessive gas, hemorrhoids, diarrhea, ulcer;
    - Musculoskeletal: painful shoulders, legs or knees, tremors, twitching;
    - Genitourinary: increased frequency of, or discomfort during urination, increased or decreased sexual interest;
    - Dermatologic: oily skin, pruritus, acne, athlete's foot, cold sore, alopecia;
    - Psychiatric: depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams;
    - Special Senses: eyes- blurred, burning, light sensitive, swollen, aching, strained; ears "clogged", aching, tinnitus;
    - General: increased appetite, weight loss, weight gain, yawning, somnolence, fever, dry mouth, head "pounding", inguinal pain, swollen glands, "side" pains, cold feet, "hot spells"

Data collected since the approval of naltrexone shows that most adverse events occur early in treatment and are transient in nature[29].

Adverse Events Reporting
We will implement REDCap alerts for adverse events noted through the questionnaires. Any adverse events (AE) will be assessed by the qualified investigator or their delegate as soon as possible upon becoming aware of the AE. All serious adverse events (SAE) will be reported as per local REB and Health Canada regulations. Adverse events determined to be serious, unexpected, and related to the study drug will be reported to Health Canada within:

- 15 days of becoming aware of the SAE, if it is not fatal or life-threatening.
- Immediately where possible, but within 7 days of becoming aware of the SAE, if it is fatal or life-threatening.

All SAEs that meet the criteria of an unanticipated problem will be reported to the REB. An unanticipated problem meets the following criteria: 1) unexpected; 2) related or possibly related to participation in the research; 3) suggests that the research places participants at greater risk than previously known.

SAE related to study treatment will be followed by the study team until it resolves.

AE reports will be submitted to the DSMB at intervals defined in the DSMB charter.

Appendix 4: Consent form

PARTICIPANT INFORMATION AND CONSENT FORM

A Double Blind Randomized Trial of Low-Dose Naltrexone for Post-COVID Fatigue Syndrome

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Protocol Number/ Trial ID: H21-02254

Short Title: LDN Trial

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Sponsor/Funder: Canadian Institutes of Health Research (CIHR)

Emergency Contact Number: 604-786-2473

1. Introduction/Invitation
You are being invited to take part in this study because you are a current or former patient of the BC Post-COVID Recovery Clinics (PCRC), or you have indicated that you are interested to participate in our clinical trial through the REACH BC Platform and have previously had SARS-CoV-2 (COVID-19) virus, and are continuing to experience symptoms.

2. Your participation is voluntary
Participating in this study is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving.

You should be aware that there is a difference for both you and your study doctor between being a patient and being a research participant. As a patient, all medical procedures and treatments are carried out for your benefit only according to standard accepted practice. As a research participant, you and your study doctor also must take into account the requirements for the research study. These may include procedures and treatments that are not part of standard practice or are not yet proven. This consent form describes the treatment procedures that are being carried out for research purposes. Please review the consent document carefully when deciding whether or not you wish to be part of the research and sign this consent form only if you accept being a research participant.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. Who is conducting this study?
This study is being conducted by Dr. Luis Nacul at BC Women's Hospital (BCW) and is funded by the Canadian Institutes for Health Research. Dr. Nacul is the Research Director of the Complex Chronic Diseases Program (CCDP) at BCW. Dr. Nacul is a well-established researcher and doctor in the area of complex chronic diseases. Other members of the study team are: Dr. Jane McKay who is the Head of Division of Internal Medicine and Medicine Program Director at Providence Health BC, Co-chair of the Post-COVID Interdisciplinary Clinical Care Network (PC-ICCN), and is a myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) specialist, and the Physician Lead of the clinical coordination working group at the PCRC; Dr. Adeera Levin is the Medical Lead for the PC-ICCN and PCRC in BC, Head of the Division of Nephrology at University of British Columbia; Dr Xiaowei Song is a Clinical Neuroimaging Senior Scientist with Fraser Health; and Dr. Jeffery Bone is a Biostatistician with BC Children's Hospital Research Institute, Dr. Hiten Naik is a research fellow with the Post-COVID Interdisciplinary Clinical Care Network.

4. Background
There are individuals who do not recover to their previous level of health following infection by SARS-CoV-2 (COVID-19). Many of them have similar symptoms to those with a condition called post-viral fatigue syndrome. This is known as post-COVID-19 fatigue syndrome (PCFS). The main symptoms of PCFS are profound and persistent fatigue, sleep problems, and brain fog. There is currently no treatment for PCFS.

Naltrexone is a medication that attaches to opioid receptors and blocks the effects of opioid drugs. It is approved by Health Canada for the treatment of alcohol and opioid use disorders. It is believed that when naltrexone is used in low doses, about $1/10^{th}$ of a normal dose, it has the effect of increasing the amount of opioid-like substances made within the body (met-enkephalin and beta-endorphin), which may help reduce pain and inflammation.

Low-dose naltrexone (LDN) has been used in individuals with a number of conditions, such as ME/CFS and fibromyalgia, which have similarities with PCFS. There have not been any clinical trials with LDN for ME/CFS or PCFS. However, there has been an observational study (treatment is part of routine medical care), for ME/CFS, and two small clinical trials for fibromyalgia. These studies have reported benefits of LDN treatment and have shown that LDN is safe and well-tolerated. The Complex Chronic Diseases Program at BC Women's Hospital has extensive experience prescribing LDN treatment for fibromyalgia and ME/CFS patients. Their studies suggest LDN treatment may improve energy, pain, and sleep in many patients, with only minor side effects.

This study aims to determine if treatment with LDN reduces fatigue and improves the related symptoms of PCFS, and thus improve quality of life and health of those with PCFS.

Health Canada, the regulatory body that oversees the use of drugs in Canada, has not approved the sale or use of naltrexone for PCFS. However, Health Canada has allowed naltrexone to be used in this study.

5. What is the purpose of the study?

This study aims to determine if low-dose naltrexone improves fatigue, pain, and related symptoms of individuals with PCFS. It will also determine if it reduces inflammation in the body, by measuring markers of inflammation in the blood.

This study is a double-blind randomized controlled trial. A randomized controlled trial is a study in which participants are randomly assigned to either the study drug (low-dose naltrexone) or placebo (an inactive substance). Randomization is like the flip of a coin so that there is an equal chance of being in either group. This is done to examine the potential benefits and side effects of the drug with a direct comparison group. A double-blind trial is where both participants and researchers directly involved in the trial will not know which treatment is being given (i.e. whether the active treatment or placebo).

6. Who can participate in this study?

You may be able to participate in this study if you:

- Are between the ages 19 to 69 years old
- Had COVID-19 at least three months ago, as confirmed by a physician or positive test result
- Meet the clinical diagnostic criteria for PCFS (this will be confirmed by a physician at your appointment)
- Agree to maintain any other regular medications at their current doses for the duration of the trial (essential need of new medication or dose change, as prescribed by physician, is permitted)

- Agree to use effective contraception while receiving the study treatment (if you could potentially become pregnant)
- You reside within the delivery area for the drug as determined by FedEx Clinical Trial Services

7. Who should not participate in this study?

You will not be eligible to participate in this study if you:

- Are pregnant, planning to become pregnant, or breastfeeding
- Have used opioid medications within the last 15 days or use of opioids during the trial^
- Have a positive urine test for opioids (test to be done after you sign the consent form)
- Have a history of alcohol, opioid or other substance misuse
- Participated in another interventional clinical trial in the last 30 days or plan to during the trial period
- Have a confirmed ME/CFS or fibromyalgia diagnosis existing prior to COVID-19.
- Are allergic to naltrexone or medication components (gelatin†; cellulose)
- Have acute hepatitis, liver failure, or severe kidney failure
- Are currently using or have used naltrexone in the last 30 days

^If you are taking any opioids and wish to stop them to become eligible for the trial, you can enter a washout period, where you will stop taking the opioids for 15 days before continuing with the screening process.

†The study treatment is prepared with gelatin, which is an animal-based product.

8. What does this study involve?

This study is a 16-week double-blinded randomized trial, meaning that neither you nor your study doctor will know which study medication you take. However, this information is available in case of an emergency, and will be available at the end of the trial to those analyzing the results. A total of 160 SARS-CoV-2 survivors are anticipated to be enrolled in this study with 80 randomized to the placebo and 80 randomized to the low-dose naltrexone treatment. Study treatment will be administered for 16 weeks and will start at 1 mg/day, increasing each week by 1 mg for a maximum of 4.5 mg/day at week 4. The latter dose will be continued until the end of the trial.

If you agree to take part in this study, the procedures and visits you can expect will include the following:

- Review and completion of the consent form
- Meet with a Study Physician virtually who will confirm a diagnosis of PCFS and confirm it is safe for you to take the study drug. To do this, the study doctor may need to review your medical record and/or call your family doctor for additional information. If you sign this form, you are agreeing to the study doctor reviewing your medical record and/or calling your family doctor. If you decide you do not want your study doctor to know about your participation in this study, the study doctor will not be able to call your family doctor and this may make it harder for the study doctor to determine if you are eligible.
- Completion of research questionnaires. These questionnaires will ask about items like fatigue, sleep, pain, other symptoms you may be experiencing, demographics, medical history, quality of life, mental health, medications & supplements you take, details about your COVID-19 infection, vaccination status, questions to check your daily use of the study drug, and if you have experienced any side effects. These questionnaires will be emailed to you to complete at home. If

you don't have access to a device with which you can complete the questionnaires on, you can arrange for the questionnaires to administered to you by telephone.

- Blood sample collection at LifeLabs (you can collect samples at any location that is convenient for you). Some of the blood collected will be analyzed at LifeLabs, and some will be sent to Eve Technologies in Alberta for analysis. The samples will be stored at the BC Children's Biobank until they are sent for cytokine profile testing. LifeLabs will use the study ID to collect, process, analyze and/or ship the samples for this study (your name will not be used to send the samples). When the sample arrives at the BC Children's Biobank, the samples will be stored until they are shipped to Eve Technologies in Alberta.
    - All of the study test results will be reported to the ordering physician (the study principal investigator Dr. Luis Nacul).
    - Samples taken at LifeLabs may be referred to a testing laboratory outside of BC (this may be in another province or in the USA).
- Hand grip strength assessment is a short test of the strength you have in your hands (if you don't have any in-person contact with the study team, this assessment will not be done). This involves squeezing a hand device with all your strength and is done three times with each hand.
- Completion of a short study drug diary daily for the first 4 weeks of taking the study treatment, and for a week after any change in the dose, if that happens (unlikely).
- Completion of study visits and check-ins with study personnel. The study visits can be done in-person, through phone call, or video call. The check-ins can be done by phone call, text, email, or video call.
- Wear a pedometer (step counter) for 7 days, while awake, at two time points during the study, and record the number of steps per day in the diary. Note: The pedometer does not collect any information besides your daily steps.
- Return the empty containers and unused study drug to the study team by mailing it back via Canada Post (pre-paid) or returning it in-person to the study site (BC Women's Hospital).

Study Timeline

Screening & Eligibility

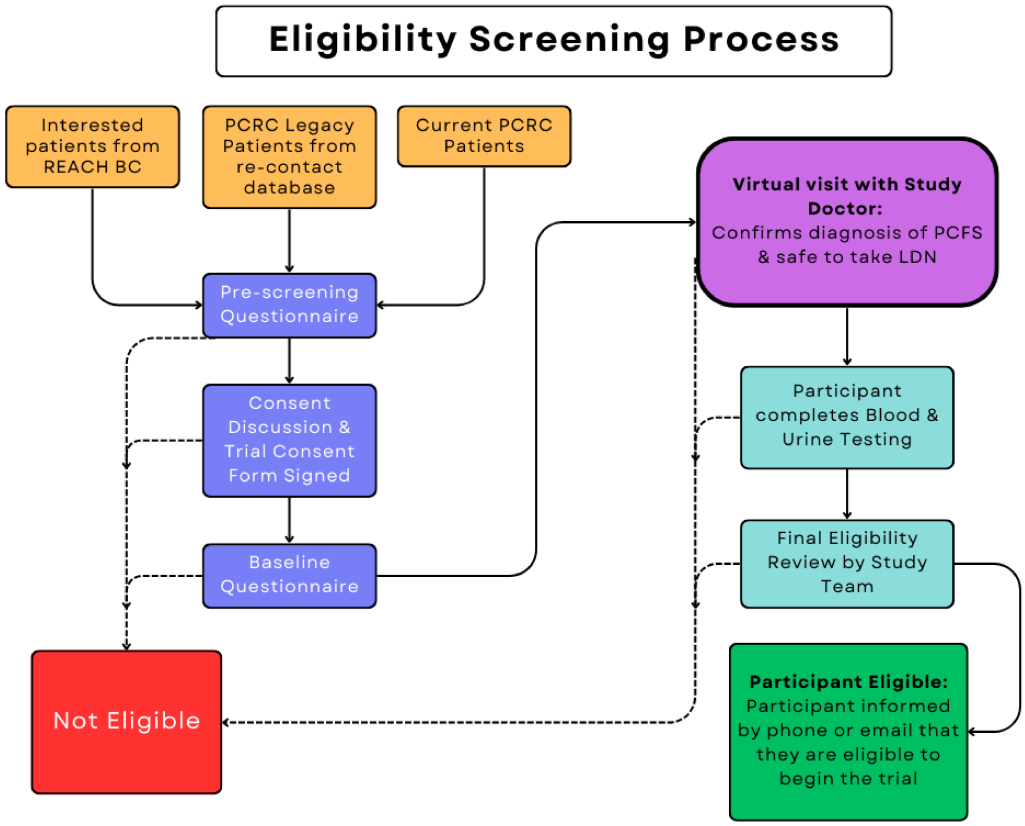
After consenting to the study, you will be asked to complete the following study procedures:

- Completion of questionnaires
- Have a scheduled phone, or telehealth visit with the study doctor in which they will confirm you meet the clinical diagnostic criteria for PCFS and that it is safe for you to take naltrexone.

After the study doctor confirms you have PCFS, blood and urine samples will be collected to confirm your eligibility to the study and as study data that will help with the analysis of the trial results.

Eligibility Process

The flowchart below outlines the eligibility screening process from introduction to the study, to final eligibility review before acceptance and enrollment into the clinical trial. You will be informed of your acceptance into the clinical trial by email or phone call from our clinical trial staff.



Baseline and Treatment Initiation (Week 1)

During the screening period, after completing our Baseline Questionnaires, we will mail you a pedometer with diary sheets and the Participant Instructions. This will be before confirming you are eligible to participate in the study, so there is the possibility you may not be eligible to participate after receiving the pedometer. You can then keep the pedometer and do not need to return it to the study team.

- You will wear a pedometer for 7 days and record the number of steps each day in the diary.

After passing the screening period, you will be asked to complete the following study procedures:

- Have a scheduled in-person, phone, or telehealth visit with study personnel in which they will explain the study procedures and confirm your eligibility to receive the study treatment.
    - If having in-person study visits, additional assessments include: weight, height, blood pressure and pulse at laying down and over 5 minutes following passive standing, sit and stand test, and hand grip strength test.

Once the study team has confirmed you are eligible for the trial, you will be randomized into one of the two treatment groups (low-dose naltrexone or placebo).

The study treatment for the first 6 weeks will then be delivered to you, or you can pick it up in-person at the study site (BC Women's Hospital). You will be asked to take the study treatment once daily at the same time each day.

You will start the study treatment at 1 mg per day; this will be one 1 mg capsule daily. You will also record your dose and any side effects that you experience on the paper diary every day.

Week 2
Towards the end of the first week or after the first week of study treatment, you will meet with the study team via a scheduled telephone or video call. You will be asked about your use of the study treatment, report of any potential side effects, and have the opportunity to ask any questions you may have.

In week 2, you will start at 2 mg per day; this will be two 1 mg capsules daily. You will continue to record your dose and any side effects on the paper diary daily.

If you experience any side effects, such as problems with sleep or gastrointestinal (digestive system) upset, it is suggested that you stay at your current dose, as they will usually decrease as the treatment continues. You will have instructions that outline how and when to change your dose, and can contact the study team at any time if you have questions. Severe side effects to the treatment are very rare. However, if you experience any side effects that persist and/or you find difficult to tolerate, you can return to the dose you were taking in the previous week. If you go back to a lower dose, you will then use this dose for the remainder of the study. You will also be asked to complete the diary for 7 days after you make this change to the dose.

Week 3
In week 3, you will start at 3 mg per day (if you were at the 2 mg dose at the end of the previous week); this will be three 1 mg capsules daily. You will continue to record your dose and any side effects on the paper diary daily.

Week 4
In week 4, you will start at 4.5 mg per day (if you were at the 3 mg dose at the end of the week), this will be three 1 mg capsules and one 1.5 mg capsule daily. This capsule will have a slightly different colour. You will continue to record your dose and any side effects on the paper diary daily.

Weeks 5-6
You will continue taking the study treatment based on the last dose you took in week 4. If you haven't needed to go back to a lower dose, it will stay at 4.5 mg daily.

During week 5, you will have a brief check-in with the study team by email, text, phone or video call, to confirm the study treatment dose you are taking and will be using for the rest of the study duration. At this check-in, the study team may also ask about your experience taking the treatment and you will have the opportunity to ask any questions.

During week 5 or 6, you will receive your second package of study treatment (delivered or picked up at BCW). You will be asked to return any unused study drug, empty containers, and your completed diary sheets from the first package via Canada Post using the prepaid return label provided or in-person to the study site.

In week 6, you will be expected to complete another round of study questionnaires. There is an optional study visit available if you wish to meet with the study team.

Week 7
You will continue taking the study treatment based on the last dose you took in week 4. The only difference is that the whole dose will be in one capsule instead of multiple, and you will only need to take one capsule daily for the rest of the treatment period.

Week 12
You will continue taking the study treatment daily.

At this time, you will be expected to complete another round of study questionnaires. There is a study visit to meet with the study team and check-in with you.

Week 16
You will continue taking the study treatment until the end of week 16.

You will be asked to provide a blood sample at LifeLabs.

You will be asked to wear the pedometer again for 7 days after, while awake, from the beginning of week 16 (you will receive an email reminder) and record the number of steps each day on a paper form. You can then keep the pedometer and do not need to return it to the study team.

After completion of treatment at 16 weeks, you will meet with the study personnel one last time via a scheduled telephone, video call, or in-person, according to your preference.

You will be asked to return any unused study drug, empty containers, and your completed diary sheets from the second package via Canada Post using the prepaid return label provided or in-person to the study site.

You will be expected to complete the final round of study questionnaires.

Study Team Contact during the study
The study team is available to answer any questions you may have at any time during the study. You can contact Dr. Luis Nacul (email: luis.nacul@cw.bc.ca; phone: 604-875-2174), or the study team (email: LDNtrial@phsa.ca; phone: 236-990-9519). The study team email will be monitored daily by multiple staff.

Text messages, phone calls and/or emails will be used to contact you while you are in the study. These may be for items like to remind you of tasks to complete, to thank you for completing

task, scheduling study visits, completing study check-ins, or following up on questionnaire items the study team may have questions about.

Summary of Study Procedures:

Timeline	Participant Procedures	Anticipated Time
Screening	Screening Visit with Study Physician	15-60 min
	Complete study questionnaires	25-60 min
	Collection of blood and urine sample at LifeLabs	30 min (time will vary)
	Wear a pedometer (7 days), record number of steps each day	2-5 min/day
Baseline & Week 1	Study Visit – Study procedures & instructions	30-60 min
	Hand grip strength assessment (in-person only)	3 min
	In person assessments (for those agreeing to in person visits)	15 min
	Receive first treatment package for weeks 1-4	n/a
	Take study treatment (1 mg daily) & fill out diary daily	2 min or less/day
Week 2	Study Check-in - Side effects & questions	5-10 min
	Take study treatment (2 mg daily) & fill out diary daily	2 min or less/day
Week 3	Take study treatment (3 mg daily) & fill out diary daily	2 min or less/day
Week 4	Take study treatment (4.5 mg daily) & fill out diary daily	2 min or less/day
Week 5-6	Take study treatment (4.5 mg daily)	2 min or less/day
	Study Check-in – Confirm final dose & side effects	5-10 min
	Complete study questionnaires	15-45 min
	Receive second treatment package for weeks 7-16	n/a
	Return unused study drug & paper documents (post office or in-person to BCW)	10-30 min*
Week 7-11	Take study treatment (4.5 mg daily)	2 min or less/day
Week 12	Study Visit – Check-in & reminder to book blood draw	15 min
	Take study treatment (4.5 mg daily)	2 min or less/day
	Complete study questionnaires	15-45 minutes
Week 16	Wear a pedometer (7 days), record number of steps each day	2-5 min/day
	Collection of blood sample at LifeLabs	30 min (time will vary)
	Hand grip strength assessment (in-person only)	3 min
	Study Visit – Check-in, side effects, questions & instructions for end of study	30-60 min
	In person assessments (for those agreeing to in person visits)	15 min
	Complete study questionnaires	15-45 min
	Return unused study drug & paper documents (post office or in-person to BCW)	10-30 min*
Total Duration: 16 weeks	**Total Anticipated Time:** 5 hours & 4 min - 9 hours & 38 min	

* timing may vary depending on wait times at the post office.

Study Drug Shipment

The drug will be shipped via the FedEx Clinical Care Service which specializes in shipment solutions for clinical trials or delivered by a local courier to those who live in the Lower Mainland. The exterior of the box has no indication of the contents, and will have your name, address, and the BC Women's Hospital return address. You will be asked how you would like your package delivered. You will be asked if you will allow the package to be handed to an adult within your household, or you can specify that your package will only be handed directly to you. The package will only be handed off by FedEx upon a valid ID check and signature.

- If you receive your study drug from FedEx, you will need to be available for the delivery window (8 am -12 pm). The driver will wait as you remove the study package and reseal the outer shipping box for return. Instructions and tape will be provided inside the outer shipping box.

9. What are the possible harms and discomforts?
Naltrexone in the low doses used in this study are considered safe. Although it is not anticipated with the doses of naltrexone being given in this study, you may experience side effects. It is not known what the impact of Post-COVID fatigue syndrome may have in terms of potential side effects with LDN. In the very unlikely event you experience any serious side effects, you should contact Emergency Services immediately and inform the study doctor.

If you need to go to Emergency or be admitted to the hospital for any reason, please let the study team know via the 24 hour phone number (604-786-2473). If you experience any serious side effects due to the study treatment, the study doctor will assess your symptoms and withdraw you from the study if necessary. Even if withdrawn from the study, the study team will follow your recovery progress until the side effects have fully resolved.

Side effects of taking low-dose naltrexone were seen in less than 10% of patients (from the experience of the CCDP at BCW) and they include:

- Sleep dysfunction
- Gastrointestinal upset
- Skin rash
- Vivid Dreams

If you experience severe or persistent side effects after going back down to a lower dose of the study drug, you can stop the study treatment without tapering. You may withdraw from the study or you can continue even after you have stopped the study treatment.

Other symptoms & possible harms:
If other symptoms, such as shortness of breath, oral swelling, faintness, or any other severe symptom, you should seek emergency medical attention.

Naltrexone has been identified as a hepatotoxin, which is a toxic chemical that damages the liver. This was found using doses five times the recommended dose for opioid blockade or the treatment of opioid/alcohol dependence. No cases of liver failure due to naltrexone have ever been reported. The doses in this study are significantly less (4.5 mg) than the recommended doses (50 mg). Even though the risk of this is very low, if you experience any symptoms of hepatitis (inflammation of the liver) or liver problems, such as feeling very unwell, with jaundice (your skin becomes yellow), fever, vomiting and/or

drowsiness (reduction of level of consciousness), please seek emergency medical attention and advise the study team.

Side effects that have been reported during clinical trials with naltrexone at the recommended doses (50mg tablets) are outlined in the table below. To note, study participants will be receiving less than 1/10th of the recommended dose.

More than 10% of participants experienced the following:
Difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, headache
Less than 10% of participants experienced the following:
Loss of appetite, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, chills
Less than 1% of participants experienced the following:
Respiratory: nasal congestion, itching, rhinorrhea (runny nose), sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, cough, shortness of breath Cardiovascular: nose bleeds, phlebitis (inflammation of the vein), edema, increased blood pressure, non-specific EGG changes, palpitations, tachycardia Gastrointestinal: excessive gas, haemorrhoids, diarrhea, ulcer Musculoskeletal: painful shoulders, legs or knees, tremors, twitching Genitourinary: increased frequency of, or discomfort during urination, increased or decreased sexual interest Dermatologic: oily skin, pruritus (itchy skin), acne, athlete's foot, cold sore, alopecia (hair loss) Psychiatric: depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams Special Senses: eyes – blurred, burning, light sensitive, swollen, aching, strained; ears – "clogged", arching, tinnitus General: increased appetite, weight loss, weight gain, yawning, somnolence (drowsy), fever, dry mouth, head "pounding", inguinal pain (groin pain), swollen glands, "side" pains, cold feet, "hot spells"

Data collected since the approval of naltrexone shows that most side effects occur early during treatment and only last for a short time.

Pregnancy and Breastfeeding

It is not known what effect naltrexone may have on a fetus or if it is secreted in breastmilk. You cannot participate if you are pregnant, may become pregnant, or are currently breastfeeding. If you are a female participant who can become pregnant, you can participate if you agree to use an effective method of birth control during the study. The approved methods are the following:

- Hormonal birth control (for at least 1 month before study drug start)
- Intra-uterine device (IUD)
- Condom with spermicidal foam/gel/film/cream/suppository
- Male partner who has had a vasectomy

- Abstinence

If you get pregnant during the study, inform the study doctor immediately. The study treatment will need to be stopped and you will be withdrawn from the study.

Questionnaires
Completing the questionnaires may or may not make you feel tired. We encourage you to complete the surveys at your own pace.

10. What are the potential benefits of participating?
Participants may experience improvements in fatigue, pain, other symptoms, and well-being. However, there may not be direct benefit to you from taking part in this study.

We hope that the information learned from this study can be used in the future to benefit other people with a similar disease.

11. What are the alternatives to study treatment?
There are no alternatives to the study treatment at this time. You can discuss available options with your study doctor on how to treat your symptoms.

12. After the study is finished
You may not be able to receive the study treatment after your participation in the study is completed. There are several possible reasons for this, some of which are:

- The treatment may not turn out to be effective.
- The treatment may not be approved for use in Canada to treat PCFS.
- You may not feel it is the best option for you.
- You may decide it is too expensive and insurance coverage may not be available.
- The treatment, even if approved in Canada, may not be available free of charge.

The study treatment (naltrexone) is available in Canada but it is not approved for treating PCFS. It can be used off label if a physician prescribes it for you. LDN treatment needs to be compounded by a compounding pharmacy and these costs may not be covered by most insurance plans.

After study completion, we ask that you return any unused study drug, empty containers, and completed paper forms in-person to the study team or via Canada Post.

The leftover biological samples will be stored for up to 10 years after the completion of the study. These samples will only be used for analysis related to this protocol. Samples for this specific research question will not be shared with outside researchers. You will not get the results of any of the research blood test for this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. We would also be happy to provide a summary of the study results via your preferred method of contact.

13. What if new information becomes available that may affect my decision to participate?
If you choose to enter this study and at a later date, a more effective treatment becomes available, it will be discussed with you. You will also be advised of any new information that becomes available that may affect your willingness to remain in this study. You may be invited to sign an amended consent form to indicate your continued consent to participate in the study.

14. What happens if I decide to withdraw my consent to participate?
You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, all information about you collected up to the point of your withdrawal (including information obtained from your biological samples) will be retained for analysis in order to protect the integrity of the research, which may benefit future research participants and patients. However, no further information will be collected. If you decide to withdraw, you may still be asked to come in for a final safety visit to ensure your safety.

If samples have been collected before you withdraw, they will be destroyed or returned to the facility from which they were obtained. There may be exceptions where the samples will not be able to be withdrawn, for example, where the sample is no longer identifiable (meaning it cannot be linked in any way back to your identity).

15. Can I be asked to leave the study?
You may be asked to leave the study if the study doctor judges it is not in your best interest to continue, you experience serious side effects due to the study treatment, you become pregnant during the study, if you are unable to fulfill the requirements for the study, or for any other reason. 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 you decide to take opioid medication over a short time during the study to manage acute pain, you will be allowed to continue in the study, and your study doctor and team will reinforce guidance on taking alternative medication. Please let the study team know if you take any opioid medication or if you start any new medications during the study. You should be aware that naltrexone is an opioid antagonist, which is medication that blocks the effects of opioids. If you do take opioids for pain relief during the study, they may not work well due to the naltrexone.

In the event that you need to take long-term opioid medication, you will be asked to withdraw from the study. All information about you collected up to the point of your withdrawal (including information obtained from your biological samples) will be retained for analysis in order to protect the integrity of the research.

The study doctor will arrange for you to continue your care outside of the study. The study may also be stopped at any time by the sponsor, the C&W Research Ethics Board or Health Canada if new information rises about the safety of the study treatment. The reasons for study stoppage will be explained to you by the study doctor.

16. How will my taking part in this study be kept confidential?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his/her designate by representatives of Health Canada and the C&W Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. You also have the legal right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

The study doctor may need to review your medical record or call your family doctor to help determine if you are eligible for the study and that it is safe for you to take naltrexone. Only the study doctors will access your medical record, the other members of the study team (research coordinator, research assist, etc.) will not be accessing your medical record. If you sign this form you are agreeing to the study doctor reviewing your medical record and/or calling your family doctor.

You should be aware that all of the study test results will be reported to the ordering physician (the study principal investigator Dr. Nacul).

The samples taken at LifeLabs may be referred to a testing laboratory outside of BC to be analyzed (this may be in another province or in the USA). This is because not all tests are performed at LifeLabs and they use other laboratories in these cases.

Studies involving humans now routinely collect information on race and ethnic origin as well as other characteristics of individuals because these characteristics may influence how people respond to different medications. You should be aware that providing this information is not mandatory.

We are asking you to provide a personal email address and phone number (for phone calls and texts, if you prefer) so that we can communicate with you about the study, your participation, send you an electronic copy of your consent form and other study documents, and send reminders.

Before you provide your consent, please carefully consider whether this email account is secure, whether other people have access to it, or whether you have concerns about the security of any information sent to this account. We will only send your personal information to the email address and/or phone number you have provided to us, and all of the information which you provide to us will be kept confidential by the research team. However, you should be aware of the fact that some webmail services (e.g. Gmail, Hotmail, etc.) may store the contents of your email account outside of Canada (for example, in the United States), where privacy and data security standards may be different than they are in Canada. Due to the fact that future emails may contain some personal information about you, including your name, the Freedom of Information and Protection of Privacy Act (British Columbia) requires that we obtain your consent. Providing your email address means that you voluntarily agree and give your consent for the study team to email your consent form, containing personal information, to you.

Your de-identified research data (which means your name, birth date, and other identifiers have been removed) may/will be deposited into a publicly accessible location at the time of publication. This can enhance the transparency of the research data and allows for external validation and fraud control, but it also allows others to access the data for re-analysis of this study, or to do other kinds of analyses in the future beyond those you are consenting to in this study. Also, this future use of your data may not be subject to oversight by a research ethics board, and thus the data may be publicly shared and used in currently unknown ways. Once the data is made publicly available, you will not be able to withdraw your data. Even though the identifying information will be removed from the data, it is possible that others may be able to find out who you are. The chance of this is currently thought to be quite low.

17. What happens if something goes wrong?
By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

In case of a serious medical event, please report to an emergency room and inform them that you are participating in a clinical study and show them your study card. They can contact the study team and/or Dr. Luis Nacul for further information with the phone numbers listed on the study card. The Emergency Contact Number is 604-786-2473.

18. What will this study cost me?
All research-related medical care and treatment, and any related tests that you will receive during your participation in this study will be provided at no cost to you.

To thank you for your participation you will receive $25 gift cards or honoraria (cheque issued by UBC; need to provide personal information (contact details) to UBC for cheques to be issued) twice - one after 6 weeks of treatment and one at the end of study at 16 weeks for a total of $50.

If you agree to have the first and last visit in person, you will receive and additional $25 gift cards or honoraria (cheque) for each visit for a total of $50 for both in person visits.

19. If I have questions about the study procedures during my participation, who should I speak to?
If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact the Study Team at LDNtrial@phsa.ca or 236-990-9519.

20. Who do I contact if I have any questions or concerns about my rights as a participant?
If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598.) Please reference the study number *(H21-02254)* when calling so the Complaint Line staff can better assist you.

If you are a patient from the Fraser Health and you have any concerns about your rights as a research participant, you can also contact Fraser Health Research Ethics Board Co-Chair by calling 604-587-4681.

21. Primary Care Physician(s)/Specialist(s) Notification
Please indicate, by checking the applicable box, whether you want us to notify your primary care physician(s) or specialist(s) of your participation in this study. This is not a consent to release medical information.

☐ Yes, I want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study. My primary care physician(s) and/or specialist(s) name(s) is/are:

_____

The name of the medical clinic I attend is: _____

Participant Initials: _____

☐ No, I do not want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study.

Participant Initials: _____

☐ I do not have a primary care physician or specialist.

Participant Initials: _____

☐ The study investigator is my primary care physician/specialist.

Participant Initials: _____

I understand that if I choose not to advise my primary care physician(s) or specialist(s) of my participation in this study, there may be potential medical consequences, which may affect my

comprehensive medical care or treatment. I understand that the study investigator may not be responsible for these consequences.

You may wish to discuss the consequences of your decision with the study staff.

22. Optional MRI Sub-Study
There is an optional sub-study that will available for some participants. This sub-study will involve MRI scans of the brain at study start and towards the end of the 12-week study period

If you are interested in learning more about the sub-study, check the box below and the research team will provide you further information and connect you with the MRI study personnel.

I am interested in learning more about the MRI sub-study
☐ Yes
☐ No

23. Optional Morning Blood Sampling at LifeLabs
The optional morning blood sampling is for 50 participants who agree to have their study samples drawn at LifeLabs between 8-10 am on the days they have their study bloodwork done. There are two tests, cortisol and adrenocorticotropic hormone, that require that the blood sample is taken in the morning. These tests are expected to be predictors of treatment response and we expect that treatment will be associated with an increase of these concentrations back to normal values.

If you participate in the morning blood sampling, you are agreeing to go to LifeLabs in the morning (8-10am) for your study bloodwork for both time points bloodwork is collected.

I agree to participate in the optional morning blood sampling and will go to LifeLabs between 8-10am for my bloodwork for this study.
☐ Yes
☐ No

24. Optional In Person Study Visits at BCW
Participants who agree to have their first and last study visits (baseline & 16 weeks) will have additional in person assessments completed which will include weight and height, blood pressure and pulse at laying down and over 5 minutes following passive standing, sit and stand test, and hand grip strength test. We are aiming to enroll 50 participants minimum into this sub-group.

If you agree to have the in person study visits, you will receive an additional $25 gift card or honoraria (cheque) for each visit, for a total of $50.

I agree to participate in the optional in person study visits and will attend in person visits at BCW for the baseline and 16 week visits for this study.
☐ Yes
☐ No

25. Participant Consent

A Double Blind Randomized Trial of Low-Dose Naltrexone for Post-COVID Fatigue Syndrome (LDN Trial)

My signature on this consent form means:

- I have read and understood the information in this consent form.
- I have had enough time to think about the information provided.
- I have been able to ask for advice if needed.
- I have been able to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific purposes.
- I understand that my de-identified research data may/will be deposited into a publicly accessible location at the time of publication.
- I understand that my participation in this study is voluntary.
- I understand that I am completely free at any time to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that I receive.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me.
- I authorize access to my health records and samples as described in this consent form.
- I understand that the study doctor will review my medical record and/or call my family doctor to help determine if I am eligible for the study.

I will receive a signed and dated copy of this consent form for my own records.

I consent to participate in this study.

_____	_____	_____
Participant's Signature	Printed name	Date

_____	_____	_____	_____
Signature of Person Obtaining Consent	Printed name	Study Role	Date

Please provide your contact details:

Phone: _____

Email: _____

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