



### Clinical Study Protocol

<b>Protocol Title:</b>	Low dose naltrexone in fibromyalgia: a double-blind randomised placebo-controlled 12-week, two-period, two-sequence Phase 2 cross-over trial
<b>Protocol Number:</b>	LDN-AU-UQ-001
<b>Version/Amendment Number:</b>	1.5
<b>Version Date:</b>	22 September 2023
<b>Supersedes:</b>	1.4 (31 August 2023)
<b>Investigational Product:</b>	Low dose naltrexone (escalating dose to max of 4.5 mg)
<b>Study Phase:</b>	2
<b>Brief Protocol Title:</b>	Efficacy of low dose naltrexone in fibromyalgia
<b>Sponsor Name and Address:</b>	University of Queensland St. Lucia QLD 4072
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The Medical Monitor will be consulted in the event of a severe adverse event, a serious adverse event or overdose occurring.

## PRINCIPAL INVESTIGATOR SIGNATORY

**Study Title:** Low dose naltrexone in fibromyalgia: a double-blind randomised placebo-controlled 12-week, two-period, two-sequence Phase 2 cross-over trial

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As the Principal Investigator, I agree:

- To assume responsibility for the proper conduct of the clinical trial in compliance with the stipulation of this Clinical Trial Protocol (including manuals and other documents referenced), the conditions of the NHMRC National Statement on Ethical Conduct in Human Research (2007 and all updates), Human Research Ethics Committee approval, the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments, and all applicable Institutional, national and local regulatory requirements, at this Investigational site.
- Not to implement any changes to the Clinical Trial Protocol, without prior review and approval for the Human Research Ethics Committee of record, except where necessary to eliminate an immediate hazard to the participant.
- To maintain records of each participant and all data required by the Clinical Trial Protocol.
- To ensure all site staff to which I have delegated tasks are adequately informed and trained about the investigational medicinal product. I understand that information that identifies me will be used and disclosed as described and of their trial related duties and functions, which will be evidenced and documented.

Signed by

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Date

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## Table of Contents

<b>1. Introduction</b> .....	<b>5</b>
<b>2. Background</b> .....	<b>5</b>
<b>3. Aim</b> .....	<b>6</b>
<b>4. Methods</b> .....	<b>6</b>
4a. Study design .....	6
4b. Setting .....	7
4c. Participants.....	7
4d. Research outcomes.....	8
<b>5. Procedures/Interventions</b> .....	<b>11</b>
5a. Recruitment of participants .....	11
5b. Informed Consent.....	11
5c. Randomisation/blinding .....	12
5d. Research intervention.....	13
5e. Participant withdrawal and/or discontinuation of study intervention .....	18
5f. Lost to follow-up .....	18
<b>6. Data Analysis</b> .....	<b>18</b>
<b>7. Data Management</b> .....	<b>19</b>
<b>8. Ethical Considerations</b> .....	<b>20</b>
8a. Benefit/Risk assessment.....	20
8b. Risk management strategy .....	21
8c. Data and Privacy .....	21
8d. Dissemination .....	22
8e. Data quality assurance.....	22
8f. Insurance.....	22
<b>9. Adverse events</b> .....	<b>23</b>
9a. Definitions.....	23
9b. AE and SAE Recording .....	24
9c. Time period and frequency for collecting AE and SAE information .....	25
9d. Method of detecting AEs and SAEs.....	26
9e. Follow-up of AEs and SAEs .....	26
9f. Reporting of SAEs.....	26
9g. Pregnancy.....	26
9h. Death events.....	27
<b>10. References</b> .....	<b>27</b>

## 1. Introduction

Preliminary evidence from a small number of pilot clinical trials suggests that low-dose naltrexone (LDN), an opioid antagonist, has a clinically beneficial impact on fibromyalgia pain, function and quality of life (1). Naltrexone is approved in Australia for treatment of alcohol use disorder and opioid dependence, with an initial dose of 25 mg and a maintenance dose of 50 mg daily. The use of low dose naltrexone to treat fibromyalgia pain is currently off-label but widely used in clinical practice. In fact, our partner compounding pharmacy informs us that low dose naltrexone is one of the most common medicines that they receive prescriptions for, usually by titrating up from a starting dose of 1.5 mg daily for one week, then 3 mg daily for one week, to a maintenance dose of 4.5 mg. As commercial naltrexone tablets are available only in a dose of 50 mg, use at a low dose requires the medicine to be prepared by a compounding pharmacy. The primary aim of this 12-week randomised, Phase 2, placebo-controlled double-blind two-period two-sequence crossover trial is to evaluate the efficacy of LDN in reducing pain in patients with fibromyalgia.

## 2. Background

**Fibromyalgia (FM)** is a chronic pain disorder characterised by widespread musculoskeletal pain, fatigue, cognitive disturbance and psychiatric symptoms (2). FM prevalence within the general population ranges from 1.3-8% and appears to be more common in females (3, 4). FM is a disabling disease, with approximately one third (30.2% - 34.8%) of patients in large American studies having their ability to work affected to the point of requiring supplementary disability income support (5, 6). A recent Australian survey showed a similar rate (35.1%) of financial disability support in fibromyalgia patients with a quarter (24.3%) stopping work and a third (32.6%) reducing paid work within 5 years of symptom development (7). Extrapolating these figures to the Metro South catchment of 1.12 million people using a relatively conservative FM prevalence of 3% gives a FM population of 33,600 of whom approximately one third (11,200 people) are unable to work due to their symptoms. Medications commonly prescribed in FM include gabapentinoids such as pregabalin and gabapentin, opioids, sedatives, antipsychotics, antidepressants of all classes and simple analgesics such as paracetamol and non-steroidal anti-inflammatories (3, 8, 9). These medications often have small effect sizes and duration of benefit may only be a few months, often accompanied by drug tolerance and dependence as well as side effects such as weight gain, somnolence and reduced cognitive ability (2, 3, 9). However, these side effects are often also seen as symptoms of FM, therefore attempts to treat certain aspects of the disease may be worsening the overall condition (9-11).

The precise pathogenesis of FM remains unclear; however, several mechanisms have been hypothesised in the literature. The most accepted theory points to altered central nervous system pain-processing resulting in deficient endogenous analgesic system function (12). Changes include increased temporal summation of pain, changes in endogenous opioids (endorphins and enkephalins), and dysregulation of opioid receptors and pain-related neuropeptides (13-17). These pain-amplifying

changes are often referred to under the umbrella term “central sensitisation”; however it is likely that the nature of central sensitisation differs between patients and chronic pain diagnoses, with central sensitisation in FM reflecting only one aspect of this complex process (12, 18, 19). Low dose naltrexone (an opioid receptor antagonist) may improve symptoms in patients with FM by affecting these processes. Proposed mechanisms include upregulation of endogenous opioid production and reduction in neuro-inflammatory processes (20). In contrast to other pharmacological treatments of FM, LDN has a benign safety and side-effect profile (21, 22).

It is worth recognising that many of the symptoms of FM are shared by patients suffering from long COVID. Indeed a recent study shows that 30% of long COVID patients fulfil the diagnostic criteria for fibromyalgia (23). As long COVID becomes more of a chronic public health problem, the need for effective treatments of central sensitisation syndromes increases (23).

**Low dose naltrexone (LDN)** has been proposed as an alternative option to treat pain and other symptoms of fibromyalgia (19, 23, 24). We recently published a systematic review and narrative synthesis of clinical research involving naltrexone in fibromyalgia (1). After manual screening of 376 search results, the review returned 54 relevant articles. The majority of the papers were case series or reviews and there was a paucity of experimental data. Our review demonstrated a lack of robustly constructed, revealing only three prospective, randomised, blinded trials (25-27). The largest, and the only double-blinded study, had a sample size of 31 (27). All three studies used a dose of 4.5 mg naltrexone taken once daily and even though sample sizes were small they all reported significant improvements in fibromyalgia-associated pain. There is a clear need for further experimental data using a robust double-blind trial design in a larger sample of people with fibromyalgia. The design of our trial is based on that successfully used by Younger et al. 2013 with 31 patients (27).

LDN was reported to be well tolerated in all clinical trials; a small pilot study reported two of their 10 participants reported vivid dreams and one individual experienced transient nausea and insomnia for the first few nights (26). A recent dose–response study found gastrointestinal symptoms to be the most common side effects, including abdominal ache, diarrhoea, constipation, and nausea (28). These side effects were common but generally mild and tolerable. In contrast with other pharmacological treatments of FM, LDN has a benign safety and side effect profile.

### **3. Aim**

The aim of this study is to evaluate the efficacy of low-dose naltrexone in fibromyalgia pain management compared with placebo.

### **4. Methods**

#### *4a. Study design*

This is a 12-week single-centre, prospective, randomised placebo-controlled double-blinded, two-period two-sequence crossover Phase 2 clinical trial.

We are using a superiority framework, testing the hypothesis that LDN provides greater relief from fibromyalgia pain than placebo.

Patients with fibromyalgia will be randomly assigned to receive either LDN in the first period immediately followed by placebo in the second period, or placebo in the first period followed by LDN in the second period. This study design is based on that successfully used by Younger et al. 2013 with 31 patients (27).

- The LDN period is 8 weeks long, involving up-titration of 1.5 mg naltrexone for 1 week, 3 mg naltrexone for 1 week, and then 4.5 mg of naltrexone for 6 weeks.
- The placebo period is 4 weeks long.

#### 4b. Setting

Research activities will be conducted at Metro South Pain and Rehabilitation Centre (MSPRC), with participants attending the MSPRC for assessments and otherwise living at home and going about their normal daily lives during the study.

#### 4c. Participants

Patients of the MSPRC assessed as having FM by the American College of Rheumatology (ACR) 2010 guidelines, utilising the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS). These diagnostic criteria have been the usual research tool for classifying patients as having FM and have been recently tested for validity with favourable results (29).

#### Eligibility criteria:

Table 1. Eligibility criteria

<i>Inclusion criteria</i>	<ul style="list-style-type: none"> <li>a) male or female <math>\geq 18</math> and <math>\leq 65</math> years of age</li> <li>b) diagnosis of FMS according to the American College of Rheumatology (ACR) 2010 criteria utilising the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) by a pain specialist or rheumatologist</li> <li>c) oral morphine equivalent daily dose (OMEDD) less than 60mg at least 4 weeks prior to study participation</li> <li>d) agree to maintain oral morphine equivalent daily dose (OMEDD) less than 60 mg for the duration of the trial*</li> <li>e) provision of written informed consent</li> <li>f) able to complete questionnaires</li> <li>g) Male participants with female sexual partners who are women of childbearing potential must agree to remain abstinent (complete avoidance of heterosexual intercourse) or use adequate contraceptive methods**</li> </ul>
<i>Exclusion criteria</i>	<ul style="list-style-type: none"> <li>h) current treatment with naltrexone</li> <li>i) severe medical or psychiatric illness likely to limit life or participation in trial</li> <li>j) pregnant participants or planning pregnancy during study period***</li> </ul>

	<p>k) known allergy to naltrexone or naloxone</p> <p>l) currently participating in an interventional clinical trial or has participated in another clinical study within the last four weeks or within five half-lives of the prior study treatment, whichever is longer</p> <p>m) a history of acute hepatitis or liver failure or hepatic impairment</p> <p>n) a history of severe renal impairment</p> <p>o) evidence of joint inflammation or any history of rheumatic or autoimmune disease</p>
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- \* If participants require a total dose more than 60 mg OMEEDD, they can continue taking LDN throughout operations or acute pain flares because LDN is an antagonist of only a very small percentage of opioid receptors. The effect on opioid analgesia is minimal. We do not suggest altering the LDN dose as opioids are introduced or withdrawn.
- \*\* Male participants should use condoms and abstain from donating sperm from screening until 2 weeks after last dose of naltrexone.
- \*\*\* Women of child-bearing potential (WOCBP) must confirm that they are not pregnant at enrolment prior to randomisation. They must use a highly effective contraceptive method including oral contraceptive pills [OCs], or an intrauterine hormone device [IUD]) from screening until 2 weeks after last dose of naltrexone. Females who are abstinent from heterosexual intercourse as part of their usual lifestyle do not need to use contraception.

*Participant replacement:* Participants that withdraw or are lost to follow-up for any reason other than safety may be replaced to ensure that an appropriate number of participants complete the study.

*Study group:* Participants will be assigned to one of two groups:

Group 1: LDN followed by placebo. Naltrexone 1.5 mg daily for one week, naltrexone 3 mg daily next week, naltrexone 4.5 mg daily for 6 weeks, followed by placebo for 4 weeks.

1 week 1.5 mg	1 week 3 mg	6 weeks 4.5 mg	4 weeks placebo
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Group 2: Placebo followed by LDN. Placebo capsule for first 4 weeks, naltrexone 1.5 mg daily for one week, naltrexone 3 mg daily next week, naltrexone 4.5 mg daily for subsequent 6 weeks.

4 weeks placebo	1 week 1.5 mg	1 week 3 mg	6 weeks 4.5 mg
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#### 4d. Research outcomes

The main outcome measure tool used will be the Revised Fibromyalgia Impact Questionnaire (FIQR). This consists of 21 items in 3 domains (physical impairment, overall impact and severity of symptoms) with a 0-10 numeric scale for each. This is then simplified into a score out of 100.

Another group of outcome measures are already routinely collected by MSPRC for the purposes of benchmarking and service development, so the investigators are experienced in the use of these



assessment tools to understand the changes in the impact of pain and the levels of depression, anxiety, and stress among participants. The suite of questionnaires is developed by the Electronic Persistent Pain Outcomes Centre (EPPOC) and consists of the following outcome measures: Brief Pain Inventory (BPI), Pain Catastrophising Scale (PCS), Pain Self-Efficacy Questionnaire (PSEQ), Depression/Anxiety/Stress Scale 21 (DASS21), Global Rating of Change (GROC). All questionnaires will be completed online through Qualtrics on a 4-weekly basis. The schedule of questionnaire activities is provided in Figure 1.

#### *Primary outcome*

1. Level of pain severity as measured by the Revised Fibromyalgia Impact Questionnaire (FIQR) Domain 3: severity of symptoms, Question 1: average pain intensity during the last 7 days on an 11- point rating scale (ranging from 0 = “no pain” to 10 = “unbearable pain”). The value is then converted to percentage of pain reduction from baseline, using the following formula:  $[(\text{baseline pain} - \text{endpoint pain}) / \text{baseline pain}] \times 100$ . The response to this question will be collected at the end of each 7-day period.

#### *Secondary outcomes*

1. Impact of fibromyalgia: assessed by the FIQR total score. Participant will rate each of the three domains with a 0-10 numeric scale for each. The total score is then converted to percentage of impact of fibromyalgia from baseline, using the following formula:  $[(\text{baseline impact of fibromyalgia} - \text{end point impact of fibromyalgia}) / \text{baseline impact of fibromyalgia}] \times 100$ . This measure will be collected at baseline, 4 weeks, 8 weeks, 12 weeks and 16 weeks.
2. Impact of pain as measured by BPI, PCS and PSEQ. Impact of pain will be assessed using the Brief Pain Inventory- short form (BPI), Pain Catastrophising Scale (PCS) and Pain Self-Efficacy Questionnaire (PSEQ). Participant will rate their pain severity by responding to question 2, 3, 4 and 5 using the BPI with a 0-10 numeric scale using a 11-point rating scale (ranging from 0= “no pain” to 10= “pain as bad as you can image”). The total score obtained will be divided by 4 and this will give a severity score out of 10. Participant will rate their pain interference by responding to question 8 using the BPI with a 0-10 numeric scale using a 11-point rating scale (ranging from 0= “does not interfere” to 10= “completely interferes”). The total score obtained will be divided by 7 and this will give an interference score out of 10. The score is then converted to percentage of pain severity or pain interference from baseline, using the following formula:  $[(\text{baseline pain severity or pain interference} - \text{end point pain severity or pain interference}) / \text{baseline pain severity or pain interference}] \times 100$ . Participant will rate their pain catastrophising by responding to 13 questions in the PCS with a 0-4 numeric scale using a 5-point rating scale (ranging from 0= “not at all” to 4= “all the time”). The total score obtained will be interpreted as follows: a score above 30 indicates a clinically relevant level of catastrophising. The change in the levels of catastrophising is calculated

from baseline, using the following formula:  $[(\text{baseline pain catastrophising} - \text{end point pain catastrophising}) / \text{baseline pain catastrophising}]$ . Participant will rate their pain self-efficacy by responding to 10 questions using the PSEQ with a 0-6 numeric scale using a 7-point rating scale (range from 0= “not at all confident” to 6= “completely confident”). The total score obtained will be divided by 10 and this will give a confidence score out of 10. The score is then converted to percentage of confidence from baseline, using the following formula:  $[(\text{end point confidence} - \text{baseline confidence}) / \text{baseline confidence}] \times 100$ . These measures will be collected at baseline, 4 weeks, 8 weeks, 12 weeks and 16 weeks.

3. Levels of depression as measured by DASS-21. Participant will rate their levels of depression by responding to the 7 depression domain questions with a 4-point rating scale (ranging from 0 = “never” to 3 = “almost always”). The total score obtained is multiplied by 2 to allow interpretation on the original DASS scale: normal (0-9 points), mild (10-13 points), moderate (14-20 points), severe (21-27 points), and extreme (28 or more points). This measure will be collected at baseline, 4 weeks, 8 weeks, 12 weeks and 16 weeks.
4. Level of anxiety as measured by DASS-21. Participant will rate their levels of anxiety by responding to the 7 anxiety domain questions with a 4-point rating scale (ranging from 0 = “never” to 3 = “almost always”). The total score obtained is multiplied by 2 to allow interpretation on the original DASS scale: normal (0-7 points), mild (8-9 points), moderate (10-14 points), severe (15-19 points), and extreme (20 or more points). This measure will be collected at baseline, 4 weeks, 8 weeks, 12 weeks and 16 weeks.
5. Level of stress as measured by DASS-21. Participant will rate their levels of stress by responding to the 7 stress domain questions with a 4-point rating scale (ranging from 0 = “never” to 3 = “almost always”). The total score obtained is multiplied by 2 to allow interpretation on the original DASS scale: normal (0-14 points), mild (15-18 points), moderate (19-25 points), severe (26-33 points), and extreme (34 or more points). This measure will be collected at baseline, 4 weeks, 8 weeks, 12 weeks and 16 weeks.
6. Change in overall fibromyalgia condition will be assessed with the GROC: Global Rating of Change with a -7 - +7 numeric scale using a 15- point rating scale (ranging from -7 = “a very great deal worse” to +7 = “a very great deal better”). The score is then converted percentage of the change in fibromyalgia condition from baseline, using the following formula:  $[(\text{end point change in fibromyalgia condition} - \text{baseline change in fibromyalgia condition}) / \text{baseline change in fibromyalgia condition}] \times 100$ . This measure will be collected at baseline, 4 weeks, 8 weeks and 12 weeks and 16 weeks.

Additionally, on a weekly basis at the same time as reporting overall pain for the primary outcome measure, participants will be asked to report any adverse events, changes to medications (e.g.

prescription, over the counter, complementary medicines) taken and compliance with the trial medications during the previous week. Assessment will be made of any increase in the severity or frequency of baseline conditions and adverse events, or increase in use of medications (e.g. indicating the need to treat breakthrough pain or mood). In the weekly check-in survey on week 13, there will be one additional question to allow participants to provide feedback on the study. A brief summary of study results and group allocation will be provided to participants via email at the end of the trial, if they express their willingness to receive it during the initial consent stage. See Figure 1 for the schedule of assessments.

## **5. Procedures/Interventions**

### *5a. Recruitment of participants*

There are approximately 600 new patients at MSPRC each year. It is estimated that 20% fulfil a diagnosis of fibromyalgia and that 50% of these would consent to being part of a trial. Therefore, after one year of recruitment we would expect a sample size of around 80 patients. A sample size of 77 has been calculated by a statistician to provide power of 80% at an alpha level of 0.05, assuming standard errors of 10 and 9, and measured outcome means in the FIQR question relating to overall pain compared to baseline of -15.5 and -11.2 for LDN and placebo.

Recruitment will be completed by MSPRC and Princess Alexandra Hospital Rheumatology Department medical staff as part of normal outpatient clinical consultation. During this time verbal consent will be sought from the patient for the research team to contact them. The flyer will also be displayed at both MSPRC and Princess Alexandra Hospital Rheumatology Department clinics, where participants can express their interest in joining this clinical trial. In case patients at MSPRC or Princess Alexandra Hospital Rheumatology Department are interested but unsure about the registration process, the medical staff can assist them in registering their interest for the trial online through a Qualtrics survey to determine their initial eligibility. Upon receiving the interest form, our research team at MSPRC will reach out to the participants to confirm their available time for further processes.

### *5b. Informed Consent*

Patients who express an interest in participating will be required to meet with a member of our research team, either in person or via teleconference, for screening evaluation to according to the eligibility criteria (Section 4c). Each participant will be provided with oral and written information describing the nature, purpose and duration of the study, participation/termination conditions, and risks and benefits. Participants will be asked to provide information regarding the following, which will be documented in the source file:

- Demographic information such as age, gender, and ethnicity

- Medical history including any pre-existing medical conditions, recent surgeries or hospitalisations
- Current medication usage, including prescription and over-the-counter medications (the name, dosage, frequency, and duration of use; enough information to allow OMEDD calculation where applicable)
- Allergies or sensitivities to any medications or substances
- Current or recent participation in clinical trials or research studies
- If they would like to receive a copy of a summary of study results and/or group allocation
- Contact information for communication and follow-up purposes.

The informed consent will be obtained by the Principal Investigator or their trained representative before recording any personal or health-related information.

Once informed consent is obtained, the original signed PDCF will be retained in the participant files with their source documents and a copy of PDCF will be provided to the participant. The participant will be informed that they can freely withdraw consent and stop participation in the study at any time with no prejudice to post-study care.

Participants who are re-screened are required to sign a new PDCF if it has been more than 30 days from the initial consent date. The re-screening visit conditions include participants who have forgotten to pick up their medications and those who can maintain an oral morphine equivalent daily dose (OMEDD) of less than 60 mg at least 4 weeks.

### *5c. Randomisation/blinding*

As each participant is confirmed eligible for the study, they will be allocated a participant number, starting from 01 and taking the next available participant code. The participant and the investigators will keep a record of the participant number. The investigators will provide the participant's name and number, and instructions to dispense the trial medication for the participant, in the form of a prescription to the compounding pharmacy.

The compounding pharmacy will create a randomisation schedule in which participant numbers are allocated to Group 1 or Group 2 in the ratio 1:1 in blocks of 10, i.e. five to Group 1 and five in Group 2 within each block of 10 participants, using random number generation.

All randomisation and blinding will be completed by the compounding pharmacy team and kept in a separate database away from clinical staff and blinded members of the research team, thus ensuring double blinding (both clinician and patient). Access to the randomisation sequence is limited to persons documented on the unblinding log. The Investigator should promptly document any premature unblinding (e.g., accidental unblinding, unblinding due to an SAE) of the treatment assignment. If unblinding is deemed to be necessary by the Principal Investigator, the duty pharmacist

at our partner compounding pharmacy will be contacted to provide the identity of the participant as being Group 1 or Group 2.

To ensure the blinding of participants regarding the timing of the crossover, no washout period will be employed between the low dose naltrexone and placebo conditions. This decision has been made to eliminate any cues that may indicate the switch between treatment and placebo.

*5d. Research intervention*

The study intervention is described in Table 2. Participants will receive their trial medications either collected from the Pain Rehabilitation Clinic, or from the compounding pharmacy, or mailed to their home address. At the end of the study, participants will return any unused medications and bottles to the Pain Clinic for destruction by the School of Pharmacy.

Table 2: Study intervention

Intervention name	Low dose naltrexone (LDN)	Placebo
Type	Investigational medicinal product	Placebo
Dosage form	Hard-shell opaque vegetable capsule	
Unit dose strength(s)	1.5 mg or 3 mg or 4.5 mg naltrexone hydrochloride in microcrystalline cellulose.	139 mg microcrystalline cellulose
Dosage	One capsule daily	
Route of administration	Oral	
Use	Experimental	Comparator
Sourcing	The capsules will be extemporaneously prepared by a compounding pharmacy using pharmaceutical grade materials. All compounding is performed in accordance with Guidelines from the Australian Pharmacy Board, and the TGA’s Compounded medicines and GMP guide. A supply agreement between the Sponsor (UQ) and the compounding pharmacy will be in place.	
Storage	Store at room temperature, 15-25°C. The expiry date for this product is six months from the date of compounding or the stated expiry of the pure naltrexone, whichever is the lesser.	
Packaging	Capsules will be packaged with 7 capsules per bottle, i.e. one week supply per bottle. Participants will receive 12 bottles, each labelled from week 1 through to week 12.	
Disposal	Medicine bottles and any unused capsules will be returned to the study site for assessment of compliance. Unused medication will be disposed of in accordance with appropriate local waste management guidance.	
Labelling	Labels will be in accordance with PIC/S Annex 13, and with WEEK 1 through to WEEK 12 labelled clearly and in large font:  <b>WEEK 1</b> This bottle contains 7 capsules for oral use	

	<p><b>Take one capsule one hour before bedtime at night</b></p> <p>Participant number: Store at 15-25°C</p> <p>Dispensed date:                      Expiry date: Batch number:</p> <p>Protocol number: LDN-AU-UQ-001</p> <p>Dr Nick Aitcheson, Metro South Pain and Rehabilitation Centre, 0461-281-728</p> <p>For clinical trial use only Keep out of reach of children</p> <p>Compounding pharmacy name, address, phone number</p>
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### *Treatment guide*

A treatment guide provides information on how to correctly follow the prescribed bottle of LDN and a strategy for managing missed doses. The guide will be individualised for each participant to contain the start date for each bottle, ensuring participants know when to begin using that particular bottle and maintain the appropriate sequence throughout the treatment period. To prevent confusion with medication bottles, our research team will send a text message every Monday morning to remind participants to change their bottle. We will also provide them with strategies, such as putting numbers on the top of the bottles, and turning bottles upside down or placing in a plastic bag after use.

If participants are unsure about the proper sequence or have any concerns regarding their LDN regimen, they can contact the provided phone number for clarification and guidance.

### *Participant card*

All participants will receive a participant card and be told that it is essential for participants to carry this card with them during their GP appointments, visits to other allied healthcare services, or in case of emergency department visits.

Participants are required to inform their GPs and healthcare professionals that they are actively participating in this clinical trial. This ensures that the healthcare providers are aware of the participant's involvement and can provide appropriate care within the context of the trial.

If any concerns or questions arise from the GPs or healthcare professionals, they have the option to contact the study team directly. The study team will be available to address any inquiries, provide additional information, or offer guidance as needed. This open line of communication between the study team and healthcare professionals contributes to participant safety and the successful execution of the clinical trial.

The participant card will contain the following information: protocol number, participant's number, and the trial email and phone number for any questions or urgent medical inquiries they may have.

### *Study intervention compliance*

Only participants who consented, found to be eligible and randomised in this study may receive study treatment. All medicinal product (including placebo) during the study will be self-administered. The weekly check-in survey will include a reminder section and a question regarding compliance and request the number of missing doses. An email notification will be sent at the designated check-in time. In the event that a participant forgets to complete the check-in survey, our study team will send a text message reminder one day after the scheduled check-in time. If the participant does not complete the survey or respond to the text message, our research team will contact them via phone to verify their medication usage. For participants that are non-compliant with dosing, the date of, and reason for, deviations will be documented in all cases.

#### *Dose modifications/interruptions*

Participants will receive the specified dose according to their stage of clinical trial. Dose modification is not allowed. Participants who are unable to tolerate the assigned dose will be required to withdraw from the study. Post-participation care will be provided at the Metro South Health Clinic, where participants will have access to comprehensive clinical support as well as other community resources to ensure they receive the necessary assistance and care.

#### *Missed dose*

Participants will be provided with instructions on what to do in case they miss a dose. If a participant misses one capsule, they should skip their assigned dose for that day, continue with the next scheduled dose, and make a record of the missed dose along with the reason for missing it on that date. In the event that a participant misses two capsules, they should skip both of the missed capsules, proceed to the next scheduled dose, and document the missed doses and the reasons for missing them on both respective days.

If a participant misses seven or more capsules consecutively, they will be withdrawn from the study. Our study team will follow up on participant safety throughout the trial, providing appropriate monitoring and support, and recording all interactions with participants.

#### *Treatment of Overdose*

The likelihood of overdosing on LDN capsules is extremely low. The typical dose of naltrexone is 50 mg per day or up to 150 mg every three days. The total amount of naltrexone in the 84 capsules contained in the trial package is 220.5 mg.

There are no specific treatments for overdose. In the event of an accidental overdose, the Investigator should contact the Medical Monitor immediately, and in consultation with the Medical Monitor, determine whether additional steps should be taken. Document the quantity of the excess dose and closely monitor the participant for any AEs or SAEs. Treat any AEs with appropriate supportive care and report any SAEs (see Section 9).

### Medication returns after end of study

After the completion of this study, participants will receive reminders to return their bottles and unused capsules to the MSPRC on week 13. Our research team will schedule a specific time for participants to return their medications or provide a postage-paid mailing envelope.

### Access to study intervention after end of study

Participants will be informed about post-trial access to intervention at the time of obtaining informed consent. This information has also been included in PICF. Post-trial LDN prescription will not be provided by the study doctor. However, if required, the study team can provide details to the patient's regular treating GP/physician who will then make a clinical judgement on the use of LDN after the end of the study.

Figure 1. Study schedule

Study stage	Screening & baseline	Treatment and follow-ups													
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	16
Window (+/- days)	Day -30 to Day -1	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2
Screening & Informed Consent	×														
Demographic and medical history	×														
Randomisation	×														
Participant number	×														
Medication collection	×														
Treatment guide & participant card	×														
Dose (mg) Group 1		1.5 mg	3.0 mg	4.5 mg	4.5 mg	4.5 mg	4.5 mg	4.5 mg	4.5 mg	P	P	P	P		
Dose (mg) Group 2		P	P	P	P	1.5 mg	3.0 mg	4.5 mg	4.5 mg	4.5 mg	4.5 mg	4.5 mg	4.5 mg		
<i>Check-in survey</i>															
Primary outcome: Pain severity	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Medication list	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Adverse events		×	×	×	×	×	×	×	×	×	×	×	×	×	



Feedback (optional)															×	
Notification of group allocation/summary results (optional)																×
Medication return															×	
Follow-up emails/texts and calls when required		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
<i>Secondary outcome questionnaires</i>																
FIQR	×				×				×					×		×
BPI	×				×				×					×		×
PCS	×				×				×					×		×
PSEQ	×				×				×					×		×
DASS21	×				×				×					×		×
GROC	×				×				×					×		×

P: Placebo; FIQR: Revised Fibromyalgia Impact Questionnaire; BPI: Brief Pain Inventory; PCS: Pain Catastrophising Scale; PSEQ: Pain Self-Efficacy Questionnaire; DASS-21: Depression/Anxiety/Stress Scale 21; GROC: Global Rating of Change

### *5e. Participant withdrawal and/or discontinuation of study intervention*

All participants are free to withdraw from participating in this study at any time for any reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary participant management.

Discontinuation of study intervention will be considered for any of the following reasons:

- The participant experiences an intolerable AE or SAE.
- The participant enrolls into another clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The participant becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 9g.
- The participant is unwilling or unable to comply with the protocol.
- Investigator decision that it is not in the best medical interest of the participant to continue participation in the investigation.

Participants who discontinue from study intervention should complete all safety follow-up activities to the best extent possible.

Participant withdrawals will be documented clearly on the source documents.

### *5f. Lost to follow-up*

If a participant does not complete a scheduled questionnaire, the study team will attempt to contact the participant during the subsequent two weeks. If the participant still cannot be contacted, the study team will write to the participant using their last known address. If no contact is made by the participant, the study team will consider the participant lost to follow-up. All follow-up attempts will be documented and kept with the participant's source documentation.

## **6. Data Analysis**

Primary analyses will be based on responses in the self-reported questionnaires. Questionnaire scores will be generated using an automated summation system within Qualtrics. The automated summation system has been thoroughly reviewed and validated by our research team. To ensure participants provide accurate answers and complete all questions, text entry questions will be set with specific validations for each field. Additionally, a reminder will be displayed on the screen if participants do not complete all questions. Our study team will cross-check all scores to ensure accurate calculations using an excel spreadsheet, and transfer all data to a CSV document for further analysis.

The baseline pain level will be determined by calculating the score using the FIQR. To contrast the placebo and low-dose naltrexone conditions, the percentage of change in the level of pain from baseline is assessed during the final week of each treatment condition (placebo versus low-dose

naltrexone). In the statistical analysis of the study data using linear mixed effects modelling, the dependent variable will be the percentage of change in the level of pain. The independent variables considered in the analysis will include the treatment condition (placebo versus low-dose naltrexone) and the group designation (whether participants received placebo first or low-dose naltrexone first). The participant number will be included as a random effect, accounting for any potential individual differences or variability among participants that could impact the results. This model will be repeated for all secondary outcomes. In addition, data analyses will be performed following an intention-to-treat plan. A 5% significance level will be used. Expert statistical input will be sought for more in-depth analysis.

## **7. Data Management**

UQ Research Data Management Policy (PPL 4.20.06) will be followed to ensure the data is managed under legal, statutory, and ethical requirements and in accordance with the Australian Code for the Responsible Conduct of Research. The data will be stored securely in durable format. UQ provides storage in its internal network (Research Data Manager).

Source documentation and signed PICF will be collected on paper and will be kept in locked premises, password protected, or in locked filing cabinets onsite at MSPRC for the duration of the trial. Paper documents will be scanned for secure digital storage alongside source data files collected electronically; digital files will be named using a consistent naming structure. After the conversion into digital format, paper records will be destroyed via a secure document destruction contract service or using local shredding equipment.

Digital records will be stored on a secure password protected server that meets UQ's secure data storage requirements (Research Data Manager). In keeping with the relevant policies regarding retention and disposal of clinical research records, the information will be retained for 15 years. This also fulfils the Australian Code for the Responsible Conduct of Research requirements for retention of research data.

The Qualtrics system is hosted on a UQ infrastructure-based server (on-premise system). The software provider (Qualtrics company) does not have any access to our system. The system gathers IP addresses and access times, and internet service logging on the server which gathers information for security purposes (standard for all web servers). The data within Qualtrics (answers to surveys, IP addresses and access times) can only be accessed by the survey owner and the system administrator (if help is requested). After completion of data collection, we will download from Qualtrics and retain in a database saved in the UQ RDM folder for longer term storage. Once the database is complete (all survey data have been entered), the original participant id code will be deleted to ensure no possibility of tracing back to the participant's identifying data. De-identified data from this study will be made available to future researchers on application to the Principal Investigator.

The digital records will be destroyed by contacting Record Management and Advisory Service (RMAS) (or the equivalent department that is current at the time of the destruction).

## **8. Ethical Considerations**

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki, ICH GCP for Guidance on Good Clinical Practice and NHMRC National Statement on Ethical Conduct in Research Involving Humans. The trial will be registered with Australia and New Zealand Clinical Trials Registry and reported by Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) and CONSORT for RCTs.

Ethical approval will be obtained from Metro South HREC and University of Queensland HREC. A site-specific agreement (governance) will also be obtained for MSPRC site.

Any amendments to the protocol will require HREC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator is responsible for the following:

- Providing written summaries of the status of the study to the HREC at least annually, in accordance with the requirements, policies, and procedures established by the HREC;
- Notifying the HREC of SAEs or other significant safety findings as required by HREC procedures; and
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the HREC, and all other applicable local regulations.

### *8a. Benefit/Risk assessment*

Potential benefits: Based on previous clinical data reviewed by Aitcheson et al. 2023 (1), LDN may (i) attenuate inflammatory processes using antagonism of immune cell receptors (ii) reduce pro-inflammatory cytokines, and (iii) reduce fibromyalgia pain. Thus, LDN may improve quality of life of patients with fibromyalgia. There is no financial incentive or reimbursement offered to participants in this trial.

Potential risks: Based on previous clinical data, LDN has been associated with some adverse effects, primarily vivid dreams when taken at night and gastrointestinal symptoms that are mild and manageable. Moderate to severe adverse effects are associated with the higher doses available commercially and used in the treatment of alcohol use disorder and opioid dependence, including hypersensitivity reactions, depression or other mood or mental changes. Due to LDN being an antagonist of only a very small percentage of opioid receptors, its impact on opioid analgesia, alcohol

consumption, and driving or operating machinery is minimal. Participants will be advised that if they experience feelings of dizziness and sleepiness, they should not drive or operate machinery.

According to the Therapeutic Goods Administration (TGA), naltrexone is classified as pregnancy risk category B3. This category is defined as follows: "Drugs that have been taken by a limited number of pregnant women and women of childbearing age, without an observed increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus. However, studies in animals have shown evidence of increased occurrence of foetal damage, the significance of which is considered uncertain in humans" (30). Therefore, contraceptive methods are required for this trial.

#### *8b. Risk management strategy*

- Participants who are allergic to naltrexone will be excluded from the study. Participants will be prompted to report any signs or symptoms indicative of hypersensitivity reaction (e.g., fever, chills, rash, myalgias, etc.) within the weekly check-in survey and this will have a reminder to seek immediate medical attention by going to the emergency department.
- Participants with high level of depression or suicidality are likely excluded based on the exclusion criteria. As the participants are all patients of Metro South Health they have the usual supportive clinical and community mental health networks available. If suicidality/excessive depression is identified, then MSPRC clinicians (psychologists and doctors) are available for triage and coordination of these supports (as would be available for any patient of the clinic).
- Participants may experience withdrawal symptoms if they discontinue opioid medications abruptly or take naltrexone at the doses used for treatment of alcohol use disorder and opioid dependence. The doses are one-tenth for LDN in fibromyalgia, so the risk is reduced. To mitigate the potential risk, the investigator will engage in discussions with participants regarding their opioid medication management plan. Additionally, participants will be closely monitored for any withdrawal symptoms throughout the study duration.

#### *8c. Data and Privacy*

Only employees of Queensland Health will be able to access a patient's medical records. UQ affiliates who are not with Queensland Health will not have access to these records. Access to medical records will not be to collect data for the study, but rather used to ensure patient safety. The study clinicians will only access patient medical records when clinical needs arise. In the case that representatives from the Sponsor, HREC or health authority inspectors require access records for trial monitoring or audit function, this will be possible under the custodianship of the research team; this information is contained in the PICF.

Participant medical information obtained by this study is confidential. All records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Upon the participant's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study documents (protocols, PICF, etc.) will be stored appropriately to ensure their confidentiality.

#### *8d. Dissemination*

- All dissemination will be undertaken using aggregated data only. Authorship of manuscripts arising from the study will be decided by mutual consensus of the research team and as per UQ's authorship and publication policies.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- Study results may be presented at international scientific meetings.
- After the completion of the study, if requested, participants will receive a brief overall result and which study group they were allocated to.

#### *8e. Data quality assurance*

- All participant questionnaire data relating to the study will be recorded on Qualtrics. All data will be transferred to a CSV document and stored in UQ RDM folders. The Investigator is responsible for verifying that data entries are accurate and correct; regular data quality checks will be undertaken by the Investigator's delegate, as will be indicated in the delegate log.
- Additional information regarding the initial assessment, changes in concomitant medications, and adverse events assessment will be documented in the participant source records. The Investigator will ensure the accuracy and correctness of data entries, and routine data quality checks will be performed by the Investigator's delegate, as noted in the delegate log.
- If any amendments are required to the protocol or documentation, the new versions will be circulated to the team and the compounding pharmacy, and confirmation obtained that superseded versions have been removed and all are working to the new version. Confirmation of understanding of the changes will be made by telephone or videoconference or personal meeting with all members of the investigator and pharmacy teams.
- The Investigator will permit study-related monitoring, audits, HREC review, and regulatory agency inspections and provide direct access to source data documents.

#### *8f. Insurance*

UQ provides clinical trial insurance coverage by Newline Australia Insurance Pty Ltd.

## 9. Adverse events

### 9a. Definitions

Definition of AE:

- any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of ADR:

- any AE for which the causal relationship between the medicinal product and occurrence is expected.
- In the case of LDN, based on previous clinical data, LDN has been associated with potential adverse events, which may include vivid dreams, nightmares, insomnia, headaches, nausea/upset stomach, dry mouth or dry throat, shortness of breath, anxiety, agitation, dizziness, increased hair growth, increased sweating, and weight gain.

Definition of SAE:

- Results in death
- Is life-threatening: an event in which the participant was at risk of death at the time of the event.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
  - admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalisation for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

Definition of events meeting the AE:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Definition of events NOT meeting the AE:

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

*9b. AE and SAE Recording*

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the screening number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.



#### Assessment of intensity:

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as ‘serious’ when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- For all severe AEs, the Investigator should contact the Medical Monitor immediately, and in consultation with the Medical Monitor, determine whether additional steps should be taken.

#### Assessment of causality:

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

After obtaining informed consent, each participant will be given the telephone number for reporting AEs and medical emergencies: this information is contained on the participant card.

#### *9c. Time period and frequency for collecting AE and SAE information*

All AEs and SAEs will be recorded from the time of informed consent until the final questionnaire at week 16 through the weekly survey.

Throughout the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the participant. If necessary, appropriate medical intervention should be provided.

#### *9d. Method of detecting AEs and SAEs*

Adverse events may be spontaneously reported by the participant, obtained through non-leading questioning, or noted during examination of a participant. When recording an AE, a diagnosis is always preferable; however, in the absence of a diagnosis, the Investigator should record each sign and symptom as an individual AE. Medical or surgical procedures (e.g., cardiac ablation) should not be recorded as AEs. Rather, the condition for which the procedure was performed should be recorded.

#### *9e. Follow-up of AEs and SAEs*

All related SAEs must be followed until resolution, until the condition stabilises, until the event is otherwise explained, or the participant is lost to follow-up. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, relevant hospital records (i.e., discharge summary), or consultation with other health care professionals. Ensure that all participant identifiers are redacted from supportive documentation prior to submission.

#### *9f. Reporting of SAEs*

It is the responsibility of the Investigator to report SAEs to the Sponsor within 24 hours of awareness of the event or safety information, whether initial or follow-up. Do not delay in the reporting of suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report.

#### *9g. Pregnancy*

The Investigator must report a pregnancy occurring in a female participant to the Sponsor or designee within 24 hours of the study site staff becoming aware of the pregnancy. In addition, if a female participant becomes pregnant within 2 weeks after last dose of naltrexone, the pregnancy must also be reported within 24 hours of the study site becoming aware of the pregnancy. According to the MIMS database, the mean elimination half-life values for 50 mg naltrexone and 6- $\beta$ -naltrexol are 4 hours and 13 hours, respectively (31). Based on this data, 2 weeks will be sufficient time to completely eliminate all naltrexone from the system. The Investigator or study site staff must also follow the pregnancy until the outcome is known and submit the outcome as follow-up within 24 hours of notification of outcome. Follow-up Pregnancy Forms may be submitted as required for additional information obtained. Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy, for medical reasons, will be recorded as an AE or SAE and followed as such. Pregnancies in partners of male study participants will

similarly be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (i.e., birth, or spontaneous or elective abortion).

#### *9h. Death events*

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate paper case report form. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor, or designee. If cause of death is not available within the 24-hour reporting period, “death” must be reported as SAE term to meet timelines and the cause of death actively queried and submitted as a follow-up report.

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