**The HARM REDUCTION Study**

**NOVEL OTP (OPIOID TREATMENT PROGRAM) FOR HARM REDUCTION DURING OUTBREAK**

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This trial will be conducted in compliance with the Clinical Trial Protocol, applicable regulations, and with the principles of Good Clinical Practice (GCP)/International Conference of Harmonization (ICH)

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**ABBREVIATIONS**

|  |  |
| --- | --- |
| AD-SUS | Alcohol & Drug adapted Adult Service Use Schedule |
| AE | Adverse Event |
| ATOP | Australian Treatment Outcomes Profile |
| COWS | Clinical Opiate Withdrawal Scale |
| CRF | Case Report Form |
| DASS-21 | Depression, Anxiety, and Stress Scales 21 |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders – 5th Edition |
| ECG | Electrocardiogram |
| EQ-5D | EuroQol five dimensions health questionnaire |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HEOs | Health economic outcomes |
| HRU | Healthcare resource utilization |
| ICD-11 | International Statistical Classification of Diseases and Related Health Problems – 11th Edition |
| ICF | Informed Consent Form |
|  |  |
| NX | Naloxone |
| OSTQOL | The Opioid Substitution Treatment Quality of Life Scale |
| PGIC | Patient’s Global Impression of Change |
| PP | Per protocol |
| PRO | Patient-Reported Outcomes |
| QALY | quality-adjusted life year |
| QoL | Quality of life |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis plan |
| SF-36 | Short Form 36 |
| SURE | Substance Use Recover Evaluator |
| TBQ | Treatment Burden Questionnaire |
| TLFB | Timeline follow back |
| TSQM | Treatment Satisfaction Questionnaire for Medication |
| UDS | Urine drug screen |
| VAS | Visual analog scale |
| WPAI: GH | Work Productivity and Activity Impairment Questionnaire: General Health |
| M&Nx | Methadone and Naloxone |

### **1.PROTOCOL SYNOPSIS**

Patients with opioid dependence have an increased risk for transmission of severe infectious viruses compared to patients in many other health facilities. Drug Health patients often have to attend clinics daily and these clinics are crowded in the reception area leading to a high risk for person-to-person contact and disease such as COVID-19 transmission.

Currently, opioid dependency has been managed with methadone treatment per NSW Health Clinical guidelines treatment of opioid dependence (1). Patients are attending the clinic every day to get treatment. During the COVID-19 pandemic, take away dose was required to maintain patients with opioid dependence and also reduce infection transmission. Methadone takeaway doses were provided for the patients as per WSLHD Drug Health policy temporarily. Methadone takes away doses creates a risk of injection and harming others.

There is a need for a new medication to maintain opioid dependence and also provide takeaway doses safely. New medication will help to minimize intravenous methadone use and harming others. The Methadone Naloxone (M&Nx) has a potential medication to maintain opioid dependence and will be given as taking away doses in this study.

The (M&Nx) has been tested in a patient group with opioid dependence (2). In this study, patients with opioid dependence were given M&Nx at different doses according to the patient’s condition and the Specialist Doctor's decision. M&Nx at 50:1 was tested for acceptability, safety, and tolerability at Drug Health Clinic and the medication was well tolerated. The clinical trial phases 1 a and 1 b for M&Nx were performed by applying multiple doses to the patients with opioid dependence (3).

M&Nx medication needs to be investigated further to identify the utility of treatment in Drug Health clinical settings by Clinical trial phase 2a (3). This study aims to use M&Nx to increase the quality of patient life with enhanced harm reduction.

Opioid prescribing has increased significantly, and diversion of prescribed opioids has become a major problem of drug misuse. Combining M&Nx treatment may reduce the attractiveness of selling, diverting, or injecting methadone.

This trial intends to study M&Nx in the treatment of adult outpatients with opioid dependence to minimize infection transmission in the drug health clinic setting. The study aimed to promote a better approach for patients by offering potential advantages over methadone maintenance alone such as minimizing the risks of diversion, injection, and selling in the black market.

### **2.INTRODUCTION**

#### **2.1.Background**

Opioid dependence is a chronic, neurobehavioral disorder and needs long-term treatment. Opioids use disorder is a major public problem and harming individuals, families, and communities(4). Worldwide around 33 million people suffering from opioid dependency(5).

Globally there were an estimated 207,400 drug-related deaths in 2015, one-third of which were due to overdoses (6). There were 2,162  accidental deaths from overdose reported in Australia in 2017, and opioids are responsible for most overdose deaths (7). In several countries, there is a trend of increasing overdose deaths from methadone and potent synthetic opioids, like fentanyl, as shown by recent statistics (8-11). The number of patients receiving opioid pharmacotherapy treatment in Australia almost doubled between 1998 and 2015. On a snapshot day in 2015, over 48,000 clients received pharmacotherapy treatment for their opioid dependence at 2,589 dosing points around Australia (12).

Opioid substitution treatment (OST) is being used for the treatment of opioid dependence. This treatment strategy is used to control drug use. Now, the most commonly used substitute therapeutic is methadone. Methadone is a synthetic opioid that was first introduced in Germany between 1937 and 1939. A long half-life of 25 to 52 hours and high analgesic effects, makes methadone suitable for maintenance therapy in opium addicts and is currently used as the basis of withdrawal management as methadone maintenance therapy (MMT) (13).

Methadone diversion and misuse of prescribed medication can result in adverse effects and is a particular concern when the medication is not administered under supervision There are concerns about the methadone onto the black market and the increased risk of harm (14). The diversion of methadone has been implicated as a key contributing factor in fatal and non-fatal methadone overdosing. Illicit methadone is commonly used as self-medication for the management of withdrawal symptoms by opiate-addicted individuals not engaged in treatment. It is also obtained by clients in treatment looking to supplement their methadone prescription or replace their prescription after failing to obtain it due to missed appointments or prescription pick-ups (13). The main motive for diverting prescribed methadone is to make money to buy other preferred substances.

The opioid-related overdose cases have been increasing in Australia significantly since 2004 and also the most of overdoses are now related to prescription opioids rather than illicit heroin (15).

Naloxone is used in opioid overdoses to reverse life-threatening depression of the central nervous system and respiratory system, help an overdose patient to able to breathe normally.Naloxone is effectivewhen a person has an opioid in the system and also doesn’t harm when opioids are not available. Currently, Naloxone is available as Schedule 3 and doesn’t require a prescription since 2016. The previous listing under Schedule 4 was retained, keeping the affordability of naloxone with maintaining access through the Pharmaceutical Benefits Scheme (16).

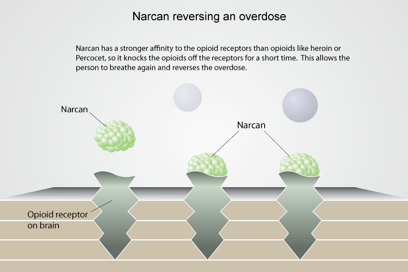
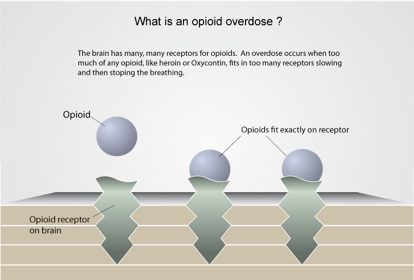


Figure 1: Maya Doe-Simkins harm reduction.org(17)

M&Nx combination will be helpful in harm minimization by decreasing the danger of diversion and injection. The published research found that the mixture of M&Nx a safe and humane treatment for harm reduction in maintenance programs (18).

M&Nx in a 50:1 was studied and published as useful pharmacological properties of combination well tolerated orally. The combination also was reported as potential therapeutics for heroin addiction with minimizing diversion risk(2).

This study aimed to investigate the effects of combined M&Nx and methadone alone on quality of life, patients satisfaction, and self-reported diversion

### **3.TRIAL OBJECTIVES AND ENDPOINTS**

#### **3.1.Primary Objectives**

To compare feasibility and harm reduction of M&Nx to methadone alone standard of care in adult outpatients with opioid dependence as given Table 1.

#### **3.2.Secondary Objectives**

a)To assess patient satisfaction with treatment

b) To assess treatment effects on illicit drug use other than opioids

c) To assess treatment effects on quality of life and patient functioning

d) To assess treatment effects of measures of social functioning, health, and wellbeing

e) To assess treatment effects on criminal activity

f) To assess treatment effects on opioid withdrawal symptoms

g) To assess treatment effects on opioid cravings

h) To assess the safety and tolerability of Methadone/Naloxone

i) Secondary objectives also cover reducing infection transmission such as COVID-19 by providing safer treatment management and

j) To measure Aboriginal and non-Aboriginal Health outcome as our 30 % of the client are Aboriginal Australian peoples.

Australian Treatment Outcomes Profile (ATOP), Substance Use EuroQol five dimensions health questionnaire (EQ-5D), global satisfaction score Opioid Substitution Treatment Quality of Life Scale (OSTQOL), Patient Global Impression of Change (PGIC) Short Form 12 (SF-12), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI: GH), Estimates of health service utilization (HSU) questionnaire, Opiate treatment index crime (OTI-C), Self-reported diversion and misuse of the trial medications using ORBIT Self-reported overdoses Clinical Opiate Withdrawal Scale (COWS) Craving VAS and Adverse events (AEs) as given at Table 2.

#### **3.3 Planned Number of Trial Patients**

The patient number will be planned for the feasibility of a pilot study. The study aims to have measurable primary and secondary endpoints. We aimed to recruit 15 participants for the standard treatment group and 30 participants for the experimental treatment group. The study will assess whether the new medication is not worse than the current standard treatment it is being compared to. This study will be a non-inferiority trial as [placebo can not be used. Non- inferiority will be a primary outcome. Methadone Naloxone treatment is expected to provide at least the same effect as standard treatment (19).

#### **3.4. Clinical Trial Phases 2 a**

This study will be conducted according to the Australian clinical trial guidance on conducting clinical trials in Australia using ‘unapproved’ therapeutic goods(3). The study medication was conducted with patients with heroin-dependent and medication dose was given in multiple doses (2). In the study of The Acceptability, Safety, and Tolerability of Methadone/Naloxone in a 50:1 Ratio(2), the participants with heroin-dependent were given the study medication (Methadone Naloxone) and found that the medication was tolerated. The methadone in the study medication is currently been used for heroin dependence management in routine clinical settings. Methadone with Naloxone was also tested for safety, acceptability, and tolerability. According to the Australian Clinical trial guideline, this study already passed phase 1 a and 1 b as the study medication was applied to the participants with multiple doses. This study will be proceeded at Phases 2 and under Australian Clinical trial guideline (3).

#### **Table 1 Objectives and End Points**

|  |  |
| --- | --- |
| **Primary Objective** | **Primary Endpoint** |
| To compare harm reduction Methadone/Naloxone and Methadone alone | |  | | --- | | Harm reduction will be assessed by Injection site assessment, modified Opioid-Related Behaviours In Treatment (ORBIT), and modified Opiate treatment index injection (OTI-I). | |
| **Secondary Objectives** | **Secondary Endpoints** |
| To assess patient satisfaction with treatment | TSQM effectiveness, side effects, and convenience score  Patient satisfaction visual analog scale (VAS) |
| To assess treatment effects on illicit drug use other than opioids. To assess treatment effects on illicit, non-prescribed, and unsanctioned prescribed use of opioids | Illicit drug use measured by UDS and self-reports of drug use by Australian Treatment Outcomes Profile (ATOP) self-reports of illicit opioid drug use by timeline follow-back method (TLFB 7) |
| To assess treatment effects on quality of life and patient functioning | EuroQol five dimensions health questionnaire (EQ-5D)  Opioid Substitution Treatment Quality of Life Scale (OSTQOL)  Patient Global Impression of Change (PGIC) |
| To assess the treatment effects of measures of social functioning, health, and wellbeing | Short Form 12 (SF-12) |
| To assess treatment effects on health economic outcomes (HEOs) including treatment utilization | Work Productivity and Activity Impairment Questionnaire: General Health (WPAI: GH)  Estimates of Health Service Utilisation (HSU) |
| To assess treatment effects on criminal activity | OTI-C Opiate Treatment Index – Crime |
| To assess treatment effects on opioid withdrawal symptoms | Clinical Opiate Withdrawal Scale (COWS) |
| To assess treatment effects on opioid cravings | Craving VAS |
| To assess the safety and tolerability of Methadone/Naloxone | Adverse events (AEs), including hospital admissions for overdose and injection-related infections |

### 

### **4. TRIAL DESIGN**

This is a randomized, prospective, open-label trial comparing treatment effects ofM&Nx with methadone in adult outpatients with opioid dependence. Opioid-dependent patients who are either currently receiving methadone treatment or patients who are seeking methadone treatment but who have not started treatment may be eligible for the trial.

The eligible participants will have a long screening period and a comprehensive medical assessment will be performed to identify any risk for the trial.

The trial will consist of a Screening Period of up to 2 weeks duration, a Treatment Period of 12 weeks duration, and a follow-up period of 3 weeks duration. Patients will be randomized either to methadone or M&Nx treatment and will be followed up every 4 weeks. Both arms will be monitored for clinical response to the treatment. Compulsory scheduled clinical visits where the study doctor performs medical assessments and where independent researchers conduct efficacy assessments will take place on Day 1 (Baseline and Randomization), and Week 4 (Day 28± 7), Week 8 (Day 56± 7), and Week 12 (Day 84± 7).

#### **4.1 Primary Objectives Assessment**

Primary Objectives will be measured every 4 weeks by injection site assessment, modified Opioid-Related Behaviours In Treatment (ORBIT) (20), and modified patient injection behavior tool which is Opiate treatment index injection (OTI-I).

#### **4.2 Secondary Objectives Assessment**

Secondary Objectives will be assessed at Baseline and Week 12 using the following tools as given in Table 2.

Treatment Satisfaction Questionnaire for Medication (TSQM)(21), Patient satisfaction visual analog scale (VAS)(22), Illicit drug use measured by UDS, self-reports of drug use by

**Table 2 Assessment Schedule**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Assessments** | **Baseline** | **Week 4** | **Week 8** | **Week 12** |
| **OTI-I, ORBIT, and Injection Site** | Y | Y | Y | Y |
| **TSQM** | Y |  |  | Y |
| **Satisfaction VAS** | Y |  |  | Y |
| **UDS** | Y | Y | Y | Y |
| **ATOP** | Y |  |  | Y |
| **EQ-5D** | Y |  |  | Y |
| **OSTQOL** | Y |  |  | Y |
| **PGIC** | Y |  |  | Y |
| **SF-12** | Y |  |  | Y |
| **WPAI:GH** | Y |  |  | Y |
| **HSU** | Y |  |  | Y |
| **OTI-C** | Y |  |  | Y |
| **COWS** | Y | Y | Y | Y |
| **Craving VAS** | Y |  |  | Y |
| **AEs** | Y |  |  | Y |

The randomization can be performed provided that patients are eligible for inclusion based on assessments performed at the Screening Visit. The randomization can be performed without the patient being present at the clinic. When the patient visits the clinic for the Day 1 (baseline) visit, the approval for starting treatment must be available before administration of trial treatment. Efficacy and safety assessments must be performed before dose administration.

Patients who miss a scheduled dosing visit by more than 28 days while receiving methadone or M&Nx will be considered as discontinued from trial treatment. Patients who discontinue trial treatment are still eligible to continue in the trial for data collection and may be treated according to standard care practice, outside the trial protocol, at the discretion of the Investigator.

Investigators will be instructed to provide psychosocial case management and counseling for patients during the trial according to current guidelines and to provide counseling visits independently of the mandatory scheduled visits.

The Follow-up Visit/Contact at Week 12 is the last protocol specified contact with the patient.

Figure 2 Trial Flow Chart

Eligible participants will be identified

Eligible participant will be provided full information, if participant interested, consenting will be performed

Participants will be invited for baseline interview in two weeks

Methadone and Methadone Naloxone dose administration will be performed

Methadone and Methadone Naloxone group will be scheduled for follow up interview

#### **4.3Trial Flow**

* Participating in the study will be available for all Drug Health patients who are eligible.
* The list of patients will be identified against exclusion criteria at the clinic
* Potential patients will be informed about the study
* If patients decide to participate in a trial, a consenting procedure will be applied
* The patients will be randomized as Methadone Standard or Methadone Naloxone maintenance treatment
* A baseline review will be performed in two weeks
* The participant who was randomized as Methadone maintenance will continue with daily dosing at the clinic. The participant who was randomized as Methadone Naloxone treatment will be given 3 days take away doses in the first week of the trial. Then take away doses will be increased to 6 days take away with medical assessment.

The participant will be transferred from 6 days take away doses to 3 days take away doses in the following conditions,

1. If the participant has an acute, severe medical condition, overdose history such as the admission of the emergency department, call out for ambulance related with the drug overdose or condition which required Naloxone in last 6 months,
2. If the participant has no stable accommodation
3. If the participant has been concerned about child welfare,
4. If the participant has any other substance dependence except Nicotine
5. If the participant had a recently injected track mark of more than 1 site
6. If the participant came to the clinic more than 1 day late
7. If the participant does not want to go from 3 days take away doses to 6 days take away doses

The participant will be transferred from 3 days take away doses to daily doses in the following conditions

If participant develop a severe illness or diversion of Methadone Naloxone

If the participant missed more than 7 days doses out of 14 days

### **5.TRIAL POPULATION**

#### **5.1.Inclusion Criteria**

Patients meeting all of the following criteria will be eligible to participate in the clinical trial:

1. Able to provide written informed consent to participate in the trial and able to understand the procedures and trial requirements

2. Willingness and ability to comply with the protocol

3. Adult male or female patient (≥ 18 years old)

4. Meet the criteria for opioid dependence as defined by either the criteria for moderate to severe opioid use disorder in the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5)(23) OR opioid dependence in the International Statistical Classification of Diseases and Related Health Problems – 10th Edition (ICD-11) according to local practice

5. Female patients of childbearing potential must be willing to use a highly effective method of contraception during the entire trial

6. At least 4 weeks on methadone before enrolling in the study

7. At least 21 days of last 28 days attendance of Methadone maintaining program.

#### **5.2.Exclusion Criteria**

Patients meeting any of the following criteria will not be eligible to participate in the clinical trial:

1.Known mental incapacity or language barriers precluding adequate understanding of the informed consent information and the trial activities

2. Patient is pregnant, lactating, or planning to be pregnant during the trial

3. Unwilling or unable to comply with the requirements of the protocol (e.g. current or pending incarceration) or are in a situation or condition that, in the opinion of the Investigator, may interfere with participation in the trial

4. Participating in any other clinical trial in which medication(s) are being delivered or have used an investigational drug or device within the last 30 days before screening

5. Any known allergy, hypersensitivity or intolerance to Naloxone or any related drug, or history of any drug hypersensitivity or intolerance which in the opinion of the Investigator, would compromise the safety of the patient or the trial

6. Severe respiratory insufficiency

7. Severe hepatic insufficiency

8. Any other contra-indicated serious medical condition, including unstable mental condition and severe pain, which in the opinion of the investigator may prevent the patient from safely participating in the trial

9. Any known child welfare or court issues

#### **5.3.Recruitment**

Participant recruitment will occur from patients of participating clinical services and patients with opioid dependence seeking to enroll in treatment during the recruitment period of the trial.

For existing patients of participating services, the approach will involve informing all participants in Methadone treatment of the trial through (a) direct communication with caseworkers and treating medical staff at routine clinical review appointments; and (b) posters informing patients of the trial in participating clinic waiting rooms, and to speak to their caseworker or treating doctor for more information. Patients will be briefly informed of the trial by the clinicians and provided with the Human Ethics approved Patient Information Consent Form. If interested in participating in the trial, a trial Investigator will then perform the consenting process and request written informed consent from the participant.

#### **5.4.Registration and Randomization**

During the registration phase, the study doctor shall complete and submit the relevant state application for an authority to prescribe. The Eligibility review process will be completed during this period by the completion of assessments required to determine the patient’s eligibility. The time between registration and randomization shouldn’t be more than 2 weeks.

Randomization occurs after receipt of Authority to prescribe. To minimize bias, eligible patients will be randomized 1:1 to one of the treatment groups (M&Nx or Methadone standard of care), using a relevant computer-based randomization system.

### **6.SCREENING AND BASELINE PROCEDURES AND ASSESSMENTS**

#### **6.1.Informed Consent**

The nature of the trial and its risks and benefits will be explained to the patient by the Investigator or designated trial personnel. The patient must voluntarily provide written informed consent on an ethics-approved ICF, before performing any trial-related procedures. The patient’s medical records must document that the consent process has been completed and that written informed consent has been obtained from the patient before the initiation of any trial-specific procedures. Documentation that the patient was given adequate time to ask the Investigator (or designee) questions about their participation in the trial and that a signed and dated copy of the ICF was provided to the patient should also be included in the medical records or clinical chart.

#### **6.2.Demographics**

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity.

#### **6.3.Medical History**

The complete medical history based on the patient interview of 5 years before the screening visit and any clinically significant medical history greater than 5 years before the screening visit will be collected, these will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the patients during the 30 days before Screening will be recorded in the source documentation as medication history.

#### **6.4.Substance Use and Treatment History**

A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained.

#### **6.5. Medical assessment**

The potential participant will be assessed by the Study Doctor. The examination will cover medical history, track mark checks such as physical examination, neck, axillar, cubital fossae. Viral infection status such as Hepatitis B, C, and Human Immunodeficiency Virus (HIV) in the last 6 months will be assessed. Pathology tests such as Full Blood Count, Liver Function Test, Electrolytes (sodium, potassium, and chloride), urea, creatinine (EUC), Blood sugar level (BSL). The CMP blood test measures levels of Albumin, Blood urea nitrogen (BUN), Calcium, Carbon dioxide (Bicarbonate), Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin and Protein, and Liver Enzymes: Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and Aspartate aminotransferase (AST).

#### **6.6. Physical Examinations and Vital Signs**

A physical examination including all major body systems will be performed at Screening. Height, weight, and body-mass index (BMI) will be measured/calculated at Screening.

Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 3 minutes.

For women of childbearing potential, a urine dipstick pregnancy test will be performed at Screening and Week 12. The results of the pregnancy test at Screening must be reviewed and confirmed to be negative before randomization to assess the patient’s eligibility for the trial.

### **7.WITHDRAWAL CRITERIA**

#### **7.1.Withdrawal from trial treatment**

A patient may be withdrawn from trial treatment at the discretion of the Investigator (if clinically indicated), at the patient’s request, or if the patient becomes pregnant.

Patients who discontinue trial treatment, are still eligible to continue in the trial and may be treated according to clinical practice, outside the trial setting, at the discretion of the Investigator.

Efforts should be made by the Investigator to continue the collection of efficacy and safety assessments at the protocol-defined trial visit intervals, including concomitant medications, and AEs in patients that discontinue trial treatment, unless the patient withdraws his/her consent at the time of early discontinuation. The Investigator should also ask the patient to return for the Follow-up assessments, provided that the patient has not withdrawn consent for those assessments. If a patient refuses to complete early termination procedures and/or Follow-up, this information will be recorded.

#### **7.2.Withdrawal from trial**

A patient is free to withdraw his/her consent and discontinue participation in the trial at any time for any reason. A patient’s participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A patient must be discontinued from the trial for any of the following reasons:

Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the Investigator, affect assessments of clinical status to a significant extent.

The patient is lost to follow-up

A patient may also be discontinued from the trial,

The patient refuses or is unable to adhere to the trial protocol

Administrative discharge due to non-adherence with site policies (e.g. violence towards other clients or staff)

The Investigator must keep a record of all patients who discontinue from the trial before completion; the reason(s) for trial discontinuation will be documented.

#### **7.3.Contraceptive Requirements**

Women of childbearing potential must agree to use the highly-effective method(s) of birth control as defined in the ICF for the duration of participation in the trial and must agree to be tested for pregnancy. Highly-effective method(s) of birth control include:

* Oral, implantable, or injectable contraceptives for 3 consecutive months before screening, in combination with a condom.
* Intrauterine device (IUD) in combination with a condom.
* Double barrier method (condom or diaphragm).
* Male patients must agree to use condoms for the duration of the trial.

### **8.TREATMENT PLAN**

#### **8.1Medication:**

**Standard treatment**

WSLHD Drug Health currently using BIODONE FORTE methadone hydrochloride 5mg/mL and manufactured by Biomed Aust Pty Ltd. Specifications are Dosage Form: Oral Liquid, solution; Route of Administration: Oral; Visual Identification: Clear, pink to red solution; Temperature Conditions: below 25 degrees Celsius. The methadone hydrochloride is currently classified in **Schedule 8**  'Controlled **Drug**' and has strict legislative controls (24).

**Study treatment**

M&Nx will be manufactured by Biomed according to current Good Manufacture Procedure c (GMP)(25). The study medication will be transferred to Australia according to the principles of the Therapeutic Goods Administration (26).

M&Nx will be provided by Biobemed Ltd without charge during the study. The company will be informed of the clinical study start date in advance to provide time for the preparation of the medication. The medication will be shipped to WSLHD Drug Health Clinic and will be stored and dispensed at the same conditions and room temperature with standard methadone medication. Visual identification of the study medication will be a clear yellow solution, unlike standard medication.

Method

**T**he standard medication will be dispensed at the clinic daily. The Methadone group one hydrochloride mixed in naloxone hydrochloride (20 mg10.4 mg). /Norbert Loimer 5mg/ml methadone+0.1 mg/ml naloxone. Baseline observations will be assessed every 4 weeks. The pregnancy status of the female patients was determined at baseline and monthly.

#### **8.2 Dispensing Medication**

will not be given to take away doses.

The study medication will be provided 3-day takeaway doses at the first week and the takeaway doses will be increased to 6 days takeaway doses depending on the patients' stability in the treatment.

#### **8.3Action Plan for patient safety management**

This trial aimed to determine providing outcome regarding take away doses of a new medication is less harmful than standard medication. However, patient safety will be managed by the following mitigation actions:

1. The study will be an open-labeled trial and new medication will be clearly explained at the consenting and medical assessment stage.
2. The first dose will be given to the participant at the clinic and the participant will be observed for 1 hour to manage any immediate adverse event.
3. The new medication will be yellow in color, unlike the standard treatment. This might be a drawback from diversion as it will not the same medication as the standard one and will make the individual think that they will not have the same effect as the standard one.
4. If the participant tries to inject the study medication, elimination of the study drug will start in 15-30 minutes and will return to the baseline level at 60 minutes after injection (2). The acceptability, safety, and tolerability of Methadone/Naloxone in a 50:1 ratio were already performed by Bell et al in 2009 (2).
5. The education campaign will be implemented for participants and staff district-wide to make all patients and staff aware that new medication is being dispensed.
6. The new medication was compared with standard methadone by Bell et al. They found that Methadone-naloxone in a 50:1 ratio has the pharmacological properties to be a useful combination product for the maintenance of heroin addiction with reduced risk of injection. A conclusion from the study was the Methadone Naloxone may reduce the attractiveness of diverting and injecting methadone (2).
7. The participant will be contacted to check the safety and well-being assessment twice after the first takeaway doses.

#### **8.4 Reimbursement**

Participants will be reimbursed just to cover their travel costs with a supermarket voucher (that cannot be spent on alcohol or cigarettes) at screening, weeks 1, 5, 9, and 13.

### **9.EFFICACY ASSESSMENTS**

**9.1. Harm Reduction Assessment**

Harm reduction will be assessed using medical harm reduction assessment methods. Injection site lesions will be assessed by location, wound size, complications, venous damage, and needle risk behaviors. The tool covers relevant questions from The Opioid-Related Behaviours In Treatment (ORBIT) and Patient injection behavior from Opiate treatment index injection (OTI-I) tools.

**Primary Endpoint Failure and Significance Assessment:** The primary endpoint tests will be assessed marking for each question and repetition of behavior against baseline marking.

**Injection Site Assessment:** Failure of the test will be defined as a 2 point increase from baseline score on two or more occasions or 3 point increase on any occasion, or a 5 point increase at any time and it is classified as a failure.

**Modified Opioid-Related Behaviours In Treatment (ORBIT):** Positive is defined 2 points increase from baseline score two or more times, or a 4 point increase from baseline score any time and it is classified as a failure.

**Modified Opiate treatment index injection (OTI-I):** Positive is defined as a 2 point increase from baseline score on two or more occasions, or a 4 point increase on any occasion, and it is classified as a failure.

#### **9.2.Treatment Satisfaction Questionnaire for Medication (TSQM)**

The TSQM is a measure of the major dimensions of the patient’s satisfaction with medication. Evidence suggests that the TSQM may also be a good predictor of patients’ medication adherence across different types of medication and patient populations (27). The TSQM comprises 14 items across four domains focusing on effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items) of the medication. Except for item 4 (presence of side effects; yes or no), all items have five or seven responses, scored from one (least satisfied) to five or seven (most satisfied).

#### **9.3.Patients Satisfaction Visual Analogue Scale (VAS)**

Patient satisfaction of treatment will be measured by a 100-mm VAS ranging from “not at all” (score = 0) to “extremely” (score = 100)(28).

#### **9.4.Self-report of Other Drug Use**

Patients will be questioned about the use of other drugs using the same questions about substance use as in the Australian Treatment Outcomes Profile (ATOP) instrument (29, 30). Timeline Follow Back (TLFB**)** tool will be used if the participant’s dailyinjected heroin, methadone, or methadone naloxone.

#### **9.5.Retention in Treatment**

Retention in treatment is calculated as days in treatment since randomization until the last day of medication during the 12 weeks of treatment (plus the respective duration of M&Nx or Methadone standard of care). Data for retention will be censored at Week 12. The Investigator should confirm a patient’s discontinuation date about the last dose in the CRF.

#### **9.6.Trial Drug Adherence**

Trial drug adherence will be measured by drug accountability for M&Nx, and self-reports of drug accountability for the comparator treatment (Methadone standard of care).

#### **9.7.EuroQol Five Dimensions Health Questionnaire (EQ-5D)**

EQ-5D is a standardized measure of health status developed by the EuroQol Group to provide a generic measure of health for the clinical and economic appraisal (31).

The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient’s health state.

#### **9.8.Opioid Substitution Treatment Quality of Life Scale (OSTQOL)**

The OSTQOL is a 38-item multidimensional PRO designed to capture aspects of QoL in patients on opioid substitution treatment (32). The items capture aspects of personal development, mental distress, social contacts, material wellbeing, opioid substitution treatment, and discrimination. The patient rates each item from 0, “does not apply to me at all” to 4, “applies to me extremely”.

#### **9.9.Patient Global Impression of Change (PGIC)**

The self-report measure Patient Global Impression of Change (PGIC) is a single-item scale, which aims to evaluate all aspects of a patient’s health and determine if there has been an improvement or not in the patient’s opioid dependence (33). Patients rate their change as (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, (7) very much worse.

#### **9.10.Opioid Related Behaviours In Treatment (ORBIT)**

The Opioid-Related Behaviours In Treatment (ORBIT) is a 10-item unifactorial scale with good discrimination between groups acceptable test-retest reliability and strong face validity(20). The ORBIT is validated for use in diverse patient groups receiving opioids. Each item is rated from Never (0) to Very Often (4).

#### **9.11.Short Form 12 (SF-12)**

The SF-12 is a widely used standardized instrument with strong psychometric properties (34). The SF-12 will be used to assess the self-perception of general health functioning across multiple dimensions (including general, physical, and emotional/psychiatric functioning). The SF-12 has shown good internal, consistency, stability, and concurrent validity in outpatients with serious mental illness. Higher scores indicate better quality of life.

#### **9.12.Work Productivity and Activity Impairment Questionnaire: General Health (WPAI: GH)**

The WPAI is an instrument to measure impairments in both paid work and unpaid work(35). It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problems during

the past seven days. It has been validated to quantify work impairments for numerous diseases such as asthma, psoriasis, irritable bowel syndrome, ankylosing spondylitis, and Crohn’s disease. Also, the WPAI questionnaire has been used to compare work impairments between treatment groups in clinical trials or between subjects with different disease severity levels.

The WPAI: GH consists of 6 questions: 1 = currently employed; 2 = hours missed due to health problems; 3 = hours missed other reasons; 4 = hours worked; 5 = degree health affected productivity while working (using a 0 to 10 VAS); 6 = degree health affected productivity in regular unpaid activities (VAS). The recall period for questions 2 to 6 in 7 days. Four main Clinical outcomes can be generated from the WPAI-GH and expressed in percentages by multiplying the following scores by 100, with higher percentages indicating greater work productivity loss and activity impairment: 1) percent work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; 2) percent impairment while working due to health = Q5/10 for those who were currently employed and worked in the past 7 days; 3) percent overall work impairment due to health Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) × (Q5/10)) for those who were currently employed; 4) percent activity impairment due to health Q6/10 for all respondents. For those who missed work and did not work in the past 7 days, the percent overall work impairment due to health will be equal to the percent work time missed due to health.

#### **9.13.Health Service Utilization**

Estimates of health service utilization (HSU), social service utilization, and criminal offenses and incarcerations during the trial will be done through the Alcohol & Drug Adapted Adult Service Use Schedule questionnaire(36).

#### **9.14.Self-reported Overdoses**

Patients will be questioned about overdoses of illicit or prescription opioids and other drugs of abuse (37).

#### **9.15.Clinical Opiate Withdrawal Scale (COWS)**

Clinical observations indicative of withdrawal will be assessed using the Clinical Opiate Withdrawal Scale (COWS) (38). This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater.

**9.16.Craving VAS**

The opioid craving will be measured by a 100-mm VAS ranging from “not at all” (score = 0) to “extremely” (score = 100) (39).

#### **10.Other Intervention**

#### **10.1Psychosocial Counselling**

Investigators will be instructed to provide psychosocial case management and counseling for patients during trial according to local guidelines and to provide counseling visits independently of the visits for the administration of the trial treatments. Documentation of counseling visits will be done by the Investigator at mandatory clinic visits. Psychosocial counseling is any intervention with a patient that is not directly related to medication treatment.

### **11.ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS**

#### **11.1.Adverse Event Definitions**

An **adverse event** (AE); synonym: adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, in a patient or clinical trial subject administered a trial treatment and which does not necessarily have a causal relationship with this treatment (i.e., whether or not considered drug-related)(40). An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of trial treatment, whether or not considered related to the trial treatment. Patients will be instructed to contact the Investigator at any time after enrolment if any symptoms develop.

***11.2.Adverse reaction:*** All untoward and unintended responses to a trial treatment assessed as related to any dose administered.

AEs or SAEs assigned a causality assessment by the Investigator of “probably related” or “possibly related” will be considered by the Sponsor to be related to defining adverse reactions and thereby also expedited reporting.

An AE is considered “unexpected” if nature, severity, or outcome is not consistent with the reference safety information section (see the current edition of the IB).

**11.3 A serious adverse event (SAE)**is any untoward medical occurrence that at any dose:

* Results in death;
* Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)(41);
* Requires inpatient hospitalization or prolongation of existing hospitalization;
* Results in persistent or significant disability or incapacity;
* Consists of a congenital anomaly or birth defect; or
* Is another medical event. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. This is based on the medical and scientific judgment of the Investigator (42).

WSLHD HREC Safety Reporting Requirements will be followed as stated below

|  |  |  |  |
| --- | --- | --- | --- |
| **Safety Report** | **Responsible Party** | **Timeframe** | **Documentation** |
| Significant Safety Issue (SSI) implemented as an Urgent Safety Measure (USM) | Sponsor through the co-ordinating Principal Investigator | No later than 72 hours after the sponsor becomes aware of the safety event | OHMR SSI Notification Form or Sponsors template |
| Significant Safety Issue (SSI) ***NOT*** implemented as an Urgent Safety Measure (USM) | Sponsor through the co-ordinating Principal Investigator | Within 15 days of the sponsor becoming aware of the safety event | OHMR SSI Notification Form or Sponsors template |
| Investigator’s Brochure Updates/Addenda | Sponsor through the co-ordinating Principal Investigator | As and when updates are generated | New edition of Investigators Brochure, Summary of Changes Document & Signed CPI Declaration |
| Annual Safety Report | Sponsor through the co-ordinating Principal Investigator | Accompanying the annual progress report or when provided by the sponsor annually. | Sponsors Annual Safety Report template accompanying WSLHD HREC Annual Report Template. |

#### **11.4.Other Reportable Information**

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

Pregnancy during exposure to trial treatment. If a pregnancy is confirmed, the use of the trial treatment must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male patient, the necessary information must be collected from the patient, while respecting the confidentiality of the partner. Lactation exposure to a trial treatment with or without an AE.

Overdose of a trial treatment as specified in this protocol with or without an AE.

Inadvertent or accidental exposure to a trial treatment with or without an AE.

Any new event, sign, or symptom occurring in the period between Screening and Baseline (Day 1) will be recorded in the same manner as an AE.

#### **11.5.Assessment of Severity**

Severity is defined as a measure of the intensity of an AE or SAE and will be classified as mild, moderate, or severe using the following criteria:

**Mild**: Awareness of symptoms, sign, illness, or event that is easily tolerated.

**Moderate**: Discomfort sufficient to cause interference with usual activity.

**Severe**: Incapacitating, with the inability to work or undertake further normal activities.

Note that a severe reaction is not necessarily an SAE (e.g. a severe headache would probably not constitute an SAE; however, a mild myocardial infarction may constitute an SAE).

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

#### **11.6.Assessment of Outcome**

The outcome of an AE or SAE will be classified using the following outcome ratings:

0 = unknown

1 = recovered/resolved

2 = recovering/resolving

3 = not recovered/not resolved/ongoing

4 = recovered/resolved with sequelae

5 = fatal

#### **11.7.Assessment of Causality**

The Investigator will assess the relationship to trial treatment for all AEs and SAEs. The relationship will be characterized using the following causality ratings:

**Probably related**: An AE with a reasonable time sequence to the administration of the trial treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

**Possibly related**: An AE with a reasonable time sequence to the administration of the trial treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

**Not related**: An AE with a temporal relationship to drug administration which makes a causal relationship improbable, or in which other drugs, chemicals, or underlying disease provide plausible explanations. There is no reasonable possibility that the event was caused by the trial treatment.

**Not applicable**: This assessment can be used, for example, in cases where the patient did not receive any treatment with trial treatment.

### **12.STATISTICAL CONSIDERATIONS**

### **12.1.Statistical and Analytical Plans**

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed before database lock. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final trial.

### **12.2.Determination of Sample Size**

The collection will be analyzed using primary and secondary endpoint outcomes. In this study at least 10% improvement in study medication comparison to standard treatment will be classified as an acceptable outcome. Sample sizes of 30, 50, and 70 provide 48%, 78%, and 84% power to detect an acceptance rate of 85% or lower if the true acceptance rate in the population is 95% using a one-sided binomial test of size *α* = 0.05 (Charity G.et al, 2011).

### **13.DATA HANDLING**

#### **13.1.Source Data and Source Documents**

The Investigator must maintain patient records.

The Investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary(43).

#### **13.2.Data Management**

A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning, and validation.

The relevant data management documents will define the data entry, data validation, electronic data capture (EDC) system settings, EDC user permission, reconciliation requirement, coding dictionary, coding setup, etc.

#### **13.3.Data Protection and Confidentiality of Patient Data**

The Investigator will ensure that the confidentiality of the patients’ data will be preserved. On the eCRF or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by their screening/randomization number. Documents that are not for submission to the Sponsor, e.g. the confidential patient identification code and the signed Informed Consent Documents, will be maintained by the Investigator in strict confidence.

The research will be performed with Health Records and Information Privacy **Act** (NSW), Privacy and Personal Information Protection **Act** 1998 (PPIP Act) (43), and International Conference on Harmonisation Good Clinical Practice (ICH-GCP) requirements as defined by the NHMRC in the National Statement on Ethical Conduct in Research Involving Humans (44).

### **14.ARCHIVING**

The Investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH GCP. The trial documentation including all the relevant correspondence should be kept by the Investigator for at least 15 years, unless local regulations or institutional policies require a longer retention period, after the completion or discontinuation of the trial, if no further instructions are given(45).

### **15.REPORTING AND PUBLICATION**

The results of this trial may be published or presented at scientific meetings.

The Investigators will comply with the requirements for publication of trial results.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

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