Guidance on Managing Heroin* Dependence during COVID-19 & Lockdowns (v1.0)

* Nyaope, Whoonga, Unga, Sugars & Thai White are all heroin.

April 2020

Introduction

Who is this guidance for?

These guidelines are for clinicians and support staff supplying services to people who use drugs during the COVID-19 pandemic.

They are also to help inform policymakers and implementing organisations gain an understanding of what is needed and how it can be achieved.

Who compiled this guidance, and how was it compiled?

This guidance was compiled by the University of Pretoria, Department of Family Medicine and TB HIV Care. The processes, protocols and clinical guidelines were drawn from existing local and international guidelines. The first draft was then circulated to a group of experienced clinicians familiar with OST. Edits were then made, and the guidelines shared to a broader group. The document is fluid and may be updated as informed by emerging data and pragmatism under the current circumstances.

Disclaimer

COVID-19 is a rapidly evolving pandemic with guidance updated regularly. This document is pragmatic and may not fully comply with some of the regulations specific to the South African context, but does comply with international guidelines and places the safety, human rights and dignity of people above ideologies and punitive policies. Due to the urgency, we have drawn most of the material from existing guidelines and publications.

Background

On 11th March 2020, the World Health Organization (WHO) declared the current outbreak of SARS-CoV-2, which causes COVID-19, a pandemic. Although the COVID-19 disease is usually mild and most people recover quickly, it can be life-threatening for certain groups of people, including the elderly and people with stressed immune systems or underlying conditions.

This guidance aims to assist in planning for the consequences of the COVID-19 pandemic and provide modified guidelines for people who are dependent on heroin. People who use drugs (PWUD) are at particular risk and have specialised needs.[1]

The aim is to raise awareness of potential problems that may arise and offer suggestions as to how these risks might be mitigated. The COVID-19 outbreak is a rapidly evolving situation, presents a significant threat and is unprecedented in our time. It requires an unusual and radical response to ensure the minimum loss of life and rights.

In South Africa, people who use drugs have been a neglected population, and there was has been a distinct lack of evidence-based services and, in many cases, conscious and sustained denial of services considered essential in other settings. This exclusion has led to a state of unpreparedness. Contributing factors include:

- A reluctance to believe that Nyaope, Unga, Whoonga are all street heroin
- Lack of opioid agonist medication for maintenance on the Essential Drugs List
- Methadone is 10-30 times more expensive than in other settings, with a single supplier
- A lack of political will to provide services for people who use drugs
- No national government funding for harm reduction services
- A reliance on abstinence-based services and a rejection of harm reduction services
- eThekwini Municipalities closure of the only needle and syringe services in Kwa-Zulu Natal
- The continued punitive response to the use of drugs and the criminalisation of people who use drugs.

These guidelines focus on people dependent on opioids, whether on opioid substitution therapy (OST) or not, and those in need of sterile injecting equipment and related paraphernalia. The COVID-19 pandemic and shut down brings unique problems and unique opportunities to address some of the

[1] EMCDDA. (2020) *The implications of COVID-19 for people who use drugs (PWUD) and drug service providers | www.emcdda.europa.eu.* http://www.emcdda.europa.eu/publications/topic-overviews/covid-19-and-people-who-use-drugs.

previous shortfalls and turn the innovative and essential responses developed during this time into a sustainable set of interventions that extend beyond the pandemic.

The exact numbers of people dependent on heroin are unknown, but we are seeing significant numbers each day.

On 26th March 2020 at 00:00, South Africa went into shutdown. People were instructed to remain home, and our freedom of movement was curtailed for 21 days. The impact on street-dwelling and marginalised people is significant, and the solutions are limited. Solutions adopted are generally sub-optimal and include 'safe spaces' under highways, the re-purposing of warehouses and stadia, and the rapid conversion of buildings and establishment of triage facilities.

Potential issues

- The shutdown will limit the availability of drugs
    - People will go into withdrawal
    - People in opioid withdrawal suffer immense pain and discomfort, with vomiting, severe diarrhoea, and a sense of anxiety or restlessness.
- The symptoms of opioid withdrawal can be confused with those of COVID-19.
    - People in withdrawal could be placed with COVID-19 patients, and become infected, and may be discharged into the community to further spread COVID-19 among an extremely vulnerable community that is not physically distanced.
- Interruption to the existing provision of OST and associated clinical care as a result of COVID-19 will put people at increased risk of overdose and, in turn, drug-related death.
- People in withdrawal from heroin and other drugs are unlikely to remain in their current spaces and are unlikely to maintain physical distancing.
- Without access to sterile injecting equipment, PWID will share or reuse needles spreading COVID-19, HIV, Hepatitis C virus (HCV) and other diseases.
- More potent synthetic opioids will likely enter the market. This includes fentanyl and the various derivatives, and overdose rates will increase dramatically.
- It is essential to establish adequate response services for people who are dependent on drugs, especially heroin.

Changes in approach

Under a state of national shut-down during a pandemic, things change, and we have to change the way we work and look after the health needs of people, specifically marginalised people.[2]

There should not be a change in the quality of care, but a change in the way care is accessed, the removal of bureaucracy and the judicious use of resources. The areas that should not be compromised are dosing, up-titration of dose (particularly methadone), the provision of accurate information and the application of the best available evidence.

[2] Farhoudian, Ali et al (26 Mar. 2020.). COVID-19 and Substance Use Disorders: Recommendations to a Comprehensive Healthcare Response. An International Society of Addiction Medicine (ISAM) Practice and Policy Interest Group Position Paper. *figshare*. Retrieved from https://figshare.com/articles/COVID-19_and_Substance_Use_Disorders_Recommendations_to_a_Comprehensive_Healthcare_Response/12033567

Things that must change are: Where and how clients are accessed and receive services – it is better to go to them than have them come from various directions to a central facility. In the current context people are housed in shelters or 'Safe Spaces'. Teams should go there.

Barriers to services should be removed, and exclusion criteria should be minimised to exclude only people who will suffer significant clinical risk.

Principles

These principles will inform the interventions:

Harm Reduction

Services are all based on a harm reduction approach that seeks to mitigate the potential risks and harms related to drug use with no prerequisite for abstinence. Services are based on best available evidence and best practice guidelines.

Harm reduction principles for health care settings include: [3]

- Humanism: Care is given without moral judgement and with an understanding that choices are contextual.
- Pragmatism: The priority is the here and now, and the mitigation of immediate risk is what matters most.
- Individualism: People are different and have their own needs and strengths.
- Autonomy: People have a right to make informed choices, even against expert advice.
- Incrementalism: Any positive change is viewed as an improvement in current circumstances.

Low Threshold

- Many barriers to entry and retention should be removed, with consideration for safety. Psychosocial and similar services are voluntary.
- Services are non-judgemental, affirmative and non-confrontational. Accountability without termination: People have the right to make choices, without being denied access to the highest standard of care.
- There are almost no barriers to entry, and same-day initiation should become the standard.

Level of care

- Services are inclusive, non-judgemental, affirmative and non-confrontational.
- Reduce pain and discomfort as quickly, effectively and pragmatically as possible.
- Maintain tolerance. If tolerance is not maintained through sustained opioid doses, there is a risk of overdose when they use again
- The priority is to reduce harm, no matter what choices the individual makes.
- Holistic care per individual needs.

Peer support

- Peers (people who use drugs) are a valuable resource

[3] Hawk M, Coulter RW, Egan JE, Fisk S, Friedman MR, Tula M, Kinsky S. Harm reduction principles for healthcare settings. Harm reduction journal. 2017 Dec;14(1):70. Retrieved from https://harmreductionjournal.biomedcentral.com/articles/10.1186/s12954-017-0196-4

- Peers can:
    - Provide insight into the whereabouts of PWUD
    - Identify people in withdrawal
    - Be the first point of contact
    - Help establish trust
    - Educate other people who use drugs about the correct way to use medications
    - Identify shortfalls in services delivery
- Peers are an essential part of the response to heroin use during COVID-19

Overdose and Naloxone

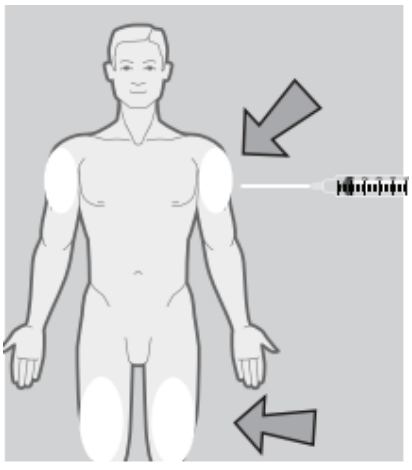
Signs of overdose include:

- Pinpoint pupils
- Nausea and vomiting
- Dizziness
- Excess sedation
- Slurred speech
- Snoring
- Slow pulse and shallow breathing
- Frothing at the mouth
- Unconscious and unable to be awakened

Opioid overdose is managed with Naloxone (Narcan®), a non-selective short-acting opioid antagonist.

Administering naloxone

1. If the person is not breathing, perform a few quick rescue breaths.
2. Administer 0.4mg-2mg, naloxone IV, IM or subcutaneous injection.
3. Use a 2,5-3cm IM needle to administer naloxone into muscle



4. After injection, continue rescue breathing 2-3 minutes.
5. If there is no change in 2-3 minutes, administer another dose of naloxone and continue to breathe for them. Continue every 2-3 minutes up to 10mg total.

6. If the dose of naloxone does not revive them, something else may be wrong—either it has been too long, and the heart has already stopped, or there are no opioids in their system.
7. There is no good evidence to suggest that naloxone improves outcome in patients with opioid-induced cardiac arrest.
8. If a cardiac arrest has occurred, airway control is a priority before the administration of naloxone.

Operations

Establishing a plan

Most homeless people are accommodated either in shelters, large safe spaces or are living in small clusters in the suburbs. To slow the spread, the teams should travel to the clients.

Teams must map the shelters and places where the people who use drugs are congregating Peers are the best source of street information. It is best to pre-determine the needs by calling or visiting the shelters – for example:

Initiation rounds				
Shelter	# PWUD	# in withdrawal	Time needed	Manager + number
Haven 1	20	18	2hrs	Clive XXX XX XXXX
Haven 2	50	20	3,5hrs	Bob XXX XX XXXX
Haven 3	20	18	2hrs	Zinzi XXX XX XXXX
Haven 4	5	5	1hrs	Amandla XXX XX XXXX
Totals	95	61	8,5 hrs	Excl travel

Dots Rounds				
Shelter	# PWUD	# in withdrawal	Time needed	Manager + number
Haven 1	20	18	1.25hrs	Clive XXX XX XXXX
Haven 2	50	20	2hrs	Bob XXX XX XXXX
Haven 3	20	18	1,5hrs	Zinzi XXX XX XXXX
Haven 4	5	5	30 min	Amandla XXX XX XXXX
Totals	95	61	8,25 hrs	Excl travel

The schedules are worked out to ensure that teams are able to sustain the directly observed treatment (DOTS) or followups. Unless the shelter has a responsible staff member, daily observed treatment (DOTS) will be the norm and is essential for the first 14 days unless there are medical personnel at the site.

The teams

Establish the teams who will deliver the services. Task shifting in these times is essential. Teams will take on a new look and new operating procedures. It is essential to establish dual redundancy. Each team should have a backup plan if they are sick, and teams should not meet face-to-face to reduce risk.

Teams can consist of many combinations of health care workers. Examples of teams are

Member	Initiation			DOTS			Follow-ups		
Peer outreach worker	x	x	x	x	x		X		X
Professional nurse					X		X	X	
Clinical associate				X		X			X
RN			X			X			
CHW		X		X			X	X	
Social worker	X		X		X				X
Doctor	X	X	X					X	

A doctor may be needed to provide an initial script, but it would be impossible for a doctor to attend every DOTS session therefore the team will carry ward stock, and the PNC can observe DOTS.

Preparation

The following is suggested:

1. A list of potential recipients and initiates is established
2. If not possible, estimate the number of initiates
3. Prepare 15ml/30mg doses ready for consumption according to the numbers
4. Separate containers per dose are needed
5. Ensure there is 'ward stock' available and symptomatic withdrawal packs are available
6. All documentation is available and ready
7. All team members are screened for COVID-19
8. All members have Personal Protective Equipment

Security

If there is low coverage of methadone, it will become a sought after commodity. It is advised that teams travel as a group and with a mix of male and female members. People who have complaints should be listened to rather than ignored.

Record keeping

It is essential to keep accurate records that are available to others. The appropriate forms are included as addenda. If electronic systems are available, these would be preferable to paper systems alone.

Each team must report their data daily.

Initiation

First contact

- Peers establish report and trust
- Screen for withdrawal using the Objective Opiate Withdrawal Scale (OOWS) (see appendix)
- Clinician to take a brief medical history and rule out any life-threatening exclusion criteria
- Each case should be assessed on individual merits.
- Basic medical examinations are done (BP, pulse, respiration and basic cardio exam) are done.
- Special investigations are not standard practice. If screening reveals a potential risk, further examination or investigations may be needed before initiation or deciding on a choice of medication.
- Urine testing is not appropriate unless clinically indicated – many of the medications used to treat COVID-19 will give a positive urine screen [4]

[4] Farhoudian, Ali et al (26 Mar. 2020.). COVID-19 and Substance Use Disorders: Recommendations to a Comprehensive Healthcare Response. An International Society of Addiction Medicine (ISAM) Practice and Policy Interest Group Position Paper. *figshare*. Retrieved from https://figshare.com/articles/COVID-19_and_Substance_Use_Disorders_Recommendations_to_a_Comprehensive_Healthcare_Response/12033567

Inclusion criteria

- More than 12 months' history of heroin/nyaope use (unless clinically indicated) and/or scored as High-Risk opioid use (≥ 27) on the ASSIST 3.0.
- The client understands the procedures.
- Agrees to be contacted for follow-up.
- The client provides informed consent.
- Can access DOTS

Exclusion criteria

(evaluated on an individual basis)

- No history of opioid use or withdrawal (peers are best at identifying this)
- History of heart disease may exclude methadone as an option
- Be cautious with clients with an alcohol use disorder and/or benzodiazepine misuse.
- History of respiratory depression or other chronic respiratory condition, including asthma (unless recommended by assessing physician).
- Severe liver impairment.
- Severe head trauma or any other condition that causes increased intracranial pressure.

For further information consult the SAAMS guidelines

ASSIST and history

- Complete the ASSIST 3.0 See https://www.who.int/management-of-substance-use/assist
- Complete the eligibility form (Appendix)
- Complete physical
- Sign consent form (appendix)

Initiation on Methadone

- Do not take short-cuts with the dosing and up-titration – this can be fatal.
- Initiate on 10-15 ml (20-30mg)
- The client may still experience withdrawal, but only an experienced doctor, CA or NC can increase the dose by 5mg after 3-4 Hours if there are objective signs of opioid withdrawal
- The dose can be increased by 5mg every three days

Do not allow people to top-up with methadone. Because of the long half-life, it has a cumulative effect and only reaches peak levels on day 5-6. (see below)

		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**
	Constant Dose	30mg	30mg	30mg	30mg	30mg	30mg
	50% ($T^1/_2$=1day)		15	22.5	26.25	28.125	29.0625
	Effect		45	52.5	56.25	58.125	59.025
	Increasing dose	30mg	40mg	50mg	60mg	70mg	80mg
	50% ($T^1/_2$=1day)		15	27.5	38.5	49.375	59.8675
	Effect		45	77.5	98.75	119.375	139.6875

The primary risk associated with methadone is an overdose. It is a particular concern at the beginning of treatment, and when methadone is used in combination with other depressant drugs (especially alcohol, benzodiazepines, and heroin). It may take three to four hours after taking the drug(s) to observe the first signs of overdose.

The first 14 days of methadone treatment may increase the risk of mortality.

People may not feel entirely comfortable in the early stages of initiation before a steady state is reached. They should not top up with methadone as the effect could only be felt much later. It is safer to "top up" with a short-acting opioid, although this also poses a risk.

Procedures

STAGE	ACTIONS	DOCUMENTS
Preparation	Teams plan routes and resources needed based on pre-assessment. Needs are discussed.	Route plan, schedule, list of potential clients, medicine register
At site or shelter	Peers and community members speak with the population and confirm numbers in withdrawal Severe withdrawal is prioritised Screening takes place	OOWS Consent
Baseline assessment	Additional information and questions are answered. baseline assessment procedures using ASSIST Eligibility evaluated, forms completed	ASSIST 3.0 Road to Linked Care Booklet Med010
Initiation	The first dose of between 10-15ml (20-30mg) is given Daily doses are given from ward stock the nurse carries	Tx Contract Data recording mechanism
Dose adjustment	The outreach team will provide observed daily doses, and in consultation with the doctor dosages will be adjusted as per the guidelines over the next 14 days. The maximum increase is 5ml every three days.	

	If the clients are experiencing discomfort, withdrawal symptoms or appear intoxicated, they will be referred to the most qualified clinician. The doctor or experienced PNC to see clients weekly during initiation period, i.e. until a stable dose is reached.	
Stable dose	Once clients are comfortable on their doses, showing no objective or subjective withdrawals for seven days, they will move to the maintenance phase.	
Maintenance	The clients will receive observed daily doses when in unstable accommodation or if the shelter has no management system Take home dosing: The client must have stable housing. Initial maximum prescription for seven days A client with a good support structure can receive take-home doses for 7, then 14, then 28 days Shelters can retain medications under lock and key	Standard records
Voluntary termination	The clients must be down titrated per the SAAMS guidelines. The clients must have the risks explained and sign an indemnity form. Clients to be offered an exit interview.	Indemnity form
NOTES		
Missed doses	If the clients skip three days, they must see the doctor or experienced nurse who will re-initiate on a lower dose as per the SAAMS guidelines.	
Drop-outs	Attempts will be made to find clients who miss more than two appointments. Clients will be given the opportunity of re-joining the project	
Illicit drug use	Illicit drug use will not be grounds to terminate participation in the programme unless there are indications that this may lead to drug poisoning. The dose may need to be increased.	

Initiation on Buprenorphine

Adapted from the SAAMS guidelines:

Buprenorphine is a partial agonist, and acts as an antagonist when there are other opioids present, or an agonist, and therefore relieves withdrawal symptoms when there are no opioids in the system.

Suboxone or Subutex are the forms of buprenorphine available in South Africa. Suboxone is 4-part buprenorphine (partial agonist) to 1-part naloxone (antagonist). Suboxone contains an antagonist to prevent people from injecting because the antagonist becomes bio-available if the drug is injected, and this causes the person to withdraw. For some people, suboxone may cause discomfort due to the addition of the antagonist.

It is available as a sublingual tablet in 2mg/0.5mg or 8mg/2mg doses. The maximal effects of buprenorphine appear to occur in the 16–32 mg dose range for sublingual tablets.

Only initiate buprenorphine when the person is in withdrawal!

- If initiated too early, it will cause precipitated withdrawal.[5]
- If withdrawal is precipitated, treat symptomatically, not by providing further buprenorphine
- Clonidine can be administered to relieve symptoms of withdrawal
- Most people are initiated on 4 mg
- When starting buprenorphine or buprenorphine-naloxone, start low and titrate rapidly, providing there are no problems.
    - Use caution in patients who are using alcohol, other opioids (for chronic pain) and sedating drugs; or have comorbid medical conditions (e.g. severe respiratory, renal, or hepatic disease)
    - Caution in patients who take a long-acting opioid like methadone- increased risk of precipitated withdrawal.
- Further doses of 2-4 mg or 2/0.5 – 4/1mg can be given every 2-4 hours (as peak plasma levels are only reached after 2-4 hours) until the patient is comfortable and not experiencing objective withdrawal.
- Ideally patients should be observed after each dose to ensure they are not overly sedated, but where this is not possible, the prescriber should be telephonically available to discuss adequate dosing.
- The maximum registered dose in South Africa is 16mg or 16/4mg.
- Prescriptions may be given as fixed, increased doses (e.g. 4mg+4mg day 1; 12mg day 2 and 16mg day 3); or a flexible regime allowing some control by the patient, may also be used.
- The total dose used on day one can then be repeated the next day and increased further by 2-4 mg or 2/0.5 – 4/1mg daily (usually 4 mg for severe withdrawal) according to clinical response over the next few days, up to a maximum of 16 mg or 16/4 mg (the maximum registered dose).
- Some patients may require higher doses, up to 32mg.
- The ideal dose is one where there are no withdrawal symptoms, no cravings and where

[5] Prcipitated withdrawal occurs because the suboxone has a high affinity but low intrinci valued compared to the morphine that heroin becomes in the body. It therefore knocks the morphine off the receptor and causes a rapid loss in effect and so the person begins to withdraw.

the use of any illicit opioid does not have any effect/only minimal effect.

Tramadol

Tramadol can be tried in the absence of methadone. Some people do well on it, but others don't, and drug expectation may play a role in the success or failure of tramadol.

There is not much literature on Tramadol, but in a current article, the authors say[6]:

"Dosage of tramadol

Based on the review of the studies available on the use of tramadol in opioid use disorders and in various pain conditions, it is evident that the use of tramadol in the dose range of 300–400 mg/day is safe, with few side effects. The guidelines for the management of pain conditions suggest initiating tramadol treatment with the lower dose and increase it gradually.[42,43] However, the patients of opioid use disorders, who are already tolerant to opioids, can be started with the maximum dose, that is, 300 mg to400 mg per day from day one itself if indicated. Because of the short half-life of tramadol, it should be prescribed in 3–4 divided doses per day. If possible, shift to the extended-release or long-acting formulations of tramadol after stabilization of the daily dose."

[6] Balhara, Yatan Pal Singh, Arpit Parmar, and Siddharth Sarkar. "Use of tramadol for management of opioid use disorders: Rationale and recommendations." Journal of neurosciences in rural practice 9.03 (2018): 397-403.

Symptomatic treatments

Symptomatic treatments often result in relapse, but it is ethical to try and relieve as much discomfort and pain as possible. This procedure can be used to assist people when there is no methadone available. It is taken from the KZN Department of Health Guidelines.

Administer the OOWS (appendix)

If score < 4 – No Treatment necessary. Manage psychosocially.

If score ≥ 4 – Administer a "rescue pack" to the user, consisting of medication for symptomatic relief for TWO days:

FOR STOMACH CRAMPS	Hyoscine butylbromide (Buscopan®) 10mg PRN up to TDS
FOR DIARRHOEA	Loperamide (Imodium) 4 mg stat followed by 2 mg after each loose stool up to 8mg
MUSCLE PAIN	paracetamol PRN
VOMITING	Metochlopramide (Maxalon®) 10 mg PRN
IRRITABILITY/ANXIETY	Promethazine (Phenergan®) or Chlorphenaramine, Allergex, 25 mg PRN up to TDS
	Diazepam (Valium) 5mg nocte

After two days, the "rescue pack" may be repeated.

If the user remains symptomatic after four days using the "rescue pack", repeat the OOWS, If OOWS > 6, then refer to the closest hospital for management.

From the SAAMS Guidelines:

"Although co-prescribing of benzodiazepines with OST is frowned upon, it is not uncommon. Some prescribers use benzodiazepines to reduce treatment costs, by using it to minimise substitute opioid dose. Others prescribe at the insistence of patients, to aid with insomnia, to cope with day-to-day stress or to medicate an underlying anxiety disorder. ***Prescribers are advised that this is not good practice and it should be avoided where possible****. Not only are the benzodiazepines associated with unwanted side-effects, like impaired judgement, memory, cognition and sleep architecture, but it also increases the risk of overdose and the risk from complications from injecting use of the benzodiazepines. Furthermore, benzodiazepines are addictive drugs; they are associated with tolerance, withdrawal and dependence.*

Clonidine:

Clonidine (Dixarit®) is a medication marketed for the treatment of hypertension used for many years to treat the sympathetic hyperarousal that occurs in opioid withdrawal. It is most effective when used for detoxification in an inpatient setting because of potential side effects.

Advantages include:

- It is not a scheduled medication
- The use of opioids can be discontinued immediately
- It does not produce opioid euphoria and is not addictive

Although Clonidine alleviates some symptoms of opioid withdrawal, it is not effective for muscle aches, insomnia or drug craving. These symptoms require additional medication (see symptomatic medication).

- Ensure patient does not have blood pressure or cardiac abnormalities
- Give a test dose of 50 micrograms orally or sublingually (75 micrograms may be used for patients weighing more than 80 kg)
- Measure the patient's blood pressure after 30 minutes. If diastolic blood pressure is normal and there is orthostatic hypotension (a drop in systolic blood pressure of 10 mmHg upon standing), the patient may continue the regime
- Clonidine 75-150 micrograms orally 6 hourly may be used
- Taper this dose over 4-6 days

OST-SCREENING-COVID OST-001

Date:	Site:
Client Name:	Unique number:

Screening for COVID-19	Positive	Negative	
If positive referred for testing	Yes	No	
Test results	Positive	Negative	

Please answer the following questions about the client:			Comments
>12 months of heroin/nyaope use **or** <12 months but high risk	Y	N	
High-Risk opioid use (≥ 27) on the ASSIST 3.0	Y	N	
Understands procedures and protocols	Y	N	
Agrees to be contacted for follow-up	Y	N	
Provided informed consent	Y	N	
Stable accommodation, fixed site and contactable?	Y	N	
History of heart disease	Y	N	
Acute alcohol use disorder	Y	N	
Acute benzodiazepine use disorder	Y	N	
Clinical diagnosis of schizophrenia or any other psychotic disorder	Y	N	
History of respiratory depression or other chronic respiratory condition	Y	N	
Severe liver impairment	Y	N	
Severe head trauma or any other condition that causes increased intracranial pressure	Y	N	
HIV/TB Screening done?	Y	N	
Client on treatment for HIV/TB?	Y	N	
Other Contra-indications to OST	Y	N	

Task			Comment
ASSIST	Y	N	SCORE:
Consent forms	Y	N	
Admission booklet	Y	N	
Medical evaluation	Y	N	
Psychosocial evaluation	Y	N	

Initiation date:	Medication	Dose	Take away dose	Next appointment	Site
Notes:					

Completed by:

_____ (Name and Qualification)

_____ (Signature)

Objective opioid withdrawal scale: (OOWS):

Patient:

Date ..... Time .....

OBSERVE THE PATIENT DURING A

5 MINUTE OBSERVATION PERIOD

THEN INDICATE A SCORE FOR EACH OF THE OPIOID WITHDRAWAL SIGNS LISTED BELOW (ITEMS 1-13). ADD THE SCORES FOR EACH ITEM TO OBTAIN THE TOTAL SCORE

	Sign	Measure		Score
1	Yawning	0 = no yawns	1 = >1 yawn	
2	Rhinorrhoea	0 = < 3 sniffs	1 = >3 sniffs	
3	Piloerection (observe arm)	0 = absent	1 = present	
4	Perspiration	0 = absent	1 = present	
5	Lacrimation	0 = absent	1 = present	
6	Tremor (hands)	0 = absent	1 = present	
7	Mydriasis	0 = absent	1 = >3 mm	
8	Hot and Cold flushes	0 = absent	1 = shivering / huddling for warmth	
9	Restlessness	0 = absent	1 = frequent shifts of position	
10	Vomiting	0 = absent	1 = present	
11	Muscle twitches	0 = absent	1 = present	
12	Abdominal cramps	0 = absent	1 = Holding stomach	
13	Anxiety	0 = absent	1 = mild - severe	
	TOTAL SCORE			

Range 0-13

Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse,* 13, 293-308

CONSENT TO OST

This agreement has been prepared to both inform you about OST, as well as to document the rules/obligations contained in this agreement.

Acknowledgement

I acknowledge that:

1. Methadone/Suboxone is an opioid (opioids are drugs like heroin, cocaine, morphine, pethidine, etc.), and that I may develop a physical dependence on this medication. A sudden decrease in dose or discontinuation of this medication will likely lead to symptoms of opioid withdrawal.
2. I am already physically dependent on at least one form of opioid, and I'm unable to discontinue the use of opioids.
3. I have tried, to the best of my ability, other possible treatments for opioid dependence and these attempts have been unsuccessful.
4. Taking any mood-altering substance with OST can be potentially dangerous. There have been reported deaths caused by the combination of OST with alcohol, opioids, cocaine, barbiturates, and/or tranquillizers.
5. I may voluntarily withdraw from the OST programme at any time.
6. It is important to inform my physician/dentist that I am taking OST.
7. Regarding pregnancy, I understand that there can be effects on the developing foetus caused by OST and that specialized care will be required to reduce any harm to my foetus if I am or become pregnant while on OST.
8. It is unsafe to drive a motor vehicle or operate machinery during the stabilization period after starting methadone/suboxone and during dose adjustments.
9. Poppy seeds and certain over-the-counter medication may result in a positive drug urine screen.
10. I have been informed that the most common side effects of the medication are sweating, constipation, decreased sexual function, drowsiness, increased weight, water retention and other side effects listed in the registered package insert.
11. OST will be discontinued or tapered off if the clinician determines that it has become medically unsuitable

Behaviour while in our practice/site

I agree to maintain positive, respectful behaviour towards other programme patients and staff at all times when in the clinic. While on clinic property, threats, racist or sexist remarks, physical violence, theft of property, vandalism or mischief, the possession of weapons, and selling or buying illicit substances are serious programme violations.

Obligations of being on this programme:

I agree to take only one dose of OST a day (unless advised otherwise by the clinician), and to have the ingestion of my dose witnessed on those days that I don't have take home OST.

I understand that I will not be given a dose of OST if I:

Appear to be intoxicated or under the influence of some other substance. I may be asked to see a clinician. For the sake of my physical safety, I may be asked to wait before receiving my dose or refused a dose for that day.

Consents:

- I allow the OST prescribing physician to speak to other doctors/clinical associates or healthcare professionals about my care.

- I allow the clinic's pharmacist and nursing staff to talk to pharmacists or other healthcare providers to verify my recent dose(s), which I receive at another pharmacy or institution.

Confidentiality:

Everything that you tell the clinic staff is confidential. However, it is essential to realize that under exceptional circumstances, we may be obliged to report something you tell us to the appropriate authority. This can occur under the following conditions:

- If we suspect that a child is at risk of emotional or physical harm or neglect, it is the law that we report this information.

- If you become suicidal, homicidal, or are unable to take care of yourself due to a psychiatric condition, you might be held against your will to be assessed by a psychiatrist.

- If you reveal to the staff that you intend to harm another person, we will be obliged to protect that person by notifying the appropriate authority.

- If a court subpoenas your chart, we must release it under the subpoena.

- Certain infections must be reported to the local public health department, e.g. tuberculosis.

I agree to respect the confidentiality of other patients in the programme.

My signature below indicates that I agree to follow the obligations and responsibilities outlined in this agreement. Should I fail to meet the terms of this agreement, I understand that I may be asked to leave the OST programme. I have discussed and reviewedw this agreement with my attending physician/clinical associate, and my questions (if any) have been answered to my satisfaction.

Date (dd/mm/yyyy) Client's Name Client's Signature

Date (dd/mm/yyyy) Staff's Name Staff's Signature

ROLES & RESPONSIBILITIES

An effective way to implement the services is a multidisciplinary team approach with planned services at predetermined sites. The team consists of the Family Physician or General Practitioner, Clinical Associate, Professional Nurse Counsellor, Social Worker, Community Health Workers, Peer Liaison/Educators and other allied health care workers supported by Team Leaders.

The following roles and responsibilities have been identified for this programme:

POSITION	RESPONSIBILITIES
Peer Liaison/Educator/social worker/community health worker	The first point of contact. Make clients feel comfortable. Encourage and guide through the process and manage expectations. Mini-Triage: Assess clients and see why they are here and where they need to go. Be familiar with referral pathways and redirect appropriately. Provision of handouts and other relevant reading materials. Assist clinical staff and family members with communication, translation, and interpretation of situations. Obtain a signed informed consent. Complete a screening consent process and assess eligibility.
	Complete ASSIST 3.0. Identify high-risk behaviours and prioritise: Overdose. Injecting. Life-threatening wounds. In such cases, liaise with Clinical staff to prioritise immediate medical assessment. Distribute harm reduction materials and keep records. Deliver behavioural interventions and supportive services Education on the risks and prevention of COVID-19 Referral pathways and redirection if the client is at the wrong place. Schedule appointments and assist with follow-ups and locating PWUD who are lost to follow-up, in consultation with other team members. Assist with the administration where necessary. Provide feedback to project teams on community issues and suggest improvements. Identify an emergency and administer basic first aid. Be equipped and trained to be able to deliver naloxone in case of overdose. Maintain records
Community Health Worker/nurses	Assist peers with their duties. Complete ASSIST 3.0. DOT and document.

	Assist with the administration. Help with screening for medical conditions, e.g. Screen for TB and collection of sputum, STI, etc. Help with HCT. Home visits. Community Outreach. Link with ward-based outreach teams Provide daily doses as per doctor's prescription. Observe for discomfort, withdrawal symptoms or intoxication and refer to the doctor or Clinical Associate. Document procedures for medication supply chain management, daily observed therapy and take-home doses as appropriate. Screen for infectious diseases. Assess adherence to treatment as appropriate. Assess participation in psychosocial support services. Refer to other services as needed.
Case Managers - Can be: Social Worker, Auxiliary SW, Counsellor Also, Clinical Associates can perform this role where they are available	Case management role: Establish rapport with clients. Work collaboratively with clients where they wish to engage. Keep up to date with progress. Help clients develop personal development plans. Track referrals. Enter information into Synaxon. Feedback to clinicians. Update staff on issues. Regular follow-ups as per research protocols.
Clinical Associates, PNCs and specialist nurses	Baseline assessment including: An assessment of substance use, medical and related history will be conducted using the Addiction Severity Index (ASI) Lite Version 2. Medical examination as needed/informed by history. Complete a screening consent process (if not done by the peer already) and assess eligibility. Complete ASSIST 3.0. Perform client specific special investigations that may be needed AND are consented to (viz. ECG and blood sampling [ALT] and HIV testing [testing for viral hepatitis B and C may be offered], including drug urinalysis where applicable). Can also do mental health screening where a mental health practitioner is not available on site. OST administration, supply chain management in liaison with the Family Physician or Medical Officer. OST adherence management. Management of referrals. Engagement with outreach teams Can also perform many of the duties of the PNC should a PNC not be available Lead Team Meetings in liaison with the supporting doctor.

Doctor	Attend to clinically significant events and medical emergencies. Perform initiation visit tasks which include: Review of laboratory results. Provide additional counselling around COSUP or OST. Discuss treatment contract for OST if eligible. Prescribe and initiate the client onto methadone or buprenorphine at an appropriate dose by good clinical practice. See or communicate with the client twice per week during the initiation phase i.e. until a stable dose is reached. Identify health and non-health problems. Provide harm reduction support and brief interventions. Manage co-morbidities. Refer clients who need specialists' services. Conduct weekly clinical meetings with staff.
Social Worker	Counselling clients and family members. We are working together with multidisciplinary teams to formulate individualised development plans and treatment plans. Assess and enrol clients with substance, mental and emotional challenges into the programme. Organise and conduct groups to address psycho-social needs and/or skills training. Referral to other service providers for further assistance. Provide after care support to the individual and/or family and monitor the basic functioning of the client. Assessment to determine skills and assist with skills development programmes to be self-sufficient. Administrative duties such as report writing, statistics, referrals, and networking, attending meetings, supervision. Provide harm reduction support and brief intervention. Statutory roles.

Methadone vs Buprenorphine

	Methadone	Buprenorphine
	"Start slow, go slow and aim high."	"Start low, go fast and aim high"
Pharmacology	Full Opioid Agonist 24-36 hour half life	Partial agonist 36-48 hour half life
Metabolism	Slow onset and is well absorbed from the gut with 80% passing into the blood stream. Metabolism involves the CYP450 enzymes. 90% protein bound. There is a high risk of interactions with other medications and even foods, resulting in a wide range of bioavailability form 35%-100%. Due to fast metabolism the drug may need to be taken twice per day, and peak blood concentration is in about 2-4 hours.	Metabolised via the CYP450 system. Peak blood concentration is reached in about 2hrs. 97% protein bound.
Administration	Liquid with 2/1 ratio (Equity Methadone)	Sub-lingual tablet
Evidence base	Considered "gold standard"with many years of research	Increasing evidence base
Dosing	60-120mg per day, but higher doses are not uncommon. 60mg of methadone = approximately 16mg buprenorphine, but this varies between patients. May need to be taken twice daily by fast metabolisers.	Doses range between 8 and 32 mg per day in initial stages, may be down-titrated to 4-8mg per day. Under-dosing can result in anhedonia and general feeling of unease. Can be taken every second day in some cases, particularly during down-titration.
Pregnant women	First choice for treatment with strong supporting evidence	Increasing evidence base, supports use during pregnancy
Risk of overdose	Initial increased risk of overdose during initiation phase. Because it is a full agonist there is still risk of overdose when opioids or other respiratory suppressants are used on top of the methadone.	Reduced risk of overdose due to high binding affinity and partial agonist properties. Risk does still exist, particularly when the effects of the buprenorphine wear off.
Other risks	Methadone can lead to prolonged Qt interval in some patients. An ECG is usually recommended prior to initiation.	Cytolytic hepatitis and hepatitis with jaundice reported in some individuals. Liver function may need to be monitored.
Diversion and abuse	Due to methadone being a full agonist, there is more abuse potential Diversion does occur.	Less abuse potential. By combining buprenorphine with naloxone (as with suboxone) there is less risk of abuse, particularly injecting.
Illicit opioid use	Tends to be higher	Tends to be lower
Treatment protocol	Internationally methadone treatment tends to be clinic based with DOTS.	In the USA, Buprenorphine tends to be more office based with take-home doses.
Initiation	Doses need to be gradually up-titrated, which may leave the patient with a feeling	Patients need to be in early stages of withdrawal to avoid precipitated

	of unease, causing them to crave and want to “top up”. This needs to be managed and discouraged as peak plasma levels are usually only reached after 5 days of treatment. Start low and up titrate. During this period there is increased risk of overdose. Recommended DOTs for a longer period of time before take-home doses are recommended.	withdrawal. There could therefore be some levels of initial discomfort. Initial doses can be high. Start high and down titrate. Take home doses are usually initiated earlier. Dosing easier to monitor because of pill format.
Drug interactions	Bioavailability can be significantly affected by other medications and foods. Typically doses need to be increased when patients are on TB medications.	
Costs	Internationally Methadone is usually cheaper. In South Africa, costs are currently similar.	Internationally Buprenorphine is usually more expensive In South Africa, costs are currently similar.

Low vs High Threshold Services

Low	High	Comments
Easy to enter	Difficult to enrol	To have maximum impact, programmes should look to include the most vulnerable of populations who would struggle to come to high threshold programs.
Harm reduction orientated	Abstinence only acceptable outcome	The realities of many accessing services may make total abstinence an initially unachievable or undesirable goal. To apply a punitive approach would reduce retention. Benefits have been shown to be similar in high and low threshold programs. Retention is considered a valid primary outcome measure and indicator of treatment outcomes (Veilleux et al., 2010)
Urinalysis only at initiation	Regular urinalysis	Correlations between self-report and confirmatory testing have been shown to be good where there is a strong therapeutic bond. Regular testing could be seen as punitive and "breaking the trust" even if that is not the intention, which can negatively affect retention in the programme. Testing is expensive and requires resources and procedures that are onerous on the individual and programme.
Voluntary additional psychosocial services and peer support	Compulsory additional psychosocial services	Additional services, such as counselling, have been shown to have little effect on outcomes, but can significantly increase complexity and cost of programmes. OST should not be held back because of lack of additional services. Support and engagement with peers on OST will be encouraged to provide additional support and connection (Amato et al., 2008, 2005; Dugosh et al., 2016).

Assessing for intoxication & withdrawal

Withdrawal

SIGNS AND SYMPTOM OF OPIOID WITHDRAWAL	
Dilation of pupils	Lacrimation
Anxiety	Rhinorrhoea
Muscle and bone ache	Abdominal cramps
Muscle cramps	Nausea
Sleep disturbance	Vomiting
Sweating	Diarrhoea
Hot and cold flushes	Palpitations
Piloerection	Rapid pulse
Yawning	Raised blood pressure

Intoxication

Intoxication with central nervous system depressants such as benzodiazepines and alcohol increases the risk for overdose in combination with methadone or buprenorphine.

SIGNS OF OPIOID OVERDOSE	SIGNS OF OPIOID INTOXICATION
Pinpoint pupils Loss of consciousness Respiratory depression Hypotension Bradycardia Pulmonary oedema	Constriction of pupils Itching and scratching Sedation and somnolence Lowered blood pressure Slowed pulse Hypoventilation

Intoxicated presentations

Client safety is the key consideration in responding to those who present for dosing while intoxicated due to opioids, alcohol, or other drugs. Clients should be made aware at the commencement of treatment that medication will be withheld in the event of intoxication ('nodding').

Clients should always be assessed by the person dispensing the dose (nurse or pharmacist) for signs of intoxication before the dose is given. Clients who appear intoxicated with CNS depressant drugs should not be dosed or given a takeaway dose of methadone or buprenorphine.

Clients can be asked to re-present later in the day (or the following day) for dosing. The prescribing doctor must be notified to determine the need for the client to be assessed by the prescriber prior to the next dose being administered.

Investigations

Special Investigations

Use of investigations should be based on history and clinical indications.

Urine drug screening is not needed in the current circumstances. It should only be used if there is doubt that the individual is a heroin user.

RECORDS & REPORTING

Case records detailing the client's clinical history and progress in treatment should be established and adequately maintained. There should be clear and concise notes, duly signed, named, and dated. A separate structured sheet for recording prescriptions must be kept. Client notes to be filed following the Client File Index (COSUP_PAT017_Compiled Patient File Index).

Management of acute pain in opioid Use disorders

Patients with acute pain and opioid use disorders (OUD) can be challenging to manage, partly due to central sensitization, tolerance, and opioid-induced hyperalgesia (OIH).[17] Clinician-related barriers also lead to poor analgesia in opioid-tolerant patients. These include a lack of knowledge about opioid equivalent doses, stigmatization and fear of overdose.

Pain is not controlled with methadone or buprenorphine used for OST as it is dosed daily and the analgesic effect lasts 4-8 hrs

There is no evidence that exposure to opioid analgesics in the presence of acute pain increases rates of reuse of illicit opioids.

The additive effects of opioid analgesics and OST have not been shown to cause clinically significant respiratory or CNS depression.

Reports of acute pain with objective findings are unlikely to be manipulative gestures.

Management

A careful history, physical examination, and relevant diagnostic studies to identify the cause of the acute pain are the essential first steps.

Patients receiving OST	Patients who are actively using opioids
Often require high opioid doses due to tolerance. Methadone maintenance therapy patients with acute pain should be treated for pain with opioid or non-opioid medications as would be appropriate if they were not on methadone.	The setting of acute pain is not the time to attempt detoxification [2] Opioid users face stigma and discrimination and may not readily disclose their opioid use. Use a non-judgmental screening tool to assess substance use. Baseline quantity may be difficult to ascertain.
Steps: Confirm the patient's outpatient daily OST dose and continue Use multimodal analgesia, in appropriate combinations of short-acting opioid (as required), local anaesthesia, and	Steps: Plan for inpatient opioid withdrawal management and initiate OST with patient consent [8] Follow steps as described above.

[7] Arnold RM, MD, Childers JW. Management of acute pain in the patient chronically using opioids. Abrahm J, Saxon AJ, Savarese DMF, editors. UpToDate [internet]. Wolters Kluwer: UpToDate Inc; 2019 [Retrieved 2019 Oct 4]. Available from: https://www-uptodate-com.uplib.idm.oclc.org/contents/management-of-acute-pain-in-the-patient-chronically-using-opioids?search=Management%20of%20acute%20pain%20in%20the%20patient%20chronically%20using%20opioids&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

[8] Ward EN, Quaye AN, Wilens TE. Opioid Use Disorders: Perioperative Management of a Special Population. Anesth Analg. 2018 August; 127(2): 539-547.

adjuvant anti-inflammatory analgesics and paracetamol Morphine (short-acting opioid) can be used safely. Doses are higher than in opioid-naive patents, and rapid titration may be needed. Short-acting opioid analgesics should be given on a schedule (every three to four hours) On discharge: Provide last methadone dose verification letter, clear instructions for pain management and opioid taper (for pain). Encourage follow-up.	Be prepared to titrate opioid doses rapidly if initial doses are ineffective due to tolerance. Arrange outpatient follow-up for OST treatment and pain management

Appendix One: Summary of data for Opioid Substitution Therapy (OST)

Brief description	Rational
Opioid substitution therapy involves providing a medication so as to alleviate the symptoms of opioid withdrawal and reduce the cravings associated with a hypoactive opioid system, as well as reduce craving response to environmental cues. It does this without producing a "high". OST is initiated and then maintained indefinitely. The medications available in SA are Methadone at 2mg/1ml syrup and Suboxone 2mg & 8mg Slt OST is not currently available in the public sector for maintenance purposes. I the private sector it is often poorly prescribed and knowledge amongst doctors is poor.	Opioid dependence is particularly challenging to resolve due to the dependence and withdrawal. Migration to injecting is common, and this adds significant health risks, including HIV, HCV and other blood borne viruses. Evidence for treating heroin use disorders using OST is very strong, and the benefits would be significant. Focus groups with heroin users have shown that there is a strong demand for OST. OST can provide significant benefits beyond reducing drug use and has been shown to have a number of secondary outcomes. While OST is currently expensive, with the increase in heroin use and injecting drug use, the consequences could be catastrophic if an effective and proven treatment is not pursued.
Expected Outcomes	**Other key findings and benefits**
- Retention in Tx [1–6] - Reduced drug use [1,2,6,7] - Reduced criminal activity [7–9] - Reduced HIV risk[10–12] - Improved QLM [13,14] - Improved health [15–17] - Reduced mortality [8,18–20]	- Correct dosing is vital – Various Cochrane reviews listed and guidelines [21–24] - Urinalysis is not required - - Psychosocial services are not required and add little, but regular contact is a form of BI [2,25,26]

Delivered to	Delivered by	Where	When	Dose/duration	Frequency
Opioid dependent users	GP/Psychiatrist	Clinic	Once assessed and screened	Variable 20-120mg	Daily
	Nurse for initiation DOTS	Clinic	First 2 weeks	Variable 20-120mg	Daily
	HCW can monitor	Home	After stabilised	Variable 20-120mg	Daily
Missed 4 doses-reinitiated	GP prescribes initial dose	Clinic	If miss 4 doses		

Key Tools, Manuals & Guidelines		Training			
Name	**Description**	**Who**	**By**	**Duration**	**Frequency**
SAAMS Guidelines	South African Addiction Medicine guidelines	Drs	SAAMS	2 online sessions 1x6hrs f2f	once
WHO, UNODC UNAIDS Technical Guide	HIV targets and recommended interventions	Clinicians			
		PNCs			
		Social Workers			
		Psychologists			
		CHW	T/leader	45min	2 with regular comp test
		Px	Nurse/Social worker	45	Once unless needed
Barriers to implementation		**Notes**			

Currently there is no OST on the EDL for maintenance Expensive to rollout Lack of political will	The inclusion of psychosocial interventions is controversial. The literature suggests that they add no benefit, but then add the caveat that the programmes all include counselling in the form of brief interventions. Also, the research uses highly structures homogeneous approaches. It is difficult to measure the outcomes when heterogeneous and holistic approaches are offered due to the number of confounders. Conclusion: **OST should not be refused or not delivered because of the unwillingness or unavailability of psychosocial services, but helping meet the needs of the community should not be ignored because there is OST!**

Opioid Substitution Therapy cont.
References and Quality of Evidence

Quality of evidence

Evidence is consistent and very high with a number of Cochrane reviews.

Who uses it?

Over 90 countries have OST programmes.

1. Veilleux JC, Colvin PJ, Anderson J, York C, Heinz AJ. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. *Clin Psychol Rev*. 2010;30(2):155-166. doi:10.1016/j.cpr.2009.10.006.
2. Amato L, Minozzi S, Vecchi S, Davoli M, Perucci CA. An overview of cochrane systematic reviews of pharmacological and psychosocial treatment of opioid dependence. *World Heal Organ*. 2005;(November):57. http://www.who.int/entity/substance_abuse/activities/overview_of_cochrane_systematic_reviews.pdf.
3. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. *Drug Saf*. 2000;22(3):179-190. doi:10.2165/00002018-200022030-00002.
4. Lingford-Hughes AR., Welch S., Peters L., et al. BAP updated guidelines: Evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: Recommendations from BAP. *J Psychopharmacol*. 2012;26(7):899-952. doi:10.1177/0269881112444324.
5. van den Brink W. Evidence-based pharmacological treatment of substance use disorders and pathological gambling. *Curr Drug Abuse Rev*. 2012;5(1):3-31.
6. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008;165(2):179-187. doi:10.1176/appi.ajp.2007.06111851.
7. Connock M, Juarez-Garcia a., Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(9):1-171, iii - iv. doi:10.2165/11632820-000000000-00000.
8. Mattick RP, Breen C, Kimber J, et al. *Buprenorphine Maintenance versus Placebo or Methadone Maintenance for Opioid Dependence*. Vol 2.; 2014. doi:10.1002/14651858.CD002207.pub4.
9. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane database Syst Rev*. 2008;(2):CD002207. doi:10.1002/14651858.CD002207.pub3.
10. UNODC, WHO, UNAIDS. *WHO, UNODC, UNAIDS Technical Guide for Countries to Set Targets for Universal Access to HIV Prevention, Treatment and Care Fro Injecting Drug Users - 2012 Revision*. Geneva; 2012.
11. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). *Int J Drug Policy*. 2007;18(4):262-270. doi:10.1016/j.drugpo.2006.12.014.
12. World Health Organization, United Nations Office on Drugs and Crime, Joint United Nations Programme on HIV/AIDS. Substitution maintenance therapy in the management of opioid dependence and HIV / AIDS prevention. *Position Pap*. 2004:1-33.
13. Strang J, Groshkova T, Uchtenhagen A, et al. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *Br J Psychiatry*. 2015;207(1):5-14. doi:10.1192/bjp.bp.114.149195.
14. Van Den Brink WW. b e, Haasen C. C d. Evidenced-based treatment of opioid-dependent patients. *Can J Psychiatry-Revue Can Psychiatr*. 2006;51(10):635-646. https://www.scopus.com/inward/record.uri?eid=2-s2.0-33749517855&partnerID=40&md5=4d5c462131926262d6fecba411c0373f.
15. Degenhardt L, Larney S, Gisev N, et al. Determining the impact of opioid substitution therapy (OST) on mortality post-release. *NDARC Annu Res Symp*. 2014.
16. Kourounis G, Richards BDW, Kyprianou E, Symeonidou E, Malliori M-M, Samartzis L. Opioid substitution therapy: Lowering the treatment thresholds. *Drug Alcohol Depend*. 2016;161:1-8. doi:10.1016/j.drugalcdep.2015.12.021.
17. Deering D, Horn J, Frampton CM a. Clients' perceptions of opioid substitution treatment: an input to improving the quality of treatment. *Int J Ment Health Nurs*. 2012;21(4):330-339. doi:10.1111/j.1447-0349.2011.00795.x.
18. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*. 2011;106(1):32-51. doi:10.1111/j.1360-0443.2010.03140.x.
19. Larney S. Opioid substitution treatment in prison and post-release : Effects on criminal recidivism and mortality.
20. Fallis A. *DETERMINING THE IMPACT OF OPIOID SUBSTITUTION THERAPY UPON MORTALITY AND RECIDIVISM AMONG PRISONERS: A 22 YEAR DATA LINKAGE STUDY*. Vol 53.; 2013. doi:10.1017/CBO9781107415324.004.
21. Kumar MS. *Opioid Substitution Treatment (Buprenorphine)*.; 2012.
22. Kumar MS. *Methadone Maintenance Treatment: Intervention Toolkit*. United Nations Office on Drugs and Crime; 2012.
23. American Society of Addiction Medicine. *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use*. Vol 33.; 2015. doi:10.1073/pnas.0703993104.

24. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. *Treat Improv Protoc Ser 40 DHHS Publ No 04-3939*. 2004:1-172. http://www.buprenorphine.samhsa.gov/Bup_Guidelines.pdf.
25. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. *J Addict Med*. 2016;10(2):93-103.
26. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane database Syst Rev*. 2011;(9):CD005031. doi:10.1002/14651858.CD005031.pub4.