SUPPLEMENTARY FILE 5

Summary of evidence on key ethical considerations to inform NHI coverage decisions

Case study

Opioid substitution therapy

Case prepared by Debbie Marais, with input from the SAVE-UHC team.

Edited for plain language by Karen Hurt

Case study: Opioid substitution therapy

Health condition: opioid use disorder (OUD) / opioid dependence
We use the terms opioid use disorder (OUD) and opioid dependence for the same health condition. We do not use the term addiction because it is vague. It can also have negative consequences, such as stigma and self-stigma for the user and their families and friends. OUD is characterized by:

- → a strong desire or compulsion to take the drug
- → difficulties controlling the levels and frequency of use
- → continuing to use the drug despite harmful consequences
- → a higher priority given to drug use than to other activities and obligations
- → increased tolerance
- → and in some cases a physical withdrawal state.[1,2]

Opioid substitution therapy (OST): a health intervention option for people who are dependent on opioids.

What are opioids?

Opioids are the class of drugs that include heroin, and synthetic opioids such as codeine and other prescription pain medications. Some opioids, such as heroin and heroin combinations (nyaope, sugars and woonga), are illegal.

Opioid use disorder (OUD) is the health condition which people who have a problematic use of and / or dependence[i] on an opioid have. People with OUD:

- have a physical craving to take the drug
- find it difficult to control how much and how often they use the drug
- continue to use the drug despite its harmful consequences
- give a higher priority to using the drug than to other activities and responsibilities
- have increased tolerance, which means that ever increasing doses are needed for the same effect, and in some cases a physical withdrawal state.[1,2]

Opioid withdrawal symptoms
Opiate withdrawal symptoms can be very severe. Symptoms include muscle cramps, severe diarrohea and vomiting, bone and joint aches, anxiety, restlessness and irritability, distrubed sleep, craving, and hot and cold flushes.

Treatment of OUD includes a set of pharmacological (medication) and psychosocial interventions such as psychotherapy, social integration and group support. OUD aims to help the patient:

- reduce or stop their use of opioids
- prevent future harms associated with opioid use
- improve their quality of life and wellbeing.[3]

[i] The term "addiction" is no longer used for diagnosis due to its "uncertain definition and its potentially negative consequences," per the Diagnostic and Statistical Manual of Mental Disorders (DSM–5). Although OUD includes dependence with varying levels of severity depending on the number of diagnostic criteria met, this report will use OUD and opioid dependence interchangeably.

Opioid dependence treatment is usually long-term and possibly lifelong.3 However, when OUD is identified early, treatment usually requires less intense interventions.[4]

Opioid substitution therapy (OST) and opioid agonists

Opioid substitution therapy (OST) is a medical intervention that prescribes medicines called opioid agonists. Patients take them, instead of the opiate, in controlled amounts to:

- prevent experiencing the euphoric effects (highs) of opioids
- reduce cravings for the opioid
- prevent withdrawal symptoms.[5]

Opioid agonists: Methadone and buprenorphine

Two of the most common opioid agonists used for OST are methadone and buprenorphine. OST aims to assist patients:

- to adhere to treatment for the long-term
- function normally
- reduce the harm caused by their opioid use.[6]

Although OST has been piloted at several sites in South Africa, it is not yet available as a treatment option in the public health sector.[7] Currently in South Africa, methadone and buprenorphine:

- are not included on the essential medicines list
- are not available for patients with OUD in public health facilities.

Government is currently considering whether to include OST as part of the health benefits package funded under National Health Insurance (NHI).

Population target for opioid substitution therapy (OST)

The primary population targeted for OST would be users of illegal opioids, particularly those dependent on heroin or heroin combinations. These include “sugars”, nyaope and woonga. People who use Illegal opioids make up the largest documented group of people with OUD.4 However, NHI coverage could also include people dependent on other classes of opioids, such as prescription pain killers.

Your job as the Appraisal Committee

The government has commissioned a Health Technology Assessment (HTA) to thoroughly evaluate the case for or against using public funds to cover the health intervention of OST for opioid use disorder.

As the Appraisal Committee, your job is to review the evidence, discuss the pros and cons across the criteria, and provide a recommendation to the government. Here are the main recommendation options for the health condition OUD:

Recommend coverage for all medically indicated cases.	Recommend coverage for an optimised subset (e.g. key populations, illegal users, prisoners).	Recommend only in the context of research or pilot studies.	Reconsider after improvements in service delivery.	Do not recommend coverage.

The 12 domains for making ethical decisions

What follows is a summary of the available evidence, and what we need to consider regarding of opioid substitution therapy (OST) across the 12 domains in the *Framework for making ethical decisions: what to include under National Health Insurance*. The 12 domains are:

1) **What is the burden of the health condition for the country?**
2) **What health benefits or harms can we expect of the intervention?**
3) **Will the intervention be good value for money?**
4) **How might systems factors affect the delivery and use of the intervention?**
5) **What will the budget impact and benefits of the intervention be?**
6) **Will the intervention promote equity?**
7) **Will the intervention promote respect and dignity?**
8) **Will the intervention affect how people form and maintain important social relationships?**
9) **Will the intervention affect people's personal financial situation?**
10) **Will the intervention ease people's suffering?**
11) **How might the intervention affect people's safety and security?**
12) **Will the intervention affect social cohesion?**

1. What is the burden of the health condition for the country?

Heroin use has risen steadily in South Africa since 1994 across all provinces.[8] Heroin is the most commonly used illegal opioid in South Africa.6 It is the third most commonly used drug, according to treatment admission rates, after alcohol and cannabis.[9,10]

The South African context: opioid use disorder

During a 2012 study, participants were asked if they had used opioid drugs, such as heroin, in recent months. Three out of every 1,000 participants responded "Yes". From this, the estimate for opioid use prevalence in South Africa is 0.3% (see Box 1).[11,12]
South Africa has a population of over 58 million. Our 0.3% prevalence would be about 176,000 opioid users.

Table 1 gives more details from a 2012 survey on the characteristics of opioid drug users. Opioid use disorder (OUD) was highest among people:

- classified Coloured
- living in rural formal and urban formal areas
- between 15–35 years old
- living in the Free State and Northern Cape.[12]

Box 1 Opioid users in Southern Africa

A 2012 study estimated the number of people aged 15–64 using opioids in Southern Africa to be between 210,000–280,000, with a 0.3% prevalence estimate (based on 2009 data from South Africa, Mauritius, and Kenya). [11]

A more recent national study using data from a 2012 representative household survey of 26,453 people also found a 0.3% three-month prevalence of opioid use. **[12]**

In 2015 research to map the number of people who inject drugs such as heroin estimated the number of people injecting opioids to be approximately 75,000 (42,000 men; 33,000 women).[13] The research estimates the number of opiate users who were injecting heroin at approximately 75,000 (42,000 men; 33,000 women). There is not enough data to estimate dependence on over-the-counter and prescription opioids.6

Many experts believe that, because of the challenges of gathering data on illegal drug use and because some data is missing, the actual number of people with OUD is much higher than 0.3%. They believe the use of opioids has grown a great deal in the five years since the most recent survey.[14,15]

Mortality rate: the number of people who died out of every 100,000 people.
Morbidity: the health complications of a condition that do not result in death
Quality-adjusted life year (QALY): is a measure of disease burden, including both the quality and the quantity of life lived. 1 QALY is equal to one year of life in perfect health.
Chronic health condition: a long-lasting illness, such as diabetes.

OUD has high mortality rates and high morbidity.6 We do not have specific South African data on mortality, or disability-adjusted life years (QALYs) for opioid users. Regional data for Southern Africa (including data from SA) estimates the following:[16,17]

- Mortality rate: 1.5 deaths for every 100,000 people using opioids
- QALYs lost: 20,200 years of life in perfect health lost as a result of OUD

Table 1: Past 3-month prevalence of drug use. Source: Peltzer and Phaswana-Mafuya (2018)

Variable	Any drug use			Opiates†
	Total *N* (%)	Men (%)	Women (%)	Total (%)
Sociodemographics				
All	1092 (4.4)‡	7.9	1.3	0.3
Age				
15–24 (27.6%)	422 (5.7)	9.6	1.8	0.4
25–34 (24.4%)	316 (6.5)	12.0	1.0	0.5
35–44 (19.1%)	168 (3.8)	6.3	1.4	0.2
45–54 (13.1%)	93 (2.3)	3.7	1.1	0.1
55 or more (15.7%)	92 (1.5)	2.4	1.0	0.0
Education				
Grade 0–7 (18.0%)	185 (4.6)	8.4	0.8	0.2
Grade 8–11 (41.8%)	451 (4.9)	8.9	1.2	0.4
Grade 12 or more (40.2%)	320 (4.1)	6.7	1.6	0.2
Population group				
African black people (77.8%)	514 (4.0)	7.5	0.7	0.2
White people (10.1%)	114 (5.0)	6.0	4.0	0.1
Mixed race (9.3%)	361 (8.3)	13.7	3.4	0.9
Indian or Asian (2.8%)	102 (3.2)	4.8	1.7	0.1
Employment status				
Employed (39.3%)	475 (5.1)	7.4	1.9	0.3
Unemployed¶ (27.4%)	337 (6.1)	12.7	1.1	0.5
Student (16.8%)	132 (3.5)	5.6	1.4	0.2
Unemployed§ (13.7%)	59 (1.7)	4.9	0.7	0.1
Unable to work (2.8%)	21 (4.4)	7.2	0.2	0.3
Residence				
Urban formal (51.9%)	743 (5.5)	9.3	2.0	0.4
Urban informal (7.8%)	101 (4.1)	7.7	0.4	0.2
Rural informal (34.9%)	126 (2.8)	5.7	0.4	0.1
Rural formal (5.4%)	122 (5.0)	7.5	1.7	0.5
Province				
Western Cape (12.2%)	248 (7.1)	11.6	2.9	0.3
Eastern Cape (11.9%)	123 (4.1)	7.3	0.7	0.1
Northern Cape (2.2%)	94 (5.2)	9.3	1.3	0.6
Free State (5.4%)	90 (6.3)	10.3	2.3	0.7
KwaZulu-Natal (18.5%)	209 (3.5)	7.0	0.5	0.1
Northwest (6.9)	48 (2.7)	5.0	0.4	0.4
Gauteng (25.5%)	175 (4.9)	8.4	1.6	0.4
Mpumalanga (7.5%)	52 (3.6)	5.6	1.4	0.3
Limpopo (9.9%)	53 (2.9)	6.1	0.5	0.1

Health and social consequences for users

OUD is a chronic health condition. It can have devastating health and social consequences. People with OUD may face:

- the risk of relapse
- the risk of death by overdose or injury
- clinical symptoms of prolonged opioid use. This can include extreme sensitivity to pain, called opioid-induced hyperalgesia.[18,19,20]

There are also significant concerns related to infection, such as increased risk of HIV and hepatitis C transmission, particularly among people who inject drugs (PWID) such as heroin. A recent study in South Africa found that among PWID, HIV prevalence is 21% and hepatitis C prevalence is 43%.[21]

Although smoking heroin is the most common usage in South Africa, the prevalence of injecting is showing an increasing trend in most regions.4

Opioid use disorders are also associated with multiple social harms, including:

- violence
- crime
- unemployment
- homelessness
- negative impacts on relationships and families.

For more about these social harms, also refer to these domains in the case study:

→ Will the intervention affect how people form and maintain important social relationships?
→ Will the health intervention affect people's personal financial situation?
→ How might the intervention affect people's safety and security?

2. What health benefits or harms can we expect of the intervention?

There is a great deal of evidence that, compared to no medically assisted treatment, OST has been consistently effective. OST has reduced mortality and improved other wellbeing outcomes for the patients. This includes reducing:

- illegal opioid use
- risks of blood-borne infections
- risk of overdose.3,[22,23,24,25,26,27,28]

One systematic review suggests that the mortality rate among those on OST was less than a third of the deaths experienced by those not in treatment. The greatest reduction was from reduced overdoses.[24]

A meta-analysis of observational studies showed that people who were not taking methadone, or were discharged from treatment, were four times more likely to die than those on treatment.[29]
Additionally, observational and randomised controlled studies have shown that opioid substitution therapy (OST) can support improvements in people's physical and mental health.[25,30]

Studies have shown a marked reduction in risk behaviours among patients in OST programmes.[22,25] This includes HIV risk behaviours, drug injecting, and self-reported opioid use.[22,25] A Cochrane Review found that OST could reduce the risk of patients getting hepatitis C by as much as 50%.[31] Pregnant women who use OST have improved maternal and foetal outcomes.[23]

Abstinence: not doing something. In this case, people who stop using opioids.
Remission: periods of time when people with OUD are no longer dependent on opioids.
Retention: when a patient continues with or completes a health intervention programme.
Inpatient: when patients stay overnight in a health facility while getting treatment.
Outpatient: when patients go to clinics or health facilities without staying there overnight.

Although many individuals with OUD may never be able to achieve complete abstinence or remission, OST has shown its potential to offer significant improvements in patients' health and quality of life. The World Health Organisation (WHO) reports that most patients who receive OST will significantly reduce their use of heroin if not stop using it completely.3 OST programmes have had better retention in treatment compared to standard care, which aims at total abstinence through either inpatient or outpatient detoxification and relapse prevention.3,4

Many of the findings on the benefits of OST have also been demonstrated in low-and middle-income countries.[22] A study evaluating the effectiveness of publicly funded OST in South Africa showed that, individuals receiving OST were significantly more likely to complete the treatment programme (65.7%) than people not receiving OST (44.1%).5 People receiving OST also had lower rates of positive drug tests (16.8%) than those not getting OST (23.3%). Across the sites where OST has been piloted in South Africa, there have been high rates – between 67% and 85% – of retention in treatment.[32]

Potential side-effects of medications used in OST programmes

Like all medications, there are some potential side-effects with the two most common medications, methadone and buprenorphine. Some of the common side-effects are the same as those associated with all opioids, such as:

- arrhythmias (irregular heartbeat)
- constipation
- dizziness
- headaches

Specific safety concerns for common OST medications include:

- cardiac risk (risk of heart attack)
- liver abnormalities that may require monitoring of liver function
- serious breathing problems in the first two weeks of treatment, particularly if patients are still using other respiratory depressants such as alcohol.3,4

Generally speaking, the safety profile of OST medications is favourable when compared to the risks of continued heroin use as well as withdrawal. Other safety concerns include:

- the potential risks of people other than the patients using these drugs, including family members and children, who are not tolerant to opioids and could face higher risks of toxicity
- the diversion of the medications to the black market.4

3. Will the intervention be good value for money?

There have been different approaches to assess the value for money and cost-effectiveness of opioid substitution therapy (OST). Some approaches focus only on the direct medical benefits from treatment in relation to costs. Others include more indirect and societal benefits.[33]

In many cases and in many settings, OST has been found to be cost-effective. In some instances, it has shown to be cost saving when compared to other approaches that do not include medically assisted therapy.

Cost of medicines

In South Africa, it currently costs around:

- R3,000 a month for a daily dose of 100mg of methadone[34]

Some researchers have noted that this price is significantly higher than the cost of methadone in other low and middle-income countries (LMIC).[35,36]

Additional costs of providing OST, such as personnel and supply costs, are estimated to be R120 per person per month.

This brings the total **annual cost** for the programme to R37 200 per person on methadone.

Due to uncertainty surrounding the duration of treatment required, as a result of potential relapse or continued need for OST, it is estimated that most people need to receive OST for 12 months.

- **Quality-Adjusted Life Years (QALYs):** 1 QALY equals 1 year of life in perfect health.
- **Incremental cost-effectiveness ratio (ICER):** the total difference in cost, comparing OST to no intervention, divided by the difference in clinical outcomes – or the cost per QALY

To understand value for money, we look at how much health benefits we can buy for R37 200 per person. These benefits are measured in quality adjusted life years (QALYs). Compared to no intervention, we expect to gain 0.85 QALYs per person using methadone.

We then divide the additional costs of treatment (R37 200) by the expected health benefits (0.85 QALYs) to get the cost per QALY (i.e. the ICER). The ICER for methadone is R43 765 per QALY. This means that it costs R43 765 for each additional year of life in perfect health bought with OST.

To determine if this is good value for money, there is usually a threshold established, above which the number of Rands paid per QALY gained is no longer considered good value. South Africa does not yet have an established threshold. Currently, the threshold estimate is at R38 280/QALY

Figure 1 shows how the ICER for methadone compares to the threshold estimates, as well as how it compares to the threshold. The ICER for methadone falls just above the threshold for cost-effective interventions.

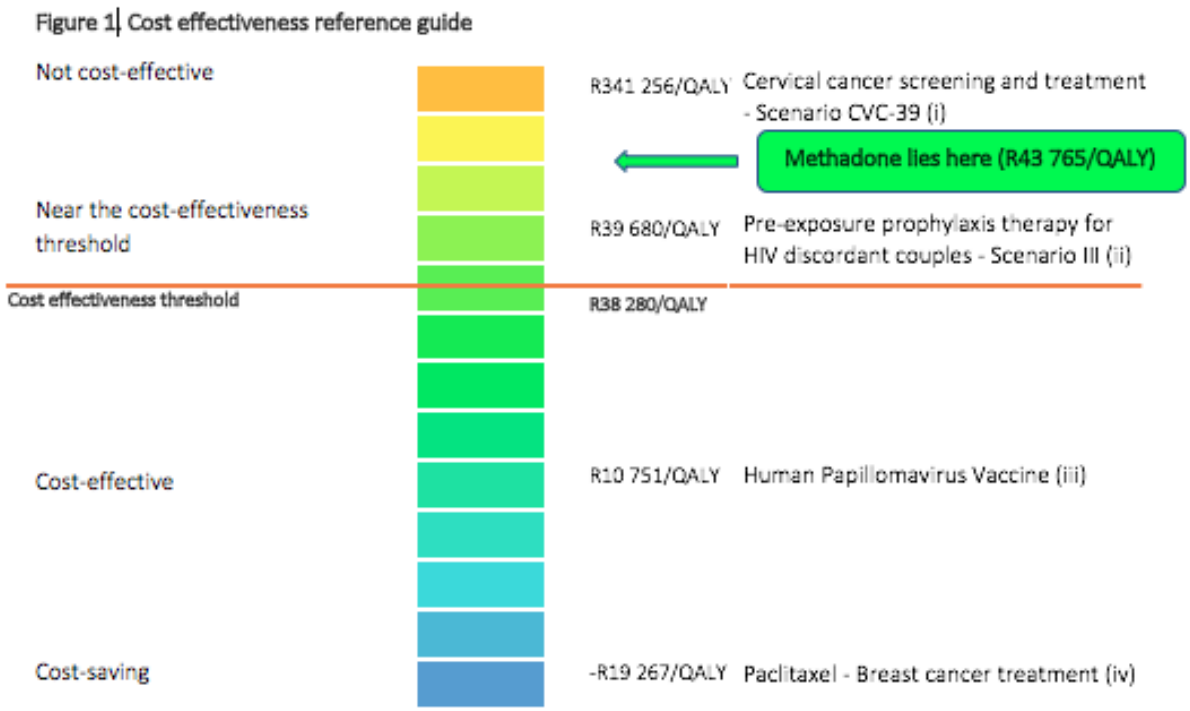

Figure 1. Cost Effectiveness Reference Guide

[i] Kohli-Lynch CN FH, Hofman KJ, Edoka IP. Effectiveness and Cost-Effectiveness of Implanon in South Africa. In Press. 2019.

4. How might systems constraints affect the delivery and use of the intervention?

In addition to considering effectiveness and cost-effectiveness, we need to consider some of the systems factors and constraints that may affect the delivery and uptake of OST.

Integration into primary health care settings and practices

Ideally, OST should be integrated into primary care settings. This may require training primary care providers. It may also require other inputs to strengthen the screening and management of patients who may benefit from OST.

Current screening situation

Currently, the Prevention and Treatment of Substance Abuse Act (2008) mandates routine screening for substance misuse. This is to help early detection and appropriate interventions.[37] However, screening and management of common mental disorders, including substance use disorders, has not been routinely integrated into our primary health care practices.[38] This may negatively affect a full uptake of OST. Inputs such as training may be needed to improve routine screening of patients with opioid use disorders who would be eligible for OST.

Inter-departmental collaboration required

The current models for treating drug use disorders in South Africa may present some challenges. Social workers under the Department of Social Development (DSD) currently provide mainly abstinence-based methods. They provide this with support services by medical practitioners and psychologists under the Department of Health (DoH).[5,39] The historical separation of mental health services means we would have to bring together staff from these two departments and manage different funding mechanisms when adopting an OST approach.8

Capacity building and training

Because of the risk of misuse or diversion to the black market of these substitute opioids, providing OST has to be tightly regulated and closely supervised.4 Additional investments in capacity building and training would be needed to do this. The requirement that methadone only be provided in daily doses would also place extra demands on the system. In addition, South African guidelines for OST recommend that:

- health professionals who prescribe OST should attend accredited training courses
- an impartial trained professional, such as a pharmacist or nurse, supervise and manage patient's daily doses4
- a patient register be established because of the risk of patients doctor- or pharmacy-hopping to divert extra OST medication.4

These additional regulatory and monitoring mechanisms would, however, come at additional costs. See the next section: *What will the budget impact and benefits of the intervention be?*

Other systems challenges to OST as a health intervention

- There have been suggestions of resistance among healthcare workers to provide OST. This is because of:
  - → negative attitudes towards people with opioid use disorder (OUD)
  - → suspicion about substitution therapy.8[,40,41]

- Also, the fact that many opioids are illegal to use and distribute may prevent people with OUD requesting assistance.

5. What will the budget impact of the intervention be?

The total health budget in 2018 year was R227 bn.

As noted under 'Burden of the Health Condition,' there are approximately 176 000 people in South Africa who use opioids. We assume that 10% of those in need will access OST, so 17 600 will receive treatment. And as stated under 'Value for Money,' the annual cost per person is R37 200.

Thus, the annual cost of the whole programme would be R654million (0.288% of the total health budget in 2018).

While these figures do not tell us how much we will gain from investing this money, they do give us an indication of affordability within the health budget.

6. Will the intervention promote equity?

Socioeconomic groups

Individuals with opioid use disorders tend to come from already socioeconomically disadvantaged and vulnerable groups. For people with OUD, their situation is worsened by their drug dependence.[14,35] Additionally, people with OUD in South Africa generally have "poor access to services, as a result of neglect, marginalisation and deliberate policies." [14] See *Table 1* and under ***What is the burden of the health condition for the country?***

Most services for people with OUD are only available through the private sector.8 The cost of getting OST through the private sector has meant that most poorer patients are unable to afford treatment.

- Opioid substitution therapy (OST) would give people who are disadvantaged/ have been neglected an opportunity to access a relatively effective treatment for their OUD.
- OST is a way to promote broader access to other health care and social services among a population that often suffers multiple types of disadvantage and marginalisation.

Including OST as part of the NHI covered package of services has the potential to reduce inequality in financial access to health care between the poor and rich.

Rural and urban divide

There is not very good data on opioid use in rural areas and townships. But the prevalence data we do have shows that opioid use rates may be similar between rural and urban formal settings.[12] More recent reports highlight the widespread use of heroin, including in small towns and rural areas.[14,42] There is much for us to learn about opioid dependence in major townships and towns located along major heroin routes in the country.

If OST were to be included under NHI, it is likely that less resourced and rural settings would face greater barriers to access. This is because:

- There is a high level of training and monitoring required to oversee the treatment. Other countries that have introduced OST into their national insurance packages have documented the problems related to lack of access in rural areas.[43]
- Patients have to visit the clinic every day to receive their treatment. The costs and time of travel may limit access to treatment. This could widen the inequalities experienced by people in rural areas. Although this may be less disruptive than opioid dependence itself.

Gender equity

With regard to gender equity, there are indicators showing that opioid dependence tends to be more common among males than females.[12,27,32] However, there are still many women who struggle with OUD.7[,32] Even though more men have OUD, women with OUD may experience distinct disadvantages in accessing services. This is because of differential gender and power norms in society, childcare, a high prevalence of violence, and poverty.[44]

Therefore, it should not be concluded that opioid use disorders exclusively impact men. OST can have direct impacts on women's health, as well as indirect benefits for women who have partners with OUD.

The existing data about patients who use the service does suggest that, overall, OST would provide greater benefits to men than women. However, there may be some gendered aspects related to a NHI coverage decision, or implementing any OST services, to ensure women who are directly or indirectly affected by OUDs can benefit from any publicly offered treatment programme.[44]

Harm reduction and equity

OST, as a type of harm reduction for opioid use disorders, has generally been described as a pro-equity approach. This is especially when it is compared with alternative approaches to OUD treatment that rely on criminalisation or ineffective, expensive abstinence programs.[45]

7. Will the intervention promote respect and dignity?

Opioid substitution therapy (OST) has the potential to impact the respect and dignity for patients who receive it, in both positive and negative ways.

Drug use and stigma

The first set of considerations has to do with the social bases of respect for people with opioid use disorders (OUD) and their experience of stigma. Drug dependence and substance use disorders are often highly stigmatised conditions. This stigma has been perpetuated by:

- The labels society has given drug users has reinforced stigma.[46]
- Historical approaches that criminalise substance use adds to the stigma. Critics have commented on how these approaches to drug users "undermines their right to dignity, privacy and service access."[45]
- The historical separation of substance and drug use disorders from the rest of the health care system in South Africa could be argued to be discriminatory. This may contribute to the social perception that people with OUD are criminal or have moral failures, rather than as people with health conditions.

Evidence shows that stigma is associated with poor health outcomes. This includes negatively affecting help and treatment seeking behaviours.[47]

OST and impact on stigma: considerations

- Including OST as a *medical* intervention for a *health* condition under NHI may decrease stigma and discrimination by changing perceptions – both by self and others – towards drug users. ***However,***
- Patients on OST may experience *greater* exposure to stigma because OST does not require them to stop taking drugs, so it is not considered true abstinence.[48] People using OST, instead of abstinence methods, could be seen have a moral failing, and this could be internalised by patients as self-stigma.[49,50]
- There is also a risk of OST patients being ostracised by people who believe in abstinence-based rehabilitation. This would be due to the belief that opioid-based medications are simply a means of substituting one drug for another. People might say OST patients should not define themselves as 'in recovery.'[50]

Public awareness around OST

As mentioned in the health system factors discussion, including OST in NHI coverage may require public awareness raising campaigns to:

- counteract negative or misinformed perceptions about OST
- inform how and where OST is provided.[49]

Individual autonomy and self determination

Opioid substitution therapy (OST) has implications for patients' experience of individual autonomy and self-determination. By definition, those affected by substance use disorders face significant challenges to exercising autonomous choice consistent with their interests because of their drug dependence.[51,52] Consider the following points:

- Opioid users are caught up in a rapidly fluctuating cycle between intoxication and withdrawal. Drug dependent individuals' lives tend to be governed by attempts to avoid withdrawal, usually through activities that will enable them to obtain the next fix.[53]

- Opioid dependence can undermine individuals' agency. It interferes with their ability to pursue their conception of a good life. Dependence also poses challenges to those who are unable to abstain from opioid use despite multiple attempts to quit.[52,54]

- Because OST can help curb the cravings to use illegal opioids and does not produce the intoxicating effects, it can enable those on treatment to resume many activities that align more closely with their self-determination interests. OST has been noted to help those with drug use disorders "improve self-reliance, and empower the individual to seek and effect changes in their life; it can even confer self-esteem and give hope."3 So, in many ways, OST could be viewed as promoting individual autonomy and self-respect.

However,

- Some patients have found aspects of OST to be harmful to their sense of autonomy and dignity. Because of tight regulation and monitoring of OST, which may include supervised doses and urine testing, some patients have described the experience as demeaning and degrading.[55]

- It has been reported that the oversight aspects of OST programmes decrease patients' sense of self-determination and puts them in a disempowered position with the healthcare service provider. The term "liquid handcuffs" has been used to describe it.[56,57]

Experts have therefore called for OST approaches that can help drug treatment clients exercise agency within the constraints of treatment. They say there is a need to explore an appropriate balance between the restrictiveness of OST programmes and respect for patients accessing the therapy.[58,59]

8. Will the intervention affect how people form and maintain important social relationships?

Opioid use disorders are a significant social problem. They affect the individual and their family, community, and society in general.[60] Impaired social functioning is one of the most debilitating features of substance use disorders. People with the health condition struggle to meet important responsibilities at work, school and home. This leads to their reduced integration in society and, as a result, decreased social support.[61]

Opioid substitution therapy (OST), compared to other interventions, reduces the risk of relapse associated with withdrawal. This enables patients to become more stable, helps their social functioning and therefore their relationships with their families and other significant others.3

"Substance abuse can be constructed as a social pathology, an action harmful to others as well as the individual."[62] Interventions such as OST can alleviate this negative social impact. However, heroin use in South Africa is driven, in part, by people having to live in economically depressed, socially fractured communities.[14] It is in such communities where a decline in social relationships and family structure is identified as one of the key contributors to South Africa's rising drug use, with people using drugs as a way of coping with these circumstances.[62] The breakdown of social relationships, then, may be as much a cause of opioid use disorders as a consequence.

Impact of opioid use disorder on families

Illegal drug use threatens family structures and intensifies interpersonal conflict.[47,63,64,] This may occur in several ways:

- Female caregivers
  The burden of caring for a family member with an opioid use disorder (OUD) tends to fall on women, as they are generally the primary caregiver in many households.[63] This affects other children and family members.[64]
- Family relationships
  There may be conflict between family members about what approach to take towards the person with OUD. There is often anger and resentment among siblings and other family members.[63,64]
- Financial toll on families
  Opioid dependence takes a significant financial toll on families, many of whom make significant sacrifices to try to help their loved one.
  Emotional toll on families
  Because of stigma around drug use, many families try to cope in isolation. This makes their sense of marginalisation worse.[65,66]
- 'Tough love' approach
  Some parents take a tough love approach and children with OUD end up on the streets. This deepens social exclusion and exposes them to greater risk of violence and abuse.[63]

With evidence that OST can provide the stability needed to improve social functioning, improve employment rates, and improve family relations,[67] there may be positive benefits on affected individuals' ability to build and maintain relationships.

However, many people with OUD are part of a drug using community and leaving this community may cause the individual to become isolated and lonely.

9. Will the intervention affect people's personal financial situation?

Opioid dependence has high costs for individuals and families.[68] One estimate of the direct costs of drug use for drug-dependent individuals, or the cost of buying the drugs themselves, notes that heroin and other opioid users may be spending as much as R32 850 (US$2 374) a year on heroin. This is based on average use patterns and street drug prices in Cape Town and Tshwane.[42]

In addition, opioid use has been associated with unemployment and an inability to hold down a formal job. This can drive affected individuals and families further into poverty.[12,42] At the same time, treatment options can also be expensive.

Although there is budget line item for substance use disorder treatment services in South Africa, the most significant financing method for treatment services is out-of-pocket payment for specialised treatment services.[69]

An estimated 60% of drug-dependent patients are treated in the private sector using medical aid and out-of-pocket payments.[69] As none of the medications used for opioid substitution therapy (OST) are currently listed on South Africa's Essential Drug List,[35] the cost (R3000 per month) remains unaffordable for the majority of patients who rely on public provision of health services.[35,70]

Under any OST programme, public or private, there are often additional out-of-pocket costs to patients. These include transport to and from clinic for the required daily visits.[8,68]

Public provision of OST through NHI could help address many direct and indirect costs to households and individuals. OST has been shown to have a positive impact on personal productivity. There has been shown to be an associated reduction in unemployment, absenteeism and premature mortality. This, in turn, may increase the potential for individual earnings[3,4] and offset some of the additional personal costs of receiving the treatment.

10. Will the intervention ease people's suffering?

Compared with other interventions to treat opioid dependence, opioid substitution therapy (OST) has the potential to significantly reduce suffering associated with withdrawal. Although opioid withdrawal is rarely life threatening, the suffering experienced is substantial.[4]

Withdrawal symptoms include: [3, 4]

- abdominal cramps
- headache
- vomiting
- diarrhoea
- severe muscle and joint pain
- profuse sweating, anxiety
- irritability and agitation
- difficulty sleeping
- delirium
- seizures
- elevated respiratory rate, blood pressure and pulse.

With abstinence-based approaches, these symptoms can persist for several days or until the patient relapses. OST offers an alternative way to stop using illegal opioids without experiencing withdrawal.[4]

11. How might the intervention affect people's safety and security?

Opioid dependence is associated with emotional instability and significant harmful behaviours towards self and others. For example, because they are criminalised, people who are dependent on heroin become marginalised. They may end up living on the street, where they face assault or extortion by police.[14]

Although there is limited data on the prevalence of drugged driving and associated road accidents in SA, there are indications that this may be a problem that goes undetected. This is due to lack of routine drug screening on drivers during roadblocks and inadequate drug testing on those who have been involved in accidents.[64,71] OST has been shown to be effective in reducing both the dependence and the harms associated with OUD. Offering OST in South Africa as part of the NHI coverage may have a positive impact on the safety and security of both patients and those around them.

There is evidence, for example, that one of the long-term outcomes of OST interventions is a significant reduction in crime.[25,67] This could also be expected to decrease the domestic abuse and gender-based harm associated with drug use, impacting on the safety of women and families.[64]

Making OST available through the public health system has also been shown to lead to a "radical decline in the interface between people who use heroin and the criminal justice system."[45] Patients on OST are also likely to stabilise without the effects of withdrawal. The effects of withdrawal result in further risk behaviours, which threaten the safety of drug users and others.

On the other hand, recent South African research suggests that "heroin has become a key commodity underpinning the criminal economy in South Africa. The trade has a corrupting effect on police, who have interdependent relationships with gangs, drug dealers, and users."[14] There may be some negative effects for safety and security of introducing OST in this context. For example, without close supervision and monitoring, opioid substitution medications can be diverted to the black market. There is a risk of increased corruption and criminality.[30]

The diverted opioids could be combined with other drugs and potential contaminants or crushed and injected. This means they may not be taken in the correct dosage, which can exacerbate the withdrawal cycle because too low a dose is ineffective.4

Diversion and misuse of OST also has consequences for personal safety, as it increases the risk of accidental exposure and intoxication and, potentially, fatalities from misuse.3,4,30

12. Will the intervention affect social cohesion?

It is not clear how OST will affect Social Cohesion. There is a possibility that it might fracture social cohesion as OUD is sometimes thought of as self-inflicted. Therefore, providing treatment for people with OUD may cause resentment in a context where there is a general lack of resources.

OST does also have the potential to improve Social Cohesion if it leads to reduced illegal activity. Additionally, it may help change how people with OUD are viewed. Seeing people with OUD as having a health condition, rather than as criminals or having moral failures, may improve Social Cohesion.

References:

For Fig 1

i. Ginsberg GM, Lauer JA, Zelle S, Baeten S, Baltussen R. Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study. BMJ. 2012;344:e614.
ii. Hallett TB, Baeten JM, Heffron R, Barnabas R, de Bruyn G, Cremin Í, et al. Optimal Uses of Antiretrovirals for Prevention in HIV-1 Serodiscordant Heterosexual Couples in South Africa: A Modelling Study. PLOS Medicine. 2011;8(11):e1001123.
iii. Sinanovic E, Moodley J, Barone MA, Mall S, Cleary S, Harries J. The potential cost-effectiveness of adding a human papillomavirus vaccine to the cervical cancer screening programme in South Africa. Vaccine. 2009;27(44):6196-202.
iv. Alshreef A, Macquilkan K, Dawkins B, Riddin J, Ward S, Meads D, et al. Assessing the Appropriateness of Existing Model Adaptation Methods for Low and Middle-Income Countries. Value in Health. 2018;21:S8.
v. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value in Health. 2016;19(8):929-35.

---

[1] Pinson RD. Opioid use disorders [Internet]. ACP Hospitalist. 2018 [cited 2019 Aug 15]. Available from: https://acphospitalist.org/archives/2018/03/coding-opioid-use-disorders-part-1.htm

[2] The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines. Accessed 29 Aug 2019. Available from: https://www.who.int/substance_abuse/terminology/ICD10ClinicalDiagnosis.pdf

[3] World Health Organization (WHO). Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Guide l Psychosoc Assist Pharmacol Treat Opioid Depend. 2009

[4] Weich L, Perkel C, van Zyl N, Rataemane P, Naidoo L, Nowbath H, et al. South African guidelines for the management of opioid use disorders [Internet]. 2015. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=124737736&site=ehost-live

[5] Michie G, Hoosain S, Macharia M, Weich L. Report on the first government-funded opioid substitution programme for heroin users in the Western Cape Province, South Africa. South African Med J. 2017;107(6):539.

[6] Weich L, Perkel C, Van Zyl N, Naidoo L, Nowbath H, Flegar S, et al. South African Guidelines for the management of Opioid use disorders (Part 1). Prof Nurs Today. 2017;21(1):24–31

[7] Weich L. "Defeating the dragon" - can we afford not to treat patients with heroin dependence? South African J Psychiatry. 2017;16(3):5

[8] Pasche S, Myers B. Substance misuse trends in South Africa. Hum Psychopharmacol. 2012;27:338–41.

[9] Siphokazi Dada NHB. Research brief: Monitoring alcohol, tobacco and other drug use trends in South Africa (July 1996 - June 2018). Vol. 21. 2019

[10] Pluddemann A, Parry CDH, Flisher AJ, Jordaan E. Heroin Users in Cape Town, South Africa: Injecting Practices, HIV-Related Risk Behaviors, and Other Health Consequences. J Psychoactive Drugs. 2008;40(3):273–9.

[11] Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet [Internet]. 2012 Jan 7 [cited 2019 Jul 15];379(9810):55–70. Available from: https://www.sciencedirect.com/science/article/pii/S0140673611611380

[12] Peltzer K, Phaswana-Mafuya N. Drug use among youth and adults in a population-based survey in South Africa. South African journal of psychiatry. 2018;24(1). https://doi.org/10.4102/sajpsychiatry.v24i0.1139 |

[13] Setswe G, Wabiri N, Cloete A, Mabaso M, Jooste S, Ntsepe Y, Msweli S, Sigida S, Mlobeli R. Programmatic mapping and size estimation of key populations: Sex Workers (male and female), Men who have Sex with Men, Persons Who Inject Drugs and Transgender People. 2015. Cape Town: NACOSA. Accessed 30 Aug 2019. Available from: www.aidsinfoonline.org/kpatlas/document/ZAF/ZAF_2015_PSE_SW_MSM_PWID_TG.pdf

[14] Haysom S. Heroin use is shooting up in South Africa - ENACT Africa [Internet]. ENACT Observer. 2019 [cited 2019 Jul 24]. Available from: https://enactafrica.org/enact-observer/heroin-use-is-shooting-up-in-south-afric

[15] South African Medical Research Council. South African community epidemiology network on drug use. SACENDU reports 1998 - 2016. Available from: http://www.mrc.ac.za/intramural-research-units/ATOD-sacendu. Accessed 30 Aug 2019.

[16] Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry. 2018;5(12):987–1012

[17] Tables A3 and A4 in the Supplementary Appendix in: Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195

countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry. 2018;5(12):987–1012 -. Available from: https://www.thelancet.com/cms/10.1016/S2215-0366(18)30337-7/attachment/0ce51f6e-29c6-409f-8914-072d43e9a31c/mmc1.pdf
[18] Marion Lee M, Sanford Silverman M, Hans Hansen M, Vikram Patel M. A comprehensive review of opioid-induced hyperalgesia. Pain physician. 2011 Mar;14:145-61.
[19] Celerier E, Laulin JP, Corcuff JB, Le Moal M, Simonnet G. Progressive enhance- ment of delayed hyperalgesia induced by repeated heroin administration: A sensitization process. J Neurosci 2001; 21:4074-4080
[20] Angst MS, Clark JD. Opioid-induced Hyperalgesia. A Qualitative Systematic Review. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2006 Mar 1;104(3):570-87.
[21] Scheibe A, Young K, Moses L, Basson RL, Versfeld A, Spearman CW, Sonderup MW, Prabdial-Sing N, Manamela J, Puren AJ, Rebe K. Understanding hepatitis B, hepatitis C and HIV among people who inject drugs in South Africa: findings from a three-city cross-sectional survey. Harm reduction journal. 2019 Dec;16(1):28.
[22] Lawrinson P, Ali R, Buavirat A, Chiamwongpaet S, Dvoryak S, Habrat B, et al. Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. Addiction. 2008;103(9):1484–92
[23] Fullerton CA, Kim M, Thomas CP, Lyman DR, Montejano LB, Dougherty RH, et al. Medication-Assisted Treatment With Methadone: Assessing the Evidence. Psychiatr Serv [Internet]. 2014 Feb 1 [cited 2019 Jul 11];65(2):146–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24248468
[24] Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. bmj. 2017 Apr 26;357:j1550
[25] Bascaran MT, Garcia-Portilla MP, Bobes-Bascaran MT, Saiz PA, Bobes J. Long term outcomes of pharmacological treatments for opioid dependence: Does methadone still lead the pack? Br J Clin Pharmacol. 2014;77(2):272–84
[26] Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD002209. DOI: 10.1002/14651858.CD002209.pub2.
[27] Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction. 2008;103(3):462–8
[28] Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harvard review of psychiatry. 2015 Mar 1;23(2):63-75.
[29] Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, Fry-Smith A, Day E, Lintzeris N, Roberts T, Burls A. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. InNIHR Health Technology Assessment programme: Executive Summaries 2007. NIHR Journals Library.
[30] Reimer J, Verthein U, Karow A, Schäfer I, Naber D, Haasen C. Physical and mental health in severe opioid-dependent patients within a randomized controlled maintenance treatment trial. Addiction. 2011 Sep;106(9):1647-55.
[31] Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, Jordan A, Degenhardt L, Hope V, Hutchinson S, Maher L, Palmateer N, Taylor A, Bruneau J, Hickman M. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012021. DOI: 10.1002/14651858.CD012021.pub2.
[32] Siphokazi Dada NHB, Jodilee Erasmus, Warren Lucas C, Parry, Arvin Bhana, TB HIV Care A, Health Institute OW& the, University of Pretoria. South African Community Epidemiology Network on Drug Use, Phase 44 January-June 2018 Update [Internet]. 2018. Available from: http://www.samrc.ac.za/sites/default/files/attachments/2019-04-30/SACENDUBriefPhase44.pdf
[33] Chetty M, Kenworthy JJ, Langham S, et al. A systematic review of health economic models of opioid agonist therapies in maintenance treatment of non-prescription opioid dependence. Addict Sci Clin Pract 2017;12:
[34] https://www.health-e.org.za/medicine-price-registry/
[35] Scheibe A, Marks M, Shelly S, Gerardy T, Domingo AK, Hugo J. Developing an advocacy agenda for increasing access to opioid substitution therapy as part of comprehensive services for people who use drugs in South Africa. South African Med J. 2018;108(10):800–2.
[36] Burgos JL, Cepeda JA, Kahn JG, Mittal ML, Meza E, Lazos RRP, et al. Cost of provision of opioid substitution therapy provision in Tijuana, Mexico. Harm Reduct J. 2018;15(1):1–8.
[37] Development D of S. Prevention of and Treatment for Substance Abuse Act No. 70 of 2008. Government Gazette Department of Social Development; 2013 p. 1–48.

[38] Petersen I, Fairall L, Bhana A, Kathree T, Selohilwe O, Brooke-Sumner C, et al. Integrating mental health into chronic care in South Africa: The development of a district mental healthcare plan. Br J Psychiatry. 2016;208:s29–39
[39] World Health Organization. ATLAS of Substance Use Disorders. South Africa. Lancet [Internet]. 2010;349(9064):1–4. Available from: http://www.who.int/substance_abuse/publications/atlas_report/profiles/south_africa.pdf
[40] Weich L, Perkel C, Rataemane ST, Naidoo L, Van Zyl N. Medical management of opioid dependence in South Africa : original article. South African Med J [Internet]. 2008;98(4):280–3.
[41] Reimer J, Wright N, Somaini L, Roncero C, Maremmani I, Mckeganey N, et al. The impact of misuse and diversion of opioid substitution treatment medicines: Evidence review and expert consensus. Eur Addict Res. 2016;22(2):99–106.
[42] Haysom, S. Hiding in plain sight: Heroin's stealthy takeover of South Africa. ENACT Policy Brief. Issue 07. March 2019. Available from: https://enactafrica.org/research/policy-briefs/hiding-in-plain-sight-heroins-stealthy-takeover-of-south-africa
[43] Stone K, Shirley-Beavan S (2018) Global State of Harm Reduction 2018. Harm Reduction International: London. Available from: https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf
[44] Kurth AE, Cherutich P, Conover R, Chhun N, Bruce RD, Lambdin BH. The Opioid Epidemic in Africa and Its Impact. Curr Addict Reports. 2018;5(4):428–53
[45] Scheibe A, Shelly S, Versfeld A, Howell S. Safe treatment and treatment of safety: call for a harm-reduction approach to drug-use disorders in South Africa. South African Health Review. 2017;2017(1):197-204. Available from: https://journals.co.za/docserver/fulltext/healthr_2017_a21.pdf
[46] Goodyear K, Haass-Koffler CL, Chavanne D. Opioid use and stigma: The role of gender, language and precipitating events. Drug Alcohol Depend [Internet]. 2018 Apr 1 [cited 2019 Jul 16];185:339–46. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0376871618300966
[47] Kane JC, Elafros MA, Murray SM, Mitchell EMH, Augustinavicius JL, Causevic S, et al. A scoping review of health-related stigma outcomes for high-burden diseases in low- and middle-income countries. BMC Med. 2019 Dec 1517(1):17. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-019-1250-8
[48] Christie T, Groarke L, Sweet W. Virtue ethics as an alternative to deontological and consequential reasoning in the harm reduction debate. Int J Drug Policy. 2008;19(1):52–8.
[49] Wakeman SE, Rich JD. Barriers to medications for addiction treatment: how stigma kills. Substance use & misuse. 2018 Jan 28;53(2):330-3.
[50] Krawczyk N, Negron T, Nieto M, Agus D, Fingerhood MI. Overcoming medication stigma in peer recovery: A new paradigm. Subst Abus. 2018;39(4):404–9
[51] Spriggs M. Can we help addicts become more autonomous? Inside the mind of an addict. Bioethics. 2003 Oct;17(5-6):542-54.
[52] Levy N. Autonomy and addiction. Canadian Journal of Philosophy. 2006 Jan 1;36(3):427-47. https://doi.org/10.1353/cjp.2006.0018
[53] Potik D, Adelson M, Schreiber S. Drug addiction from a psychodynamic perspective: Methadone maintenance treatment (MMT) as transitional phenomena. Psychol Psychother Theory, Res Pract [Internet]. 2007 Jun 1 [cited 2019 Aug 22];80(2):311–25. Available from: http://doi.wiley.com/10.1348/147608306X164806
[54] Zeldman A, Ryan RM, Fiscella K. Motivation, autonomy support, and entity beliefs: Their role in methadone maintenance treatment. Journal of Social and Clinical Psychology. 2004 Oct 1;23(5):675-96.
[55] Monwell B, Bulow P, Johnson B. The pros and cons of supervised urine tests in opioid replacement therapy: A study of patients' experiences. Heroin Addict Relat Clin Probl [Internet]. 2018 [cited 2019 Jul 24];20:5–15. Available from: http://muep.mau.se/handle/2043/25589
[56] Granerud A, Toft H. Opioid dependency rehabilitation with the opioid maintenance treatment programme - a qualitative study from the clients' perspective. Subst Abuse Treat Prev Policy [Internet]. 2015 Dec 15 [cited 2019 Aug 22];10(1):35. Available from: http://substanceabusepolicy.biomedcentral.com/articles/10.1186/s13011-015-0031-4
[57] Wood P, Opie C, Tucci J, Franklin R, Anderson K. "A lot of people call it liquid handcuffs"–barriers and enablers to opioid replacement therapy in a rural area. Journal of Substance Use. 2019 Mar 4;24(2):150-5.
[58] Holt M. Agency and dependency within treatment: Drug treatment clients negotiating methadone and antidepressants. Social Science & Medicine. 2007 May 1;64(9):1937-47
[59] De Maeyer J, Vanderplasschen W, Camfield L, Vanheule S, Sabbe B, Broekaert E. A good quality of life under the influence of methadone: A qualitative study among opiate-dependent individuals. International journal of nursing studies. 2011 Oct 1;48(10):1244-57
[60] Sartor R. The social impact of drug abuse on community life. Med Law. 1991;10(2):205–8.

[61] von Hippel C, Henry JD, Terrett G, Mercuri K, McAlear K, Rendell PG. Stereotype threat and social function in opioid substitution therapy patients. Br J Clin Psychol. 2017;56(2):160–71
[62] Fellingham RK, Dhai A, Guidozzi Y, Gardner J. The 'war on drugs' has failed: Is decriminalisation of drug use a solution to the problem in South Africa? South African J Bioeth Law [Internet]. 2012 Nov 23 [cited 2019 Jul 16];5(2). Available from: http://hmpg.co.za/index.php/sajbl/article/view/7539
[63] Jagganath G. The Bitter Reality of" Sugars" and the Youth of Chatsworth. Oriental Anthropologists. 2012 Jul 1;12(2).
[64] Pattundeen G. Missing out on Migration:"Sugars" and the Post-apartheid Youth of Chatsworth. Journal of Social Sciences Special Volume. 2008;10:61-71. Available from: http://www.krepublishers.com/06-Special%20Volume-Journal/JSS-00-Special%20Volumes/JSS-SV-10-Youth-Migration-Web/JSS-SV-10-06-061-08-Pattundeen-G/JSS-SV-10-06-061-08-Pattundeen-G-Tt.pdf
[65] Butler R, Bauld L. The parents' experience: coping with drug use in the family. Drugs Educ Prev Policy [Internet]. 2005 Feb 10 [cited 2019 Jul 28];12(1):35–45. Available from: http://www.tandfonline.com/doi/full/10.1080/0968763042000275308
[66] Myers B, Fakier N, Louw J. Stigma, treatment beliefs, and substance abuse treatment use in historically disadvantaged communities. Afr J Psychiatry [Internet]. 2009 Dec 2 [cited 2019 Jul 16];12(3). Available from: http://www.ajol.info/index.php/ajpsy/article/view/4849
[67] Sun HM, Li XY, Chow EPF, Li T, Xian Y, Lu YH, et al. Methadone maintenance treatment programme reduces criminal activity and improves social well-being of drug users in China: A systematic review and meta-analysis. BMJ Open. 2015;5(1):1–11
[68] Lynch FL, McCarty D, Mertens J, Perrin NA, Green CA, Parthasarathy S, et al. Costs of care for persons with opioid dependence in commercial integrated health systems. Addict Sci Clin Pract. 2014;9:16
[69] WHO. ATLAS of Substance Use Disorders. Country Profile: South Africa. 2010. Accessed 12 Sep 2019. Available from: http://www.who.int/substance_abuse/publications/atlas_report/profiles/south_africa.pdf
[70] Scheibe A. Opioid substitution therapy in South Africa: (slow) movement towards equitable access. 2018. Available from: https://idhdp.com/media/531402/state-of-ost-in-sa.pdf
[71] Liebenberg J, Du Toit-Prinsloo L, Saayman G, Steenkamp V. Drugged driving in South Africa: An urgent need for review and reform. South African Crime Q [Internet]. 2019 May 15 [cited 2019 Aug 23];(67):7–18. Available from: https://journals.assaf.org.za/index.php/sacq/article/view/4951