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# METHADONE MAINTENANCE TREATMENT IN INDIA

**A FEASIBILITY AND EFFECTIVENESS REPORT**



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# METHADONE MAINTENANCE TREATMENT IN INDIA

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**A FEASIBILITY AND EFFECTIVENESS REPORT**

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## MESSAGE

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I am very happy to note that the National Drug Dependence Treatment Centre (NDDTC), AIIMS, Ghaziabad in collaboration with the United Nations Office on Drugs and Crime (UNODC) is organizing a meeting on 19<sup>th</sup> December 2014 in New Delhi on "Dissemination of the findings of Methadone Maintenance Treatment in India", to share the findings of the recently concluded multi-centre study on Effectiveness and Feasibility of Methadone Maintenance Treatment (MMT) in India that was carried out in five government hospitals in the country (in Delhi, Mumbai, Punjab and Manipur).

2. Methadone which is known as a cornerstone of Opioid Substitution Treatment in majority of the countries has withstood the test of time and rigorous scientific scrutiny. However, it was unavailable in the country till a few years back. The present study, commissioned by UNODC-ROSA and coordinated by NDDTC, AIIMS has been able to provide a good understanding of operational and clinical issues related to Methadone Maintenance Treatment. The data and experience from centres from across the country, i.e. NDDTC, AIIMS; KEM Mumbai; RIMS Imphal; Civil hospital Kapurthala and Civil hospital Bathinda went into formulating this report. I take the opportunity to congratulate everyone involved with this project and for making it possible to have Methadone as an important option in the menu of treatment options for opioid dependent individuals.

3. I am happy to announce that the Drug De-Addiction Programme, Ministry of Health and Family Welfare is planning further strengthening of its services by initiation of Drug Treatment Clinics in its de-addiction centres and other hospitals in a phased manner. These drug treatment clinics will provide various treatment modalities to opioid dependent individuals (both injecting and non-injecting drug users) based on clinical practice guidelines and after proper training.

4. Given this background, I am especially happy to note that the Methadone Maintenance Treatment, being one of the interventions to be delivered through the Drug Treatment Clinics, will substantially strengthen the Drug dependence treatment services through the Drug Treatment Clinics. We are committed to use the findings from the study to carry forward as well as scale up this intervention through the drug treatment clinics and hope that it will be an important milestone towards our efforts to reduce the pain and suffering associated with substance and drug abuse in our country.

5. I wish each and every one involved with the study all success for this meeting and expect that they will continue to work with greater vigour and zeal in coming up with new initiatives on drug dependence treatment and rehabilitation options in the years to come. The success of this study, I am sure, will give them the much needed enthusiasm and energy for similar and greater achievements in future as well. On behalf of the Ministry of Health & Family Welfare, I assure fullest cooperation and support in the noble path of drug dependence treatment and rehabilitation in our country.

  
12/12/2014  
(K.C. Samria)

# FOREWORD

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## FOREWORD

It is well accepted that dependence on substances fall under the category of medical disorders, and run a chronic, relapsing and remitting course like many well-known medical illnesses. These are appropriately classified under the list of mental disorders in widely used classificatory systems like ICD (International Classification of Diseases) and DSM (Diagnostic and Statistical Manual). They also require long-term care and rehabilitation. Each chronic disease in any discipline of medicine may have multiple therapeutic options to cater to wider section of patient population. Same is the case with substance use disorders.

Use of illicit substances has grown all over the world, and a sizable population has used such substances. The use of opioids has been increasing globally, and India too has sizeable number of people who use opioids. The current estimates of opioids using people in India are in millions, and a significant number of them are dependent on it. The dependence on opioids is fraught with severe consequences like physical morbidities including hepatitis and HIV/AIDS (with injecting use) and severe impairment in functioning in all areas of life, and not infrequently criminal activity, and at times overdose related deaths. In India too, the burden of injecting opioid users is large along with its association with HIV.

Opioid Substitution Treatment (OST) is a well proven intervention not only for HIV prevention, but also for treatment of opioid dependence disorder. Methadone and Buprenorphine are the two most common medicines used for OST. Well-designed studies have proven that the long-term outcome and indirect cost savings (for example, decrease in criminality, or decreasing the medical morbidity) justify the use of methadone as an OST drug.

The present report is the outcome of a project coordinated at the national level by the National Drug Dependence Treatment Centre (NDDTC) of the All India Institute of Medical Sciences, New Delhi with a generous support from UNODC Regional Office for South Asia and in collaboration with four other Government medical institutes / hospitals. The project explored the feasibility and effectiveness of implementing methadone based OST. The project managed to recruit a wide variety of patients from different part of the country adding to the generalizability of the results. The results have been encouraging in establishing that patients maintained on methadone showed substantial improvement, which spanned across multiple domains including physical, psychological, social, quality of life, and employment opportunities. A major challenge in methadone maintenance has remained with procurement of methadone and licensing procedures. With the amended NDPS Act that has mandated the central government to notify certain opioids as 'Essential Narcotic Drugs', and subsequent measures in pipeline to make the law treatment-friendly, it is hoped that this challenge will be adequately taken care of.

We are also happy that this pilot project will be carried forward in a phased manner by the strengthening of drug treatment services through establishment of Drug Treatment Clinics in government hospitals. This activity will be supported by the Ministry of Health and Family Welfare and coordinated by NDDTC. It is planned that through these clinics, the treatment of opioid dependence including long term pharmacotherapy such as Methadone will be available for both IDU and non-IDU opioid dependent individuals besides provision of treatment for other drugs of dependence.

Prof. Sudhir Khandelwal

# PREFACE

The project titled 'Prevention of transmission of HIV among drug users in SAARC countries' (Project RAS/H13) is being implemented by the United Nations Office on Drugs and Crime (UNODC) as part of a joint UN cooperation between UNODC, UNAIDS and WHO in South Asia. The overall goal of this project is to reduce the spread of HIV among the drug using population in SAARC countries through partnerships with governments and communities to scale-up comprehensive prevention and care programmes for drug users and their sex partners.

Since the inception of the project a few years ago, four out of seven participating SAARC countries have initiated Oral Substitution Treatment (OST) using buprenorphine and/or methadone. The choice of medicine has been different in different countries. While Bangladesh and Maldives have initiated Methadone Maintenance Treatment (MMT) alone, India and Nepal have initiated OST with both buprenorphine and methadone. Bhutan, too, has shown interest in the implementation of OST interventions.

Having gained such rich experience over the years in OST implementation in the SAARC region, UNODC considered it useful to conduct a study in India on the effectiveness of MMT, titled 'Methadone Maintenance Treatment: A feasibility and effectiveness study'. To conduct this study, UNODC partnered with the National Drug Dependence Treatment Centre (NDDTC) and worked with four additional institutional centres to assess the efficacy and feasibility of MMT in India. The following centres participated in this exercise:

1. NDDTC-AIIMS, New Delhi
2. Civil Hospital, Kapurthala, Punjab
3. Civil Hospital, Bathinda, Punjab
4. KEM Hospital, Mumbai
5. RIMS, Imphal

It is encouraging to see that the findings of the study presented in this publication substantiate that drug dependence treatment, including OST, is an important measure to improve the well-being and social functioning of people with opioid dependence as well as a means to reduce its health and social consequences, including HIV infection. The inclusion of OST in the package of services that should be available for all people who use drugs has been endorsed internationally by the United Nations (WHO, UNODC, UNAIDS, 2009) as well as in the Vienna Declaration (2010) and therefore, it is rewarding to see that the study in India corroborates the feasibility and efficacy of methadone in India.

UNODC is honoured to have partnered with the prestigious NDDTC in this research study showing such encouraging results. In the recent past, UNODC and NDDTC have collaborated in developing instruments which deal with drug dependence and drug use-related health and social consequences such as HIV/AIDS, HCV, drug overdose and MDR TB. These are common causes of death amongst people who use drugs and sometimes also their sex partners, and therefore need to be addressed and overcome urgently.

I do trust that this study will be used by policy makers, service providers and people who use drugs and that it will encourage the universal use of methadone in healthcare settings as a long term treatment for clients dependent on opioids as a universally recognized evidence-based treatment option.

I would like to acknowledge and thank the Ministry of Health and Family Welfare, especially its drug de-addiction program (DDAP), for considering methadone in its plans for the expansion of drug dependence services in India. It is, truly, a landmark achievement!

This study would not have been possible without the dedicated efforts and persistent commitment of all our partners, especially NDDTC, our implementing partners and their teams as well as the reviewers. I would like to extend my deep appreciation and thanks to all of them.



Cristina Albertin  
Representative

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- Civil Hospital, Kapurthala: Dr. Sandeep Bhola, Ms. Shaminder Kaur
- Civil Hospital, Bathinda: Dr. Nidhi Gupta, Mr. Roop Singh Mann
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- National Drug Dependence Treatment Centre, AIIMS, New Delhi: Dr. Rajat Ray, Prof. SK Khandelwal, Dr. Raka Jain, Mr. Deepak Yadav, Dr. Prashant S, Dr. Vidyasagar Jaiswal, Mr. Prem
- United Nations Office on Drugs and Crime, Regional Office for South Asia: Ms. Cristina Albertin, Mr. Kunal Kishore, Mr. Debashis Mukherjee, Dr. Alpna Mittal, Ms. Archana Oinam, Ms. Shveta Aima, Mr. Kamal Gupta
- Government agencies: Drug De-addiction Programme, Ministry of Health and Family Welfare, Government of India; National AIDS Control Organisation, Ministry of Health and Family Welfare, Government of India; Central Drug Standard Control Organisation, Ministry of Health and Family Welfare, Government of India; Department of Health Services, Government of Punjab; Excise department and State Health Departments of the states where interventions were conducted.

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# TABLE OF CONTENTS

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1	List of Abbreviations	11
2	Executive summary	12
3	Introduction	17
4	Review of Literature	18
5	Project background	24
6	Feasibility findings	26
7	MMT Intervention Implementation	29
8.	Procurement and stock keeping of Methadone	34
9	MMT Quality Assurance Mechanisms	37
10	Effectiveness Findings	39
11	Results	43
12	Discussion	54
13	Reference	61
14	Appendices	63

# ABBREVIATIONS

**AIIMS:** All India Institute of Medical Sciences, New Delhi  
**ART:** Anti-Retroviral Treatment  
**ASI:** Addiction Severity Index  
**ATT:** Anti-Tubercular Treatment  
**DAMS:** Drug Abuse Monitoring System  
**DCGI:** Drug Controller (General), India  
**DOTS:** Daily Observed Treatment Strategy  
**DUSIB:** Delhi Urban Shelter Improvement Board  
**HIV:** Human Immunodeficiency Virus  
**HRBS:** High Risk Behaviour Scale  
**HRG:** High-Risk Group  
**ICMR:** Indian Council of Medical Research  
**IDU:** Injecting Drug user  
**KEMH:** King Edward Memorial Hospital, Mumbai  
**MINI:** Mini International Neuropsychiatric Interview  
**MMT:** Methadone Maintenance Treatment  
**NACO:** National AIDS Control Organisation  
**NDDTC:** National Drug Dependence Treatment Centre  
**NDPS:** Narcotic Drugs and Psychotropic Substances  
**NGO:** Non-Governmental Organisation  
**NHS:** National Household Survey  
**NSP:** Needle Syringe Programme  
**OOWS:** Objective Opioid Withdrawal Scale  
**OPD:** Out Patient Department  
**OST:** Opioid Substitution Therapy  
**PWID:** People Who Inject Drugs  
**R & D:** Research and Development  
**RCT:** Randomised Controlled Trial  
**RIMS:** Regional Institute of Medical Sciences, Imphal, Manipur  
**SD:** Standard Deviation  
**SOWS:** Subjective Opioid Withdrawal Scale  
**SPSS:** Statistical Package for the Social Science  
**SROM:** Slow Release Oral Morphine  
**TB:** Tuberculosis  
**TI:** Targeted Intervention  
**UNAIDS:** Joint UN Programme on HIV/AIDS  
**UNODC:** United Nations Office on Drugs and Crime  
**WHOQOL-BREF:** World Health Organisation Quality of Life - Brief Scale  
**WHO:** World Health Organisation

# EXECUTIVE SUMMARY

## BACKGROUND

Drug use and its attendant negative consequences pose a global problem. Opioids constitute one of the most problematic groups of drugs, known to cause major complications, including overdose related deaths and transmission of blood-borne virus infections, especially when injected. Injecting drug use is recognized as a major vehicle for the transmission of HIV, with almost one-fifth of the people who inject drugs (PWID) being affected with HIV. India has a sizeable population of opioid dependent individuals as well as PWID.

Opioid dependence is recognized as a chronic non-communicable disease, requiring long-term treatment. Opioid Substitution Therapy (OST) is a well-proven long-term intervention for the treatment of opioid dependence syndrome as well as for HIV prevention. OST involves providing opioid agonist medications for a long period of time, sometimes lasting for years, along with psychosocial interventions. Methadone is the most commonly used OST medicine worldwide, followed by buprenorphine. Numerous research studies conducted in various parts of the world have shown that OST helps the opioid dependent individual not only to stop opioid use, but also in reducing family, social, occupational and legal complications. It also helps bring about an overall improvement in the quality of life of the individual. Moreover, OST has been shown to be cost-effective.

OST was introduced in India in the early 1990s. Buprenorphine was the only medicine available in the initial period, followed later by the introduction of slow release oral morphine. Buprenorphine-based OST has been scaled up for HIV prevention in the last five years, and currently there are more than 150 centres providing buprenorphine-based OST for HIV prevention among PWID. Limited studies on OST in India show that buprenorphine-based OST is feasible and acceptable to the clients, their family members as well as the general community. Additionally, OST has been found to be effective in the short to medium term in the treatment of opioid dependence as well as HIV prevention among opioid-dependent PWID.

## PROJECT BACKGROUND

Even as the presence of buprenorphine-based OST was being expanded in the country, it was felt that the menu of options to treat opioid dependent patients needed to be enhanced. As methadone was being used most commonly worldwide, it was felt that its introduction in India would add to the medical armamentarium of the opioid dependence treatment, as well as reduce costs for OST programme providers. However, at first, it was important to understand whether it was feasible to implement methadone maintenance treatment (MMT) in India, as well as study its effectiveness in the treatment of opioid dependence.

Permission to use methadone for the long-term treatment of opioid dependence was provided by the Drug Controller (General), India (DCGI) in 2009, following which the MMT project was developed by UNODC, Regional Office for South Asia, in collaboration with the National Drug Dependence Treatment Centre (NDDTC) All India Institute of Medical Sciences, New Delhi. The project was proposed to be implemented in five government hospitals located in different regions of India. UNODC was in charge of overall coordination and financial support, while NDDTC was in charge of overall technical and research related coordination and

support. Individual MMT centres were in charge of direct service provision as well as collecting data for the research study.

Various clearances, as necessary for project implementation, were obtained between 2009 and 2012. Based on the agreed-upon guidelines, a feasibility assessment was carried out and five centres were chosen: Sundernagari community clinic, NDDTC, AIIMS; Department of Psychiatry and Drug De-addiction Centre, King Edward Memorial (KEM) Hospital, Mumbai, Maharashtra; Department of Psychiatry and Drug De-addiction Centre, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur; Drug De-addiction Centre, Civil Hospital, Bathinda, Punjab; and Drug De-addiction Centre, Civil Hospital, Kapurthala, Punjab.

## FEASIBILITY FINDINGS OF MMT IMPLEMENTATION

The five chosen centres represent different geographical regions of India. Additionally, the facilities were different from each other: two centres were located in the De-addiction centres of Government Medical College Hospitals, two in the De-addiction centres of district-based hospitals, and one in the community clinic run by a National Drug Treatment Centre. The choice of opioids used was different: two centres catered to a predominantly buprenorphine injecting population, two had a mixed population using impure heroin and buprenorphine injections, and one catered to a predominantly 'pure' heroin using population. The centres also differed in terms of the experience of handling OST medicines.

The project made use of existing infrastructure as well as staff (including medical doctors as well as nurses) available at the government hospitals. A modest amount of financial support was provided to refurbish each centre as per the local need. The staff at each MMT centre included one doctor (psychiatrist working in the hospital), one nurse (working in the hospital, transferred to the MMT centre) and one counsellor-cum-research assistant (employed full-time for the project). A number of measures were undertaken initially to build the capacity of the staff: a five-day induction training, exposure visit to a functioning MMT centre and an interim three-day refresher training programme. NDDTC, AIIMS, as the lead technical agency, was available on a regular basis to provide support to the implementing centres.

Different strategies were employed to recruit clients into the MMT programme. Linkages were established between some centres and existing Targeted Interventions (TIs) for injecting drug users (IDUs) in order to refer clients from TIs to the MMT centre. At other places, awareness programmes were conducted to inform potential clients of the treatment. After an initial 'critical mass' of 10-15 clients was reached in each centre, clients themselves started informing their peers and friends about the available MMT. Every client underwent assessment by the doctor and counsellor; after education and informed consent, methadone was initiated for those who fulfilled the selection criteria laid down in the project.

MMT followed the same three phases as OST. Most centres initiated methadone with 15-20 mg on day one, followed by a gradual increase in dosage of 5 mg every three to four days. The induction phase lasted for two to three weeks. Most of the clients were stabilized on doses of 30-50 mg methadone per day. There were some variations in the usual and maximum dose of methadone used in individual centres. Methadone was dispensed on a daily basis at the MMT centre itself, following a 'Daily Observed Treatment Strategy'. Liquid formulation of methadone in strength of 5 mg/ml was used across all the centres. A bottle with a manual dispenser was used by the nurse to give out methadone. Some clients were terminated from methadone during the project life; the majority of such clients underwent termination on outpatient basis, where the dose was tapered by 5 mg every three to seven days. Psychosocial interventions were also conducted by the doctor and counsellor at various stages of the MMT programme. Family members were kept involved and informed about the treatment; referrals

for other health services were made. Various records prescribed by NDDTC were maintained at individual centres.

Unlike buprenorphine, every MMT centre required a storage license for storing methadone in its premise, the issuing authority for which differed across the states. The storage license was to be renewed on a yearly basis. A transport license was also required for every time methadone was transported from the supplier to the individual centre. Methadone was procured centrally by NDDTC by finalizing a supplier, who then supplied the requisite amount of methadone in one-litre bottles to the individual centres. There was strict stock-keeping and a supply-chain mechanism was laid down and followed to ensure that there was no diversion of methadone. There were no reports of diversion across any of the centres in the project period.

## EFFECTIVENESS FINDINGS OF MMT IMPLEMENTATION

During the course of MMT implementation, data pertaining to the effectiveness of methadone was systematically collected. Data from 334 male opioid dependent individuals was collected at baseline as well as during follow-ups conducted during the course of one year. The protocol, data collection tools and processes/procedures were prepared by NDDTC, which then trained the staff of individual MMT centres.

The respondents were in the age group of 20-40 years. More than half of them were unmarried. More than one third were unemployed; and a similar proportion had full-time employment. Most of the respondents were living at home with their families. There was high variability in the socio-demographic profiles of the respondents across the five sites.

At baseline, 48 percent were injecting buprenorphine, 46 percent were injecting heroin and a small percentage was injecting pentazocine or dextropropoxyphene in the month prior to the initiation of methadone. Non-injecting drug use included heroin, pharmaceutical opioids, opium, alcohol, cannabis, sedatives and a very small percentage using inhalants. The use of drugs had led to various kinds of problems for users: psychological, familial, social, financial, occupational, physical and legal. Past abstinence attempts were reported by almost two thirds of the respondents. The reasons for relapse were peer pressure, withdrawal symptoms, psychological problems and craving.

The average dose of Methadone was 40 mg, with a wide range. The retention rate was 71 percent at three months, 60.5 percent at the six-month follow-up, 47.9 percent at nine months and 35.9 percent at one year. Variability was observed in the retention rates across the centres. The compliance rate among those retained in treatment was high (90.8 percent).

On follow-up, 71.5 percent respondents reported no/mild withdrawal at two weeks, which increased to 80 percent at four weeks, 86.3 percent at six weeks and 90.9 percent at the eight-week follow-up. Very few respondents experienced severe withdrawals but one third continued to report mild withdrawals even at the one-year follow-up. The severity of withdrawals, as assessed objectively, was low throughout the study but did show variability across users. The reported side effects of medication were minor and related to opioid intoxication or withdrawals. There was no report of death or overdose during the study.

The findings showed a substantial reduction in drug use by most of the respondents. Overall, 80 percent or more respondents reported no use of heroin or other opioids at the three-month follow-up and this percentage saw further increase over subsequent follow-up assessments. These findings were reinforced by negative results for urine tests conducted to gauge recent drug use. More than 90 percent reported no current injected drug use at follow-up and the percentage of those who had injected in the prior one month continued to decline further, subsequently. There was also a marked reduction in injecting risk behaviour.

A positive change was also observed in psychological terms, in family/social relationships, as well as in medical terms, along with a reduction in alcohol use, and in the legal domain within the first three months of treatment, while there were delayed improvements in terms of employment. Overall, the perceived quality of life improved substantially in all domains (physical, psychological, social relationships, environment) and the majority of respondents felt that their quality of life was good or very good at follow-up.

## DISCUSSION

This was the first pilot study to explore the feasibility and effectiveness of methadone in India. The project involved a more experienced coordinating centre (NDDTC, AIIMS) along with four other centres with varying degrees of experience and expertise. It was planned in such a manner that it could be easily incorporated in one of the ongoing national programmes or it could be scaled up in programme mode after the pilot phase was over. Thus, the resources or inputs that went into the project were modest and kept as per the national norms. Though the initial target was 50 clients per centre, the numbers were increased during the course of project implementation, in keeping with the demands at the individual centres.

The project managed to recruit a wide variety of patients from different parts of the country, adding to the generalizability of the results. The largest category of opioids being injected was buprenorphine, followed by heroin. In terms of severity of addiction at the baseline, the highest was in the domain of employment, while alcohol use had the least severity. The retention rates for methadone were modest. The compliance rate was very high among those retained. The dose of methadone was relatively low, when compared to that reported in western countries. However, this is in keeping with the experience of buprenorphine implementation in India. There was substantial improvement among those retained on methadone; the improvement spanned across multiple domains including physical, psychological, social, employment as well as in terms of perceived quality of life. There was significant reduction in high-risk behaviour of clients during the one-year period of methadone implementation.

## RECOMMENDATIONS

It is possible to implement MMT in a scaled-up programme mode, using the learnings from the project.

- In programme mode, an individual MMT centre can cater to about 100 clients on a given day.
- Though the project made use of existing staff, for smoother programme implementation, an exclusive staff of one doctor, nurse and a counsellor is required. The doctor need not be specialised in psychiatry; MBBS is the minimum qualification required for a doctor to work in MMT centre.
- The infrastructure requirement for MMT centres is similar to that of buprenorphine, with the exception of storage space, which has to be specifically created to ensure safe-keeping of methadone. Additionally, a 'storage license' needs to be issued by the concerned authority, for storing methadone at a given site.
- The training programmes and other capacity building measures designed for the project can be followed to train the staff at newly established MMT centres, as well as ensure quality implementation of the MMT programme in India.
- One need not invest heavily in recruiting clients for the MMT programme; investment is required only for recruiting the initial critical mass of

clients, after which others are drawn towards MMT through word-of-mouth publicity.

- Methadone can be used as a long-term opioid dependence treatment option for heroin users as well as pharmaceutical opioids.
- The possibility of overdose related deaths with methadone can be surmounted by efficient supply-chain and stock-keeping mechanisms as laid down in the project.
- Limited experience in termination of methadone treatment from the pilot project suggests that it is possible to terminate methadone in an outpatient clinical setting.
- With the established supply-chain mechanism in the project, the possibility of diversion is minimal. The same can be followed by a scaled-up MMT programme in the country.
- A major challenge in MMT implementation was related to the procurement of methadone, which was tedious in terms of obtaining the storage and transport license. The existing regulations can act as a major barrier to the scaling-up of methadone in the country. With the amended NDPS Act that has mandated the central government to notify certain opioids as 'Essential Narcotic Drugs' and subsequent measures in the pipeline to make the law treatment-friendly, it is hoped that this challenge will be overcome in the near future.
- There has been a demand for methadone even from those clients who are opioid dependent but are not injecting drugs. Currently, in several places, OST is restricted to those who inject drugs, as the programme is funded by the National AIDS Control Organisation (NACO) with a focus on HIV prevention. Other agencies mandated to deal with drug dependent individuals should also support the provision of MMT and other OST programmes to non-injecting opioid dependent individuals as well.

# INTRODUCTION

As per the World Drug Report 2013, there are an estimated 167 million–315 million people aged 15–64 years who have used an illicit substance in the past year, corresponding to 3.6–6.9 percent of the adult population. The use of opioids has been increasing since 2009 and there is a visible trend in Asia as well. India has a sizeable number of people who use opioids. A national survey on the extent, trends and patterns of drug use in India shows that there are about 2 million current opioid users in India, of which about 500,000 are opioid dependent. Opioid dependence syndrome is associated with a number of negative consequences leading to increased morbidity and mortality among those afflicted with the disease.

An important problem associated with the use of opioids is their use through injecting route. Injecting drug use is associated with a number of complications, including abscesses, overdose related deaths as well as blood borne viruses such as HIV and hepatitis B and C. Injecting Drug Users (IDUs) are especially vulnerable to contracting and transmitting HIV, as a result of which most National AIDS Programmes place them under the category of High Risk Groups (HRGs). It is estimated that there are 15.9 million people who inject drugs (PWID) globally as of 2007, of which about 3 million IDUs were infected with HIV. It is estimated that there are about 177,000 IDUs in India with HIV prevalence of about 7.2 percent among IDUs at national level.

A range of services and interventions have been found effective in the prevention of HIV among IDUs. The Joint UN Programme on HIV/AIDS (UNAIDS), World Health Organisation (WHO) and United Nations Office on Drugs and Crime (UNODC) have jointly endorsed a package of nine interventions for prevention, treatment and care of HIV among IDUs. Of these, three interventions—Needle Syringe Programmes (NSPs), Opioid Substitution Treatment (OST) and Anti-Retroviral Treatment (ART)—are considered essential interventions.

OST is a well-proven intervention not only for HIV prevention, but also for the treatment of opioid dependence syndrome. Globally, methadone and buprenorphine are the two most common medicines used for OST. There are at least 77 countries that use either or both of these medicines for OST. Methadone is the earliest, most extensively researched medicine as well as the commonest medicines used for OST. In India, buprenorphine has been most commonly available and used for OST, while slow release oral morphine (SROM) has also been reported to be used. Methadone, the most commonly used opioid medicine for OST worldwide, was not available for use in India until 2010. It is only after the approval for its use in India that concerted efforts were made to expand the menu of options available for service providers and policy makers for HIV prevention as well as treatment of opioid dependence.

Keeping this background in mind, a project was initiated by the UNODC Regional Office for South Asia, along with the National Drug Dependence Treatment Centre (NDDTC) All India Institute of Medical Sciences (AIIMS) to explore the feasibility of implementing methadone as well as generate local evidence on the effectiveness of methadone based treatment of opioid dependence.

# REVIEW OF LITERATURE

## A

### OPIOID USE - EXTENT OF THE PROBLEM

Opioids constitute the most problematic group of illicit drugs. About 0.7 percent of the global adult population has used opioids, while another 0.4 percent has used opiates (UNODC, 2013). While the prevalence of opioids has remained stable in some regions, it is showing an upward trend in many, including Asia. The annual prevalence rates of opioid use are 0.3-0.5 percent of the adult population, which is lower than some other regions of the world. However, in absolute numbers, Asia is home to about 60 percent opiate users globally.

The only national level survey in India was conducted a decade ago, and the report was published in 2004. One of the components, the National Household Survey (NHS), found the prevalence of 'current' opioid use (defined as use for non-medical purpose at least once in the past month) to be 0.7 percent among the adult male population (Ray, 2004). This translates into roughly 2 million current opioid users in the country. An assessment showed that about 25 percent or roughly 500,000 of these individuals were dependent on opioids. Another component was the Drug Abuse Monitoring System (DAMS), which looked at the rates at which different substances were used by treatment seekers. In this, opioid dependence accounted for about 26 percent of the treatment seekers.

Opioid use and dependence carries with it substantial negative consequences for the individual user, his family, society as well as the criminal justice system. Apart from long term physical ill health, mainly due to the mode of usage, opioid addiction leads to loss of productivity, neglect of family, and increase in crime rates as well as incarceration. A study conducted by Mark et al. (2001) on the economic costs of heroin addiction in the United States showed that the cost incurred due to heroin addiction in 1996 was \$21.9 billion. Of this, the highest cost was due to productivity loss (53 percent), followed by criminal activities (24 percent) and medical treatment (23 percent). Another study by Wall et al. (2000) showed that the annual social cost of illicit opioid use in Canada in 1996/97 was \$5.086 million or \$45,000 per individual opioid user. Here, too, the highest cost was crime victimization (44.6 percent) and law enforcement (42.4 percent). Productivity costs accounted for 7 percent, while healthcare costs were the least, at 6 percent of the total cost incurred.

Thus, opioid use constitutes a huge problem at both the national and global levels, and this is reflected in the large number of opioid users visiting the treatment centres and demanding help for stopping their opioid use. The use of opioids through the injecting route is a matter of grave concern since it can lead to several drug related complications.

## B

### INJECTING DRUG USE

As per a systematic review conducted in 2007, the total number of Injecting Drug Users across 148 countries was 15.9 million (range: 11.0-21.2 million). The largest numbers of IDUs were found in China, USA and Russia (Mathers et al., 2008). A major problem associated with injecting drug use is the high risk of contracting HIV, due to associated high risk behaviour in terms of sharing of needle/syringes used for injection. The systematic review also estimated that there are about 3 million (range: 0.8-6.6 million) HIV positive IDUs globally. HIV positivity among IDUs was more than 40 percent in nine countries, while five

countries recorded 20-40 percent HIV positivity among IDUs. Along with HIV, the prevalence of hepatitis C among IDUs is also very high. Globally, it is estimated that hepatitis C is three times more prevalent among IDUs than HIV; there are an estimated 10 million hepatitis C positive IDUs across the world. Once again, the three countries with the highest burden of IDU (China, USA and Russia) also have the highest number of hepatitis C infected IDUs.

India, too, has a sizeable population of IDUs. NACO's annual report, 2012, there are an estimated 177,000 IDUs in the country (Department of AIDS Control, 2012). While the phenomenon of injecting drug use was previously thought to be restricted to the north-eastern states as well as metropolitan cities, it is now recognized as a pan-India phenomenon. There is no state in India that does not have a sizeable population of IDUs. States such as Manipur, Punjab, Nagaland, Mizoram, Uttar Pradesh, Delhi, Kerala, have a large IDU population. As per the technical report of NACO, 2011, HIV prevalence among IDUs is 7.14 percent nationally, which is the one of the highest among any population group. Highest HIV prevalence among IDUs was recorded in Punjab (21.1 percent), Delhi (18.3 percent), Maharashtra (14.2 percent), Manipur (12.9 percent) and Mizoram (12 percent). Nine states recorded HIV prevalence of more than 5 percent among IDUs. Though there is no national level data for the prevalence of hepatitis C among IDUs, studies conducted in different parts of the country show that it ranges from 33.7percent to 98 percent.

Almost all IDUs in India use opioids for injecting. The opioids range from heroin (either in pure form or impure form, called 'brown sugar') to a variety of pharmaceutical opioids such as dextropropoxyphene, buprenorphine and pentazocine (Ambekar et al., 2014). A number of studies in India have shown that while purer heroin and dextropropoxyphene is used in north-eastern states, IDUs in other parts of the country inject either brown sugar or pharmaceutical opioids such as buprenorphine or pentazocine. A recent study conducted to assess the pattern of drug use in the country shows that almost all the IDUs fulfilled the criteria of opioid dependence.

Thus, it can be surmised here that India has a sizeable number of opioid dependent IDUs, with high HIV and hepatitis C prevalence in this group.

## C

### OPIOID SUBSTITUTION TREATMENT - OVERVIEW

Opioid dependence syndrome is now increasingly recognized as a chronic relapsing disorder similar to other non-communicable diseases such as hypertension, diabetes and chronic asthma (McLellan et al., 2000). Thus, the treatment of opioid dependence should be of a long duration. Studies show that short term treatment measures such as detoxification (i.e. treatment of acute withdrawal symptoms) alone leads to high relapse rates among opioid dependent patients. This can be due to a number of factors, including inability to address protracted withdrawals, persistence of craving, persisting socio-occupational dysfunction and instability in the family with detoxification. All of these factors are best addressed through the use of opioid agonists for a longer duration. This is called as 'Agonist maintenance treatment', or simply 'Opioid Substitution Treatment' (OST).

OST works on the philosophy that an illegal, impure, dangerous substance (such as heroin) used through a high-risk route (injecting) is substituted with legal medication of known purity and potency, taken by a safer (oral) route, administered under medical supervision. A host of agents have been used for this purpose such as methadone, buprenorphine, and Slow-Release Oral Morphine. By helping the patient to overcome the physical discomfort and drug hunger caused by quitting the opioids, these agents provide them with an opportunity to restore the balance in terms of health and the psycho-socio-occupational spheres of their

lives with the help of the comprehensive multidimensional interventions that form a part of these maintenance programmes. Moreover, by preventing the use of the opioids, the maintenance strategies help to reduce the risks associated with the use of opioids, like high risk sexual behaviour, risk of exposure to HIV, hepatitis B, hepatitis C and indulgence in illegal activities. Thus OST is conceived not only as a long term treatment option for opioid dependence, but also as an effective HIV prevention and harm reduction strategy for IDUs. Not surprisingly, OST forms an essential element of the nine intervention package endorsed by the Joint UN Programme on HIV/AIDS (UNAIDS), World Health Organisation (WHO) and United Nations Office on Drugs and Crime (UNODC). Additionally, methadone and buprenorphine, the medicines for OST, have been listed as ‘essential medicines’ in the WHO model list of essential medicines.

OST, in one form or the other, is being used in at least 77 countries as of 2012, as reported in the ‘Global State of Harm Reduction’ report, 2012 (The Global State of Harm Reduction, 2012). Most of these countries using OST use methadone, while buprenorphine is the second most commonly used OST medicine. Methadone is also the first medicine to be tried for OST, and there are extensive researches and literature which supports the effectiveness of methadone for use in OST. Buprenorphine, introduced in the 1980s, has also been used extensively in many countries. India has been using buprenorphine for the last three decades, and recently, there have also been reports of the use of SROM for OST. The National AIDS Control Programme, Phase III, has initiated and scaled up OST as an HIV prevention strategy for IDUs since 2007. As of October 2014, there are about 150 OST centres using buprenorphine that are funded by NACO.

## D

### BENEFITS OF OST EVIDENCE BASE FROM OTHER COUNTRIES

The first report on the benefits of methadone in the treatment of ‘heroin addiction’ came from Dole and Nyswander in 1965, and they showed that using methadone for ‘heroin addicts’ helps relieve ‘narcotic hunger’, induction of tolerance to block the euphoric effect of street heroin, and leads to improvement in work as well as family life. Subsequently, OST has been subjected to the most rigorous trials in almost every country where it is used and has shown the same kind of benefits. There are evidences available at the level of randomized controlled trials (RCTs), systematic reviews and meta-analysis.

A review of systematic reviews as well as updated RCTs was conducted to assess the clinical effectiveness of the use of methadone and buprenorphine for OST (Connock et al., 2007). The authors were able to identify 31 systematic reviews fulfilling the criteria set, and most of these were of moderate to good quality, used fixed-dose strategy and focused on short term follow-up (up to one year period), outcomes of retention in treatment and level of opiate use (self-report or urinalysis) in individuals retained on treatment. The results are as follows:

- Fixed dose MMT showed better retention than placebo or no treatment;
- Non-randomized observational studies showed that fixed dose MMT reduces mortality, drug-associated crimes and HIV risk behaviour;
- Two RCT meta-analysis showed that fixed dose buprenorphine treatment led to superior levels of retention in treatment, compared to placebo or no treatment. One RCT showed buprenorphine to be associated with reduced mortality than placebo alone;

- Fixed dose MMT showed better retention than comparable fixed dose buprenorphine;
- Studies employing flexible dose methadone (which is more reflective of a real world scenario) showed better retention than buprenorphine, with no significant difference in levels of opioid use; and
- Adjunct psychosocial interventions and contingency management appeared to enhance the effects of both methadone and buprenorphine therapy.

A Cochrane Review by Mattick et al. (2009) analysed the available evidence base for methadone maintenance versus placebo or buprenorphine maintenance for opioid dependence. The studies (six studies, 837 participants) using the flexible dose regimens showed that methadone was more likely to retain patients than buprenorphine. The flexible dose studies showed no significant difference between the two interventions in terms of heroin use, based on results of morphine urine analysis or in terms of self-reported heroin use. The comparison of low dose buprenorphine (dose ranges between 2 mg and 4 mg) and low dose methadone (dose ranges between 20 mg and 35 mg) (two studies, 121 participants) indicated no statistically significant difference in retention in treatment or in morphine positive urines and cocaine positive urines, self-reported heroin use. Comparing high dose buprenorphine and high dose methadone, the data on retention in treatment (5 RCTs, 449 participants) showed no statistical difference between the two interventions, although results do suggest that high doses of buprenorphine are less likely to retain patients than high dose methadone.

While the above two large-scale reviews have been on the effectiveness of OST in retention and opioid use, a Cochrane review was conducted in 2004 on the effectiveness of substitution treatment of opioid injecting drug users in HIV prevention (Gowing et al., 2004). Following certain criteria and search strategies, the authors were able to include 28 studies, involving 7,900 participants. The majority were not randomized controlled studies. However, the studies showed that OST is associated with statistically significant reductions in illicit opioid use, injecting use, and sharing of injecting equipment. It is also associated with reduction in the proportion of injecting drug users reporting multiple sex partners or exchanges of sex for drugs or money, but has little effect on condom use. The authors concluded that “Oral substitution treatment for injecting opioid users reduces drug-related behaviours with a high risk of HIV transmission, but has little effect on sex-related risk behaviours. The lack of data from randomised controlled studies limits the strength of the evidence presented in this review, but findings concur with previous systematic reviews”.

In nearby countries of South Asia, OST is currently available in Nepal, Bangladesh and Maldives. Though there have been no systematic studies conducted to demonstrate the effectiveness of OST in opioid dependence or in HIV prevention, available reports show that there is a decrease in HIV related risk behaviours, as well as improved retention on OST (Rao et al., 2012).

# E

## BENEFITS OF OST - EVIDENCE BASE FROM INDIA

Buprenorphine has been used as OST for a fairly long period, albeit in very limited centres. Reports have been published on the benefits of buprenorphine-based OST in India. Dhawan and Sunder (2008) have reviewed the Indian experience with buprenorphine. A project on community-based treatment for heroin addiction using buprenorphine was carried out by the De-addiction Centre, All India Institute of Medical Sciences as early as in 1992 (Mohan and Ray, 1992). The project included 108 male subjects with heroin dependence who were given buprenorphine maintenance (in the dose range 1.2-1.8 mg per day, for a period of 6-11 months, along with psycho-social interventions. The subjects were assessed at the end of six months, nine months and 11 months after intake. At follow-up, about 70 percent had improved, indicating no use or very little use of heroin.

Another study, carried out in Nagaland, used buprenorphine maintenance on opiate dependent subjects (Mohan & Dhawan, 2001). Fifty-four male opiate dependent clients were studied, with a six-month follow-up. The Addiction Severity Index (ASI) scores reduced significantly in the 'drug' and 'family' domain of ASI at the six-month follow-up as compared to the baseline. Drug use reduced substantially, with none of the subjects reporting daily use at the follow-up and majority reporting reduction in frequency of drug use.

A multi-site study was carried out by NDDTC, AIIMS to assess the effectiveness of buprenorphine with the support of UNODC (Dhawan et al., 2009). The study used a 'pre-post design' with assessments at baseline, three months, six months and nine months. A total of 231 opioid dependent clients from five sites across the country were identified and recruited for a two-year period (2012-2014). In the total sample, the retention rate was 79 percent at three months, 70 percent at six months, and 64 percent at the nine-month follow-up, with a compliance rate of more than 80 percent among those retained in treatment. A significant reduction in drug use was found, as the mean number of days of heroin use was  $24.9 \pm 10.1$  days at baseline, which fell to less than two days at the nine-month follow-up assessment. Similarly, there was a significant reduction ( $p < .001$ ) in injection use, which declined from 52 percent at baseline to 13 percent at the nine-month follow-up assessment. At the nine-month follow-up, the scores in all four domains (physical, psychological, social relationship and environment) of 'WHO Quality of Life' showed an increase, thus indicating an improvement in the quality of life as experienced by the clients.

Other studies carried out on a smaller scale in the northeast region also support the findings of the above studies in demonstrating the benefits of OST in India. Recently, a situation assessment of OST in India has been carried out, funded by NACO, , in which data was collected from service providers of 42 OST centres throughout the country (Rao, Ambekar and Agrawal, 2012). Additionally, 192 clients on OST from 22 of these centres were interviewed. Findings reveal that most centres that follow NACO norms and guidelines are easily accessible and have trained staff in place. Most clients, though satisfied with their dosages, were on low doses of buprenorphine (mean dose 6 mg/day). Hence it was not surprising to find that about 40 percent of clients continued to report craving or withdrawal symptoms despite a majority having been on OST for more than one year. About 70 percent clients reported that they had stopped injecting.

However, many clients were found to be missing their dispensing doses now and then; about 40 percent clients reported having missed their dose in the last one month. About 39 percent of those who missed their dose also reported using opioids in the last one month. The review of literature highlights the following points:

- There are a large numbers of opioid users globally, and substantial numbers also exist in India. Injecting drug use and attendant HIV among IDUs is a major problem associated with opioid use.
- Opioid dependence is a chronic relapsing disorder akin to other non-communicable diseases. There are a number of negative consequences associated with the use of opioids for the individual user, his family as well as society at large.
- Opioid substitution treatment has been used for more than six decades for the treatment of opioid dependence. OST has been shown to improve retention in treatment as well as improve the individual's health, family, employment and legal problems.
- OST is endorsed by many agencies and has been used in a number of countries. However, the coverage of OST still remains low in most of the countries where it is available.
- OST has been in use in India for the last two decades and there are reports available on the effectiveness of OST using buprenorphine in Indian settings.

# PROJECT BACKGROUND

Though there was a felt-need for methadone in India, serious efforts bore fruit in 2009, when the permission to use methadone in India for opioid dependence syndrome was provided by the Drug Controller General (India). Permission was granted for the use of methadone as a long-term treatment agent in Government-recognized Drug De-addiction Centres. Following this, a multi-centric project was launched with support from the United Nations Office on Drugs and Crime-Regional office for South Asia (UNODC ROSA). The National Drug Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS) was the lead technical agency in implementing this project.

## AIMS AND OBJECTIVES

The overall aim of the project was to assess the feasibility and effectiveness of MMT in Indian settings. The specific objectives were:

1. To test the effectiveness of methadone as a medication for the long-term treatment of opioid dependence in India;
2. To study the feasibility of and develop an action plan for rolling out MMT programmes in India; and
3. To develop practice guidelines for MMT in India.

While the effectiveness of methadone in HIV prevention among IDUs as well as for the long-term treatment of opioid dependence is well known, pilot projects need to be initiated in each country to demonstrate that the intervention works in that particular country and it is feasible in terms of available resources. The project was conceived mainly to demonstrate this feasibility and effectiveness.

## IMPLEMENTATION ARRANGEMENTS

The implementation modality followed by the project is indicated below:

UNODC	NDDTC, AIIMS	Implementing MMT centres
<ul style="list-style-type: none"><li>• Overall coordination</li><li>• Consensus with stakeholders</li><li>* Financial and administrative support</li></ul>	<ul style="list-style-type: none"><li>• Training of service providers at all centres</li><li>• Procurement of methadone and urine test kits for all implementing MMT centres</li><li>• Technical support</li><li>• Periodic monitoring and supervision</li><li>• Develop tools for data collection and coordinate for data collection</li><li>• Analysis and report writing</li></ul>	<ul style="list-style-type: none"><li>• Enrolment of patients for MMT</li><li>• Provide clinical services as per protocols/guidelines</li><li>* Collect data as planned and onward transmission to NDDTC</li></ul>

Thus, while UNODC was in-charge of overall coordination and financial support, NDDTC was in-charge of overall technical and research related coordination and support. The individual MMT centres were in charge of direct service provision as well as collecting data for the research study.

## CLEARANCES AND APPROVAL

As methadone was being used in India for the first time, a number of clearances and approvals were necessary. These were obtained from the following agencies:

- Office of Drug Controller General (India): for use of methadone as a long-term treatment option for opioid dependent subjects;
- Indian Council of Medical Research: for conducting the research study;
- Health Ministry Screening Committee: for obtaining funds from an international agency (UNODC);
- NACO research committee: for conducting the research study;
- AIIMS Ethics Committee: obtained by NDDTC for ethical clearance of the research study;
- Local ethics committees: obtained by the participating centres at their institutions for participation in the study; and
- Approval from Punjab Government authorities: for initiation of MMT at two civil hospitals in Punjab. Approval was obtained from Principal Secretary (Health), Government of Punjab by UNODC through a request for letter of support.

# FEASIBILITY FINDINGS

## SELECTION OF PARTICIPATING CENTRES

### INITIATING MMT IMPLEMENTATION

As per the project design, a total of five centres were to be selected for implementation of the MMT project. The broad guidelines for shortlisting the centres are as follows:

- Presence of drug dependence treatment facilities (Government de-addiction centre);
- Necessary infrastructure for compliance with the regulatory requirements;
- Trainable staff who can deliver the MMT services;
- A felt-need of opioid maintenance treatment (on account of patient load);
- Presence of a sizeable number of opioid dependent persons in the vicinity of the institution/city where the centre is located, including sizeable number of IDUs; and
- Willingness and capacity to continue the programme after UNODC support is over.

On the basis of the above broad guidelines, five institutions/hospitals were chosen for feasibility assessment through site visits. These include:

- National Drug Dependence Treatment Centre, AIIMS (including its community centres), New Delhi;
- Department of Psychiatry and Drug De-addiction Centre, King Edward Memorial Hospital, Mumbai, Maharashtra;
- Department of Psychiatry and Drug De-addiction Centre, Regional Institute of Medical Sciences, Imphal, Manipur;
- Drug De-addiction Centre, Civil Hospital, Bathinda, Punjab; and
- Drug De-addiction Centre, Civil Hospital, Kapurthala, Punjab.

After finalizing the institutions/hospitals, a visit was made to each centre for feasibility assessment. The purpose of feasibility assessment was:

- To assess whether the local hospital authorities are willing to support the initiation of MMT services;
- Sensitize the head of the hospital (Medical Superintendent/Civil Surgeon) on the MMT services;
- Assess whether there is adequate infrastructure in the institution to provide MMT services as well as to store/stock methadone;
- Finalize location for providing MMT services;
- Finalize location for storing and stocking methadone; and
- Assess the refurbishment requirements for initiating the project.

The feasibility assessment was conducted using an ‘assessment tool’ developed for the purpose. The assessment team comprised of one faculty from NDDTC, AIIMS and one Technical officer from UNODC. At the end of the assessment, the findings were shared with the respective nodal officer of the MMT centre for necessary action and refurbishment.

All five shortlisted centres were found to be suitable for implementing the MMT project. The five centres also represented different regions of the country, offering a chance to study the project outcomes in different parts of the country. The geographical spread of the centres can be seen on the map given here.

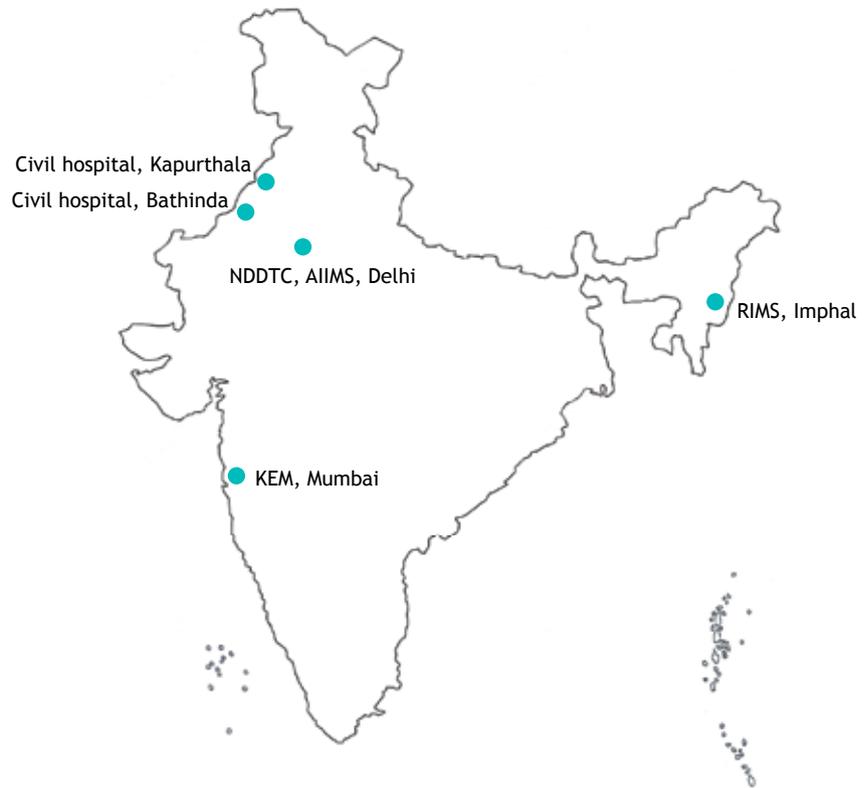


Fig 1: India map showing Study sites

## MMT CENTRE - INFRASTRUCTURE

At the beginning of the MMT project, it was conceived that every MMT centre should have the following infrastructure for running MMT services:

- **Doctor’s room:** for assessment and follow-up of MMT clients;
- **Counselling room:** for conducting counselling sessions;
- **Dispensing room:** for dispensing methadone on daily-observed treatment basis;
- **Storage room:** for storage of methadone;
- **Waiting area:** for clients to wait for their turn during assessment, follow-up and dispensing; and
- **Space for record maintenance.**

At most of the places, there was no need for a separate doctor’s room as the allocation of a doctor exclusively for the MMT services was not deemed to be required. Instead, the psychiatrist working in the hospital was expected to also cater to the MMT clients. In such cases, the client would be assessed and have his progress followed up by the psychiatrist in his/her OPD itself. Special care was taken to ensure that the storage room was well fortified to ensure no break-ins.

## MMT CENTRE - STAFF

**NO NEW CONSTRUCTION WAS CARRIED OUT** in the setting up of any of the MMT centres. Existing rooms and space available in the hospital were utilized for setting up all MMT centres, except NDDTC, AIIMS. Refurbishment, as required, was carried out at each MMT centre. At NDDTC, AIIMS, the MMT centre was planned to be initiated in geographical proximity to a community drug treatment clinic run by NDDTC. Space available with the local government agency (Delhi Urban Shelter Improvement Board, DUSIB) was taken on rent, and refurbishment was carried out to establish the MMT centre.

The project made use of staff already working with the government hospital to run MMT services. The staff composition of each MMT centre was as follows:

- **Doctor:** At all centres, the doctor running the MMT services was a full-time permanent employee of the Government hospital where the MMT centre was located. The doctor at each centre was a psychiatrist, who was involved in managing the drug dependence treatment services and also acted as the nodal officer of the MMT centre. In institutions which had an adequate number of psychiatrists (AIIMS, RIMS and KEMH), psychiatrists other than the nodal officer were also involved in delivering MMT services.
- **Nurse:** At each MMT centre, one nursing staff who were full-time employees of the Government hospital were identified and deployed to work at the MMT centre. Efforts were also made to ensure that these staff were not shifted out of the centre and posted elsewhere.
- **Counsellor:** This was the only staff employed directly by the project. The counsellor was a graduate in humanities, and was tasked with collecting research data relevant to the project. The counsellor was recruited locally by the nodal officer based on norms and terms of reference laid down in the project. Since the counsellor was also tasked with research activities (data collection), the remuneration of the counsellor was as per the norms of the Indian Council for Medical Research (ICMR).

At NDDTC, AIIMS, an additional staff of a 'Research officer', who was a medical doctor, was provided for, whose task was to help in research implementation, in addition to performing clinical work. The staff involved in the MMT services underwent various levels of capacity building.

- **Induction training** was initially held for a period of five days. This training was organized and conducted by NDDTC, AIIMS for all the staff together. The induction training covered various areas including: basics of drugs, drug related problems, drug abuse management strategies, overview of OST, pharmacology of methadone, implementing MMT services, special clinical situations, stock management, programme management, etc.
- **An Exposure visit** was organized by UNODC at Kathmandu, Nepal for a two-day period for the doctor and nurses of the MMT centres. The visit provided the MMT staff a hands-on experience of how to implement MMT services.
- **Refresher training** of three days duration was organized and conducted by NDDTC after about a year of initiation of MMT implementation. All the staff of MMT centres participated in the training. Emphasis was placed on discussing practical day-to-day problems encountered while running MMT services.

After all these processes, including project clearance, refurbishment, staff recruitment and induction training, had been conducted, the centres were inaugurated for implementation of methadone services.

# MMT INTERVENTION – IMPLEMENTATION

## RECRUITMENT OF CLIENTS

Various strategies were followed for recruitment of clients. These strategies were not uniform across centres.

- At some places, the MMT centres were able to form strong alliances with local NGOs that were implementing TI programmes for IDUs. One-to-one meetings with these TIs were conducted by the MMT centres at the local level, and the TIs were made aware of the new intervention available to opioid dependent IDUs. In some centres, workshops were held for all the IDU TIs working in the city. In such cases, prior information was provided to the concerned State AIDS Control Societies.
- Some MMT centres conducted awareness programmes at various places, including IDU hotspots, Drop-in-centres of TIs, etc., to make the opioid dependent individuals aware of available MMT services. MMT counsellors also conducted periodic visits to such hotspots and prepared potential clients for MMT initiation.
- Some MMT centres informed their existing opioid dependent clients about other treatments and encouraged them to refer other clients to the MMT programme.

All these efforts were necessary for the initial recruitment of clients. Once a critical mass of 10-15 clients was reached, these initial ‘seeds’ themselves became advocates of the MMT programme, and they started informing their peers and encouraged them to try the new medicine available in the vicinity.

## CLIENT ASSESSMENT

When clients visited the MMT centre, they were assessed by the doctor as well as the counsellor. The areas of assessment included:

- Socio-demographic profile;
- Drug use history;
- Past abstinence and treatment history;
- Medical history;
- History of high risk behaviour;
- Psychosocial history and current psychosocial status;
- General physical examination; and
- Motivation level.

The assessment also helped decide whether the client fulfils the selection criteria for initiation of MMT. The selection criteria for MMT initiation (as well as inclusion as a subject in the research study) were:

### INCLUSION CRITERIA

- Age above 18 years
- Established diagnosis of opioid dependence syndrome
- In case of injecting drug users: Using opioids by injecting route at least once in last three months
- In case of non- injecting drug users: at least two failed abstinence attempts following conventional treatment
- In case of patients with history of having received buprenorphine maintenance treatment: evidence of poor compliance and response to treatment\*
- Feasible to come to MMT clinic daily for medication
- Ability and willingness to provide informed consent

### EXCLUSION CRITERIA

- Serious medical conditions such as respiratory illnesses, acute liver disease, delirium tremens,
- Patients with concomitant severe dependence on other psychoactive dependence (except nicotine)
- Patients unwilling to comply with the treatment regime

*\* Poor compliance measured by missing medication more than 15 days per month and use of illicit drug more than 15 days per month due to non-suppression of craving after the buprenorphine dosage has been increased to at least 12 mg/day.*

After being deemed fit for initiating MMT, the client was educated on the MMT process and methadone was initiated after obtaining written informed consent. Priority was accorded to opioid dependent IDUs at all the centres, except at AIIMS, where both IDUs as well as non-IDU opioid dependent clients were enrolled for MMT.

Treatment with methadone was divided into three phases: induction, maintenance and termination.

## MMT - PHARMACOLOGICAL TREATMENT

### INDUCTION PHASE

The induction phase for MMT commenced from the first dose of methadone till the time the client became free of opioid withdrawals and/or craving for a period of at least 24 hours. The first dose of methadone was given after ensuring that the client had been abstinent from other opioids for a period of at least 8-12 hours, and signs/symptoms of opioid withdrawals were observed in/reported by the client. An examination of pupils to check for dilatation was conducted by the doctor before referring the client to the nursing staff for the first dose of methadone.

Most of the clients were initiated on a dose of 15-20 mg/day of methadone, especially in the initial phase of MMT implementation. After enough experience had been gained, some centres, notably RIMS, also started with doses of 25-30 mg/day of methadone in later phases. This was because their clients reported continued withdrawal even on day one with 20 mg/day of methadone. The client was observed for a period of two hours on the first dosing day for symptoms of withdrawal/intoxication. The same dose was continued for the next three to four days.

The dose increments were done in units of 5-10 mg of methadone, once in three to four days, till the client was comfortable for a period of at least 24 hours with no reports of withdrawal/craving or intoxication. The doctor would assess the client during induction phase every three to four days when the dose had to be increased for withdrawals, craving as well as side effects.

The induction phase lasted for about two to three weeks at all the centres.

## MAINTENANCE PHASE

The maintenance phase was proposed to last till the time the client was ready to start tapering methadone dose after achieving his psychosocial functioning as well as cessation of drug use. This phase could last for months to years; there was no pressure from the MMT staff to withdraw/stop methadone after a few months of MMT. Rather, clients were encouraged to continue the medication at least till psychosocial stability had been achieved.

In the maintenance phase, attempts were made to reach a dose of at least 50-60 mg methadone per day by increasing the dose of methadone by 5-10 mg every three or four days. However, it was observed that a dose of 30-40 mg/day of methadone was found to be adequate for stabilization at all centres. Clients would complain of drowsiness if the dosage exceeded this. The exception was RIMS, where many clients were stabilized on doses of 50 mg/day of methadone.

In a few cases, methadone doses in excess of the usual doses given needed to be provided. This was usually the case where the client was on other medications for comorbid medical illnesses. These included:

- **Anti-retroviral treatment** for HIV positive clients: especially in cases where the ART regimen included Nevirapine or Efavirenz;
- **Epilepsy:** where the client was on phenytoin; and
- **Anti-tubercular treatment (ATT)** for tuberculosis: especially in those cases where ATT included rifampicin.

The highest doses were 85 mg/day in Punjab, 90 mg/day in Delhi, and 125 mg/day in Manipur.

During the maintenance phase, the doctor and the counsellor would follow up with the client once in two to four weeks, at the minimum. The focus of assessment during such follow-up included:

- Use of opioid drugs;
- Use of other psychoactive substances;
- Side effects (if any);
- Psychosocial functioning: occupational, family, social and legal functioning; and
- Perception and attitude towards MMT.

## TERMINATION PHASE

Some clients opted for planned termination of MMT during the course of project implementation. In many cases, the termination was planned as the client had to move out to another city where methadone was not available. In others, the termination was planned as improvement noted by both the provider and the client. In a majority of the cases, the termination was accomplished in the outpatient setting itself; very few clients required admission. The frequency and amount of tapering of methadone dose was individualized; usually the dose was tapered by 1 ml, i.e. 5 mg every three to seven days. The time taken for complete termination was five to six months.

## METHADONE DISPENSING



Fig 2: Methadone Dispenser

While different formulations and strengths of methadone are used in different parts of the world, the project chose to use liquid formulation in strength of 5 mg/ml. The supply from the supplier was in one litre bottles containing a total of 5,000 mg of methadone with strength of 5 mg/ml.

A manual dispenser was used to dispense methadone from the bottle. The dispenser could be directly fitted on top of the bottle, and the lowest possible dose that could be drawn through the dispenser was 2.5 ml, i.e. 12.5 mg. For a smaller dose, the nursing staff would have to make use of a syringe to draw the required amount.

After the doctor gave a prescription for methadone on the first day, the client would be registered by the nurse on the dispensing register, and the prescribed amount of methadone would be dispensed. The client would then visit the nurse directly on subsequent days for receiving methadone. The nurse would check the client's pupils, confirm whether the client was intoxicated, and then provide the prescribed dose of methadone. The medicine would be dispensed to the client in a small plastic cup procured locally. The client was free to dilute the methadone with water, if he preferred. The nurse ensured that the client consumed his/her methadone in front of the nursing staff itself, after which he/she was free to leave the premise.

On days where the client's opioid consumption status was doubtful, the nurse would refer the client to the doctor before dispensing the medicine. Similarly, if the client had missed more than two consecutive doses of methadone, the nurse would refer the client to the doctor.

Along with pharmacological intervention, psychosocial interventions were also provided to the MMT clients by the doctor and the counsellor. These included:

- **Client education:** about the illness, modality of treatment, do's and don'ts of MMT, etc.
- **Motivation enhancement therapy:** to increase the client's motivation to initiate as well as continue treatment.
- **Family education:** Efforts were made by the counsellor in the project to establish contact with the family members of the client and request them to visit the MMT clinic. In the clinic, the family member/s was educated on the treatment being provided, the nature of the illness and need for long term treatment, and the importance of family involvement in treatment and daily dispensing.
- **Group education:** The counsellor or the doctor would address a group of MMT clients and educate them on various health and MMT related issues. The topics would range from MMT adherence, high risk behaviours and way of preventing them, HIV, hepatitis, etc.
- **Relapse prevention:** Relapse prevention sessions were conducted by the counsellor, both individually as well as in group setting, and various issues related to relapse, such as peer influence and how to handle peer pressure, coping with craving, handling family mistrust, daily activity scheduling, addressing co-morbid substance use, etc., were addressed in these sessions.
- **Education on psychosocial status:** The counsellor also worked with clients on improving family ties, regaining occupational productivity, handling stigma, etc., and efforts were made to make the clients productive.

# Psychosocial intervention

(4 individual, 3 group and 1 family session and further need based sessions if required)

At First Visit	During First two weeks	During First month	Between 1-3 months	Between 3-6 months
<b>Treatment education (one to one)</b> <ul style="list-style-type: none"> <li>Understanding client's perspective of OST.</li> <li>Explain nature of illness</li> <li>Treatment modality</li> <li>Duration of treatment</li> <li>Need for follow up and active participation</li> <li>Do's and Don't s at the clinic</li> </ul>	<b>Motivation enhancement (one to one)</b> <ul style="list-style-type: none"> <li>Feed back</li> <li>Developing discrepancy</li> <li>Decision balancing</li> <li>Self -efficacy</li> </ul> <b>Addressing Psychosocial crisis - as and when needed (e.g. homelessness, food, etc)</b>	<b>Family education (one to one)</b> <ul style="list-style-type: none"> <li>Nature of illness and treatment</li> <li>Benefit of MMT to the client and family</li> <li>Importance of Family involvement in treatment and in daily dispensing.</li> </ul> <b>Education for health conditions (group sessions)</b> <ul style="list-style-type: none"> <li>Testing for HIV</li> <li>Screening for TB</li> <li>Screening for Hepatitis (as feasible)</li> </ul>	<b>Patient Education (group session)</b> <ul style="list-style-type: none"> <li>High risk behavior and harm minimization</li> </ul> <b>Replace prevention (group session)</b> <ul style="list-style-type: none"> <li>Handling peer presure, change in peer group,</li> <li>Coping with craving</li> <li>Handling family mistrust,</li> <li>Scheduling daily life,</li> <li>Alternative high</li> <li>Addressing other substnace use</li> </ul>	<b>Reintegration (one - to one )</b> <ul style="list-style-type: none"> <li>Improving family relationship</li> <li>Managing stigma,</li> <li>Occupational rehabilitation (linkage with NGOs/ employment agencies and other facilitation as required</li> </ul>

Different psychosocial interventions were planned at different points of time.

## MMT - OTHER SERVICES

Apart from direct methadone and psychosocial interventions, the MMT centres also provided other healthcare services required by the MMT clients, such as treatment for tuberculosis, testing of HIV, treatment of HIV, treatment of other medical conditions, etc. These services were made available to the clients through referrals to the appropriate agencies.

The counsellor for the MMT project had prepared a directory of various healthcare services commonly required by the clients and made an attempt to visit these agencies and establish a formal network mechanism. Clients who required any of these services were then referred by the doctor or counsellor, as needed.

Other medical conditions, which could be taken care of by the doctor at the MMT centre, were treated at the centre itself. Additionally, treatment for comorbid substance use and psychiatric illness was also provided by the doctor at the MMT centre, being a specialist in psychiatry.

# PROCUREMENT AND STOCK KEEPING OF METHADONE

Methadone has been classified as a narcotic, as per the Narcotic Drugs and Psychotropic Substances (NDPS) Act, 1985, in line with UN conventions. The licensing requirements for methadone are, therefore, different from those required for buprenorphine, a psychotropic substance.

## LICENSING AND PROCUREMENT

The following licenses were required to make methadone available at a given MMT centre:

- 1. Storage license:** Every MMT centre required a storage license for storing methadone in the premises, except Punjab, where the state NDPS rules exempted the Government hospitals from needing a license to store methadone. The issuing authority for storage licenses was not uniform at all the centres, as laws were interpreted in different ways in different states. In Maharashtra and Manipur, the authority was the State Drug Controller, while in Delhi, it was the Excise department. In all these places, however, the process of obtaining the license was, more or less, similarly tedious.

The centre was to apply for the license in the prescribed format, following which a designated official would visit the premises where methadone was to be stored. The license was issued after the storage space was finalized by creating a map and ascertaining its safety. The entire process from application to the grant of license took around eight to 12 weeks. The license was valid for a period of one year (financial), after which a renewal application could be filed and stock registers submitted for scrutiny.

- 2. Transport license:** after finalizing the supply order, the individual MMT centres were supposed to apply for a transport license with the appropriate state designated authority, which varied in different states. In Punjab and Maharashtra, the authorised department was the State Drug Controller, while in Delhi and Manipur, it was the Excise Department. The transport license was required for every delivery of methadone, and was valid for only one-time use. The entire process from application to the grant of transport license took about four to eight weeks.

The procurement of methadone was done by NDDTC, AIIMS for all the MMT centres. Following a tendering procedure, one pharmaceutical firm, licensed by the office of the Drug Controller (General), India to produce and supply methadone in India, was chosen by NDDTC. Currently, there is only one pharmaceutical firm which has this license from DCGI. The supply order mentioning the supply schedule was forwarded to the MMT centres, based on which they were to apply to the appropriate state authorities for the transport license. After the transport license was obtained, it was forwarded to the pharmaceutical firm for supply. Based on the transport license and the supply order, the pharmaceutical firm supplied the required quantities of methadone bottles to the individual centres, following due procedure.

The entire process of initiating tendering to supply of methadone took at least four to six months.

## STOCK-KEEPING OF METHADONE

The main stock of methadone was stored at each MMT centre, separately from the dispensing site. A storage room, as identified and certified by the storage license issuing officer, was earmarked for methadone storage, and was secured with iron grills and locks, as required. No other medications were kept alongside methadone in the storage room. The room was kept under lock and key at all times, except during retrieval of bottles for dispensing, and was under the custody of the nodal officer of each MMT centre, with minimal access by other personnel.

A register (main stock register) was maintained at the storage room, which indicated:

- The amount of methadone received from the supplier; and
- The amount of methadone supplied to the MMT centre for dispensing.

The register was maintained by the nursing officer/nodal officer, and was periodically scrutinized and entries tallied with other stock related records. The nodal officer was also encouraged to sign on the registers during the checks made.

The storage license issuing officer would verify the entries made and issue the storage license for the next financial year, after being satisfied with the veracity of the records.

## SUPPLY-CHAIN MECHANISM

A robust supply-chain mechanism was maintained to ensure that the methadone stocks are not exhausted at any point of time, as well as to ensure that there is no diversion of methadone at any point during methadone handling. This was done through rigorous maintenance of records as well as through monthly monitoring of monthly reports.

### A. Stock-related record maintenance

Record maintenance at every stage of methadone handling was designed for this purpose.

- 1) **Supplier → MMT centre:** Every consignment of methadone was accompanied by a consignment note, and successful delivery of the methadone stocks would be intimated to NDDTC. Payment to the supplier would be made after confirmation of successful delivery to individual MMT centre. The onus of ensuring correct entries in the main stock register lay with the nodal officer.
- 2) **MMT centre storage room → dispensing room:** Every time the nursing staff retrieved the required number of bottles from the main storage room, entries would be made in the main stock register as well as a stock register maintained in the dispensing room. The onus of maintaining the stock register in the dispensing room lay with the nursing staff.
- 3) **Dispensing methadone to clients:** Every day, when methadone was dispensed to the clients, entries on the dose administered to individual clients as well as the total dose dispensed in the day were entered in the dispensing register by the nursing staff. The client would also sign on register after receipt of the dose for that day.

One could tally all the entries made in the different registers to check the veracity of the transactions made, and thereby rule out any possibility of diversion.

## B. Monitoring monthly reports

A monthly reporting format was prepared by NDDTC, which was to be filled in by the individual centres by the end of the reporting month and transmitted to NDDTC and UNODC by the tenth day of the next month. The monthly report format also included a section on stocks: stocks at the beginning of the month, stock dispensed in the reporting month, and stocks left at the end of the reporting month. These reports were analysed by NDDTC and projections were made as to how long the stocks are expected to last. The next procurement would be planned accordingly.

The supply chain mechanism was by-and-large successful as it helped in ensuring uninterrupted flow of methadone stocks to each MMT centre. There were also no instances of diversion noted/reported by any centre at any level, including at client level. However, problems arose on certain instances, where NDDTC was aware of impending stock-out at some centres, but supply of methadone was made possible only at the last minute due to difficulty in procurement procedures as well as obtaining the transport license well in time.

# MMT - QUALITY ASSURANCE MECHANISMS

Various steps and mechanisms were built into the project to ensure that the individual centres deliver methadone while adhering to the minimum standards of care.

- **Capacity building measures**

As mentioned in earlier sections, various capacity building measures were instituted as part of the project. A five-day training programme was conducted in the initial stages for all the staff. An exposure visit to a functional MMT centre in Nepal was organized before initiating MMT. A three-day refresher training was organized after the centres had been implementing MMT for a period of six to nine months. Finally, investigators from NDDTC were available round-the-clock to the individual MMT centre staff, for advise and clarification, which was made use of by all the centres. Clinical and operational issues were addressed telephonically as well as through mail by NDDTC and UNODC, as and when required.

- **Quality Assurance visits**

Visits to the individual MMT centres were made jointly by NDDTC and UNODC, twice during the project period. The visits were conducted to oversee the status of project implementation, assess whether the individual centres were implementing MMT as per protocol, and finally, to address various clinical and operational issues that emerged during the visit. The team conducted the following activities during these visits:

- o Interaction with the staff at the centre;
- o Interaction with the MMT clients;
- o Interaction with family members of MMT clients visiting the centre; and
- o Review of records.

The findings of the visits were duly recorded in a quality assurance tool prepared for the purpose. These visits helped the MMT centres to get feedback on project implementation, and helped them improve their knowledge and skills with regard to methadone treatment.

- **Record maintenance**

To ensure uniformity in data collection as well as recording data, record-keeping formats were prepared for individual MMT centres to follow. The list of record-keeping formats maintained at individual MMT centres is provided in table 1.

The record-keeping formats also helped individual MMT centres in internal monitoring. The doctor was encouraged to periodically check the files of individual clients and assess the progress made by the client after initiation on methadone.

- **Monthly reporting**

Every MMT centre was required to fill up a monthly report at the end of the month and send it to NDDTC by the tenth day of the next month. The monthly report helped create a monthly update on the number of clients enrolled for methadone, the number regularly on methadone and the number of drop-outs from the programme.

The monthly report was analysed and compiled by NDDTC, and the consolidated report was periodically sent to UNODC for the project update. Feedback would also be given to individual centres, as and when required.

### List Of Records To Be Maintained At Individual Mmt Centre And The Staff Responsible

Staff responsible	Name of Record*
<b>NODAL OFFICER</b>	a) Client register New
	b) Client register OST (methadone)
	c) Client register Follow up
<b>DOCTOR</b>	d) Client file containing:
	i. Client Intake Form
	ii. Format to ascertain suitability for OST
	iii. Consent Form
	iv. Prescription card
	v. Follow-up form
	vi. SOWS, OOWS, Side Effects checklist
	e) Referral register
<b>COUNSELLOR/</b>	f) Counselling register
<b>RESEARCH ASSISTANT</b>	g) Notes on individual counselling session in the files
<b>NURSE</b>	h) Dose sheet (separate / in file)
	i) Dispensing register
	j) Daily Stock register
	k) Central stock register
* This list does not contain the tools which were used specifically for the purpose of effectiveness research study. Those have been listed and described separately elsewhere in the document.	

Table 1: List Of Records To Be Maintained At Individual MMT Centre and The Staff Responsible

# EFFECTIVENESS FINDINGS

One of the important objectives of this study was to test the effectiveness of methadone as a medication for long term treatment for opioid dependence in India. Although there is adequate literature demonstrating the effectiveness of methadone from different parts of the world, it was considered important to have data generated from within India.

## METHODOLOGY

The study on the effectiveness of Methadone Maintenance Treatment was also carried out at all the five sites (National Drug Dependence Treatment Centre, AIIMS, New Delhi; Department of Psychiatry and Drug De-addiction Centre, King Edward Memorial Hospital, Mumbai, Maharashtra; Department of Psychiatry and Drug De-addiction Centre, Regional Institute of Medical Sciences, Imphal, Manipur; Drug De-addiction Centre, Civil Hospital, Bathinda, Punjab and Drug De-addiction Centre, Civil Hospital, Kapurthala, Punjab). **It was designed as an open label study with a single arm and prospective design.**

Before the commencement of the study, ethical clearance was taken from the Ethics Committee at AIIMS, KEM Mumbai, RIMS Imphal besides clearances obtained from the Secretary Health Punjab, Indian Council of Medical Research and ethics committee of NACO (R & D division). Written informed consent based on a pre-defined format was taken from all respondents included in the study. No incentives were paid to them for their participation in the study.

### Sample selection

The inclusion and exclusion criteria for the respondents included in the research study are mentioned in the client assessment section under 'feasibility findings'. Although the inclusion criteria mentioned earlier included injecting drug users and non-injecting drug users with two failed abstinence attempts, it was decided at the onset that priority would be given to injecting drug users for recruitment, and the decision to include non-injecting drug users would be taken at a later date only if the required sample could not be recruited by taking IDUs only. Therefore, all the respondents included in the research study were IDUs (injecting in last three months). A few non-injecting clients were recruited at AIIMS as well, though they were not included in the research sample.

### Intervention

**Medical:** Liquid Methadone (formulation 5 mg/ml) was used in flexible dosing schedule based on clinical assessment. Most of the clients were initiated on 15-20 mg/day of methadone based on the clinical guidelines although later on some centres started induction with 25-30 mg/day of methadone. The dose increments were done in units of 5-10 mg of methadone once in three to four days, based on clinical assessment. The doctors were trained to optimize the dosage till no reports of withdrawal/craving/intoxication were present.

**Psycho-social-**The psychosocial intervention was delivered to all respondents alongside as per a pre-decided schedule mentioned earlier. However, this was not rigidly followed and sessions were taken on a need based manner using this as a broad guideline.

The doctors who prescribed Methadone had undergone the five-day training conducted by NDDTC and most of them also had been part of the study tour to Nepal. During the training, pharmacology of Methadone as well as clinical guidelines for induction, maintenance and tapering (in case required) were covered. Dosage adjustments for Methadone in case of associated physical conditions such as diarrhoea, tuberculosis, HIV/AIDS, epilepsy, etc. requiring concomitant use of medication were also discussed. Draft clinical guidelines on Methadone developed by NDDTC were shared with all the participating centres so that they could refer to it as and when required. Besides this, the nodal officers could contact the resource persons at NDDTC through phone calls or emails as and when required.

## Assessment

The table gives the research instruments used in the study and the personnel who were responsible for administration of the research instruments as well as the frequency of administration. All instruments were interviewer administered (administered by the doctor/nurse and the research staff/counsellor).

Tool Used for Assessment	Staff responsible for administration	Frequency of administration
Checklist of Inclusion and exclusion criteria	Doctor/ Nurse	Baseline
Subject information sheet and informed consent	Doctor/ Nurse	Baseline
Semi-structured proforma for demographic information and drug use	Doctor/ Nurse	Baseline
Subjective Opioid Withdrawal Scale	Doctor/ Nurse	2 weekly for first 2 months, at 3 months, 6 months, 9 months and 12 months
Objective Opioid withdrawal Scale	Doctor/ Nurse	2 weekly for first 2 months, at 3 months, 6 months, 9 months and 12 months
Side effect check list	Doctor/ Nurse	2 weekly for first 2 months, at 3 months, 6 months, 9 months and 12 months
Urine Screening	Doctor/ Nurse	Baseline, 3 months, 6 months, 9 months and 12 months
Addiction Severity Index	Research staff/ Counsellor	Baseline, 3 months, 6 months, 9 months and 12 months
WHO Quality of Life BREF scale	Research staff/ Counsellor	Baseline, 3 months, 6 months, 9 months and 12 months
High Risk Behaviour Scale	Research staff/ Counsellor	Baseline, 3 months, 6 months, 9 months and 12 months

Table 2: Tools Used In MMT Research

**Semi structured proforma** collected information on demographic data (age, education, occupation, marital status, and employment status) besides information on drugs used at baseline.

**Subjective Opioid Withdrawal Scale (SOWS) and Objective Opioid Withdrawal Scale (OOWS)** were used to assess the signs and symptoms of opioid withdrawals (Handelsman et al., 1987).

SOWS and OOWS have been found to be valid and reliable measure of opioid withdrawals and have good test retest reliability within respondents. OOWS also has good inter-rater reliability. The scoring for SOWS is based on self-report and a score is given for each symptom of opioid withdrawal on a likert scale where 0 denotes absence of symptom and 3 denotes severe opioid withdrawal symptom. The total score of SOWS ranges from 0-48 (0-16 mild, 17-32 moderate, 33-48 severe opioid withdrawal). The scoring of OOWS ranges from 0 to 13 based on 13 signs of opioid withdrawal rated by an observer as present or absent.

**Side effect checklist:** The side effect checklist was constructed based on the common side effects related to Methadone that was reported in literature.

**Addiction Severity Index:** Addiction Severity Index (ASI) is widely used to assess the severity of problems associated with drug abuse or dependence and has been used to assess the outcome following interventions (McLellan et al., 1980). The instrument has been shown to have good reliability and validity. ASI evaluates respondents in seven domains: (1) medical (2) employment (3) drugs (4) alcohol (5) legal (6) family/social relationships and (7) psychological. The mean composite scores can range from 0 (no problem) to 1.0 (extreme problem), in each domain and are assessed based on items that focus on the past 30 days. A higher ASI score indicates greater severity. A Hindi version of the third edition of ASI, adapted at AIIMS, was used at baseline and at each follow-up assessment.

**WHO Quality of Life Brief Scale:** The WHO Quality of Life Brief Scale (WHOQOL-BREF) was developed by WHO as an international, cross-culturally valid quality of life instrument (The WHOQOL Group, 1998). It assesses individual's perceptions of their quality of life and it has been used to measure change in quality of life as an outcome measure. The WHOQOL instruments have been field-tested in various parts of the world. WHOQOL-BREF is a shorter version with 26 items, which measure the broad domains viz.: physical health, psychological health, social relationships, and environment. The four domains are scored, labelled, and transformed to a 0-to-100 scale.

WHOQOL-BREF has good psychometric properties with internal consistency in the range of 0.66-0.87 (Cronbach's alpha co-efficient), good discriminant validity and test retest reliability (Skevington et al., 2004). The WHOQOL-BREF Hindi translated version was used (Saxena et al., 1998).

**High Risk Behaviour Scale:** The High Risk Behaviour Scale (HRBS) is a brief, 11 item questionnaire which assesses the HIV risk-taking behaviour of IDUs. Two predominant areas of concern, needle use behaviour and sexual behaviour, are measured. It usually takes about 10 minutes to administer and is easy to score. For each of the two sub-sections, the score for each of the questions is added and for the total score, the two sub-totals are added. HRBS provides three scores: a total score indicating level of HIV risk-taking behaviour, a Drug Use Sub-total, indicating level of risk due to injecting drug use practices, and a Sexual Behaviour Sub-total, indicating level of risk associated with unsafe sex. The higher the score, the greater is the risk of the subject contracting and passing on HIV (Ward et al., 1990).

**Urine screening:** Urine screening for drug use was carried out at baseline and at each follow-up assessment. It has the advantage of being an objective method of assessment and has often been used to validate self-reports. It was conducted in the Methadone Clinic using a dipstick method. The Opioid Strip Drug Urine Test or cassette test is a simple and accurate one-step drug test for the rapid detection of opioids and their metabolites in urine that detects recent drug use, usually over the last 48 hours. The test strip is kept in contact with the urine specimen for five seconds or longer. After five to 10 minutes, the results are read and interpreted. The test for morphine, buprenorphine or dextropropoxyphene was used for respondents based on their primary drug of use. Urine kits for each of these were procured and made available to the participating centres, based on the primary drug of use in the setting.

## TRAINING OF STAFF

The staff was trained in the research assessments during the initial five day training. Training included going through each individual item of the questionnaire with the research staff, demonstration of the research assessments as well as supervised administration during training. Besides this, a few practice assessments were carried out by the research staff under supervision of the nodal officer before the actual process of data collection started. The ASI manual was also available to the staff as a reference.

## DATA ANALYSIS

Data collected by the respective centres was sent as hard copies to AIIMS, where it was computerized. Data quality checks were carried out and discrepancies examined. Data was analysed using SPSS 21.0. Descriptive variables such as mean, median, standard deviations and range were obtained.

ASI composite scores were calculated using an Excel-based Composite Score Program which allows for the electronic calculation of composite scores for each ASI domain. Values referring to items that contribute to the each domain's composite score were entered into the spreadsheet. For the WHOQOL-BREF instrument, quality of life was taken as an outcome variable. Estimates of the mean QOL score in each domain were calculated using an SPSS syntax of Melbourne WHOQOL Field Centre which checked, recoded and computed the four QOL domain scores by transforming them into a 0-to-100 scale using a scoring algorithm. The four domain scores denoted the users' perception of QOL in each domain which scaled in the positive direction, i.e. higher scores denoted a higher QOL. HRBS provided three scores: for the two sub-sections, the score for each question was added; for the total score the two sub-totals were added. Thus a total score was arrived at, indicating the level of HIV risk-taking behaviour, along with a Drug Use Sub-total indicating the level of risk due to drug taking practices, and a Sexual Behaviour Sub-total. For the SOWS and OOWS, total scores were used.

# RESULTS

## DEMOGRAPHIC CHARACTERISTICS

A total of 334 male opioid dependent clients were recruited from five participating centres. The clients had to travel a mean distance of  $5.4 \pm 9.5$  km (median: 2 km, range 0-80 km) to reach the methadone clinic from their place of residence. About 82 percent of the clients resided within 5 km range of the clinic.

The mean age of the sample was  $29.6 \pm 7.6$  years (range: 18-60 years). This varied between the lowest of  $25.9 \pm 7$  years in Delhi, followed by  $26.6 \pm 6$  years in Kapurthala,  $29.3 \pm 7$  years in Bathinda,  $33.8 \pm 8$  years in Mumbai and a highest of  $35.1 \pm 7$  years in Imphal.

Most of the respondents were in age range 21-30 years (52.5 percent) followed by 31-40 years (29.6 percent). There were 8 percent below 20 years of age (but more than 18 years of age as per the inclusion criteria).

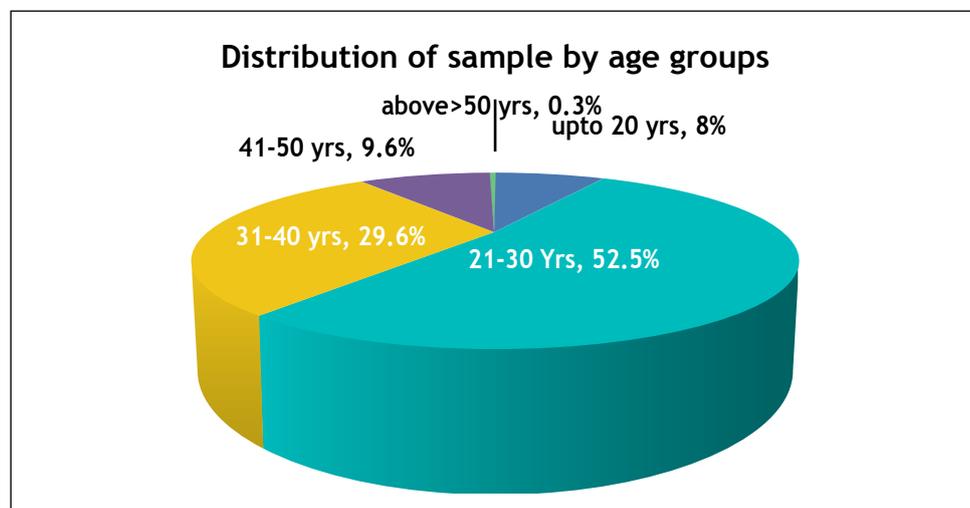


Fig 3: Distribution of sample by age groups

About 57 percent of the sample had attained between 10-12 years of schooling. A small percentage (13 percent) had higher education in college as well. Only 9 percent were illiterate/just literate.

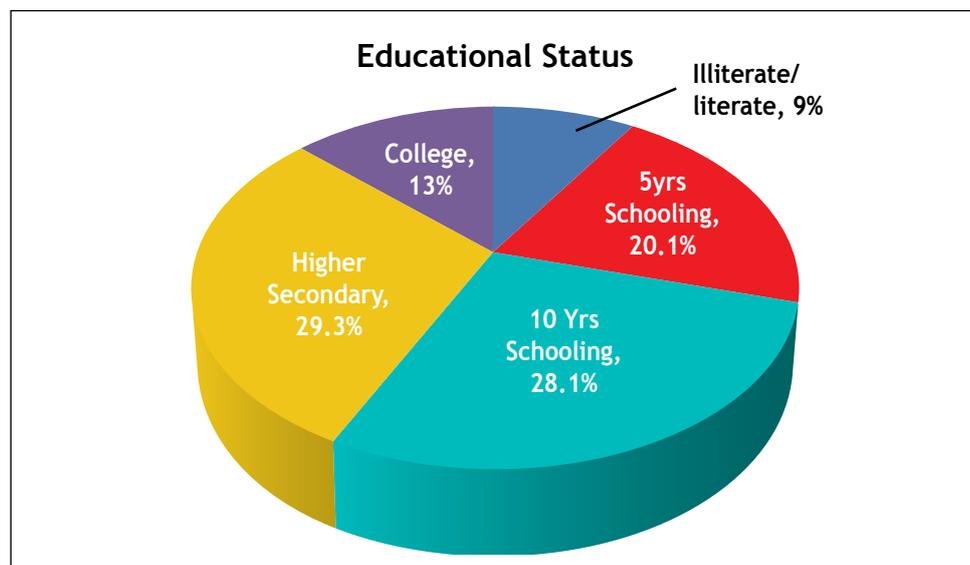


Fig 4: Distribution of sample by Educational Status

Most users from Delhi (88.6 percent) were illiterates/ literates/ five years of schooling; 58.8 percent in Mumbai had completed five to 10 years of schooling; majority of the users from Kapurthala (81.2 percent) and Bathinda (62.8 percent) in Punjab had completed 10-12 years of schooling; in Imphal the users had the highest educational status and 43.6 percent users had completed high school and 34.5 percent users had completed college education.

More than half of the sample (54.9 percent) was unmarried, followed by about 40 percent who were married. A small percentage was married but single (divorced/ separated).

The percentage of unmarried respondents was higher in Delhi (65.9 percent) and Kapurthala (61.6 percent). The percentage of divorced/separated was higher in Mumbai (11.8 percent) and Delhi (11.4 percent).

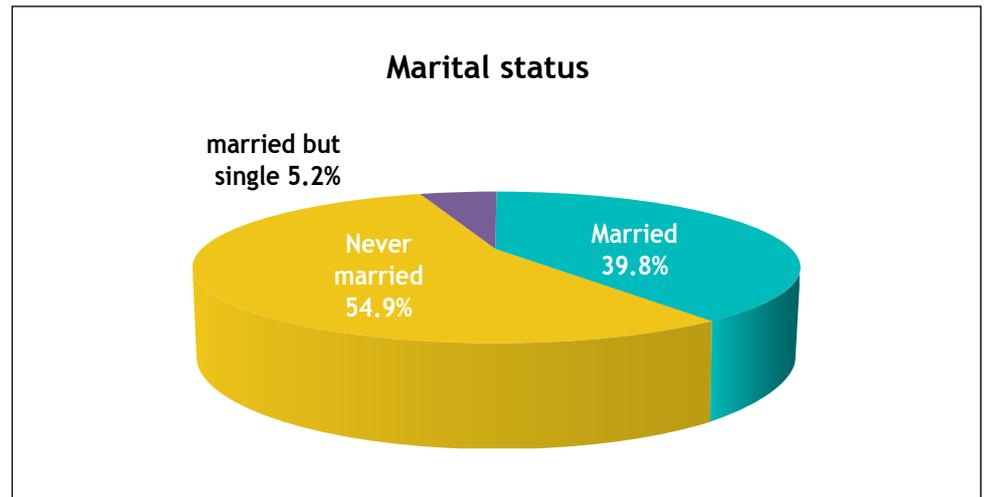


Fig 5: Distribution of sample by Marital Status

There were 45.7 percent Sikhs in this sample (as two of the participating sites were from Punjab state) followed by Hindus (35.2 percent). An equal percentage of the respondents were Christians and Muslims (9.3 percent). A small percentage was Parsis (0.6 percent).

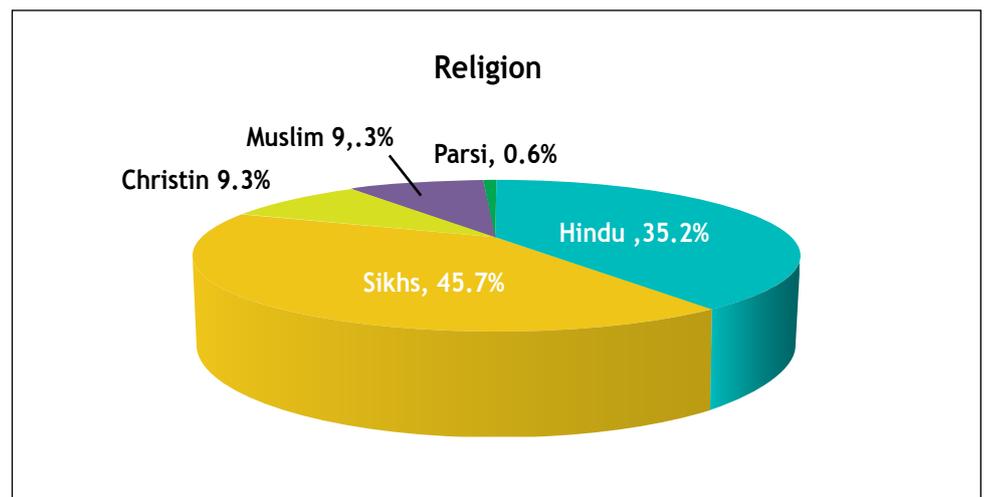


Fig 6: Distribution of sample by Religion

More than one third of the sample was unemployed; more than one third was employed full-time; and 13.8 percent had part-time employment. About half the sample in Kapurthala and Bathinda had full-time employment, while 80 percent in Delhi and 67.6 percent in Mumbai were currently unemployed. About one third each were employed/ employed part-time/unemployed in Imphal.

In terms of occupation, the sample included unskilled workers, self-employed, skilled workers, and about 5 percent each were professionals and students.

Majority (92.3 percent) were living with their respective families and only 1.5 percent reported living on the streets.

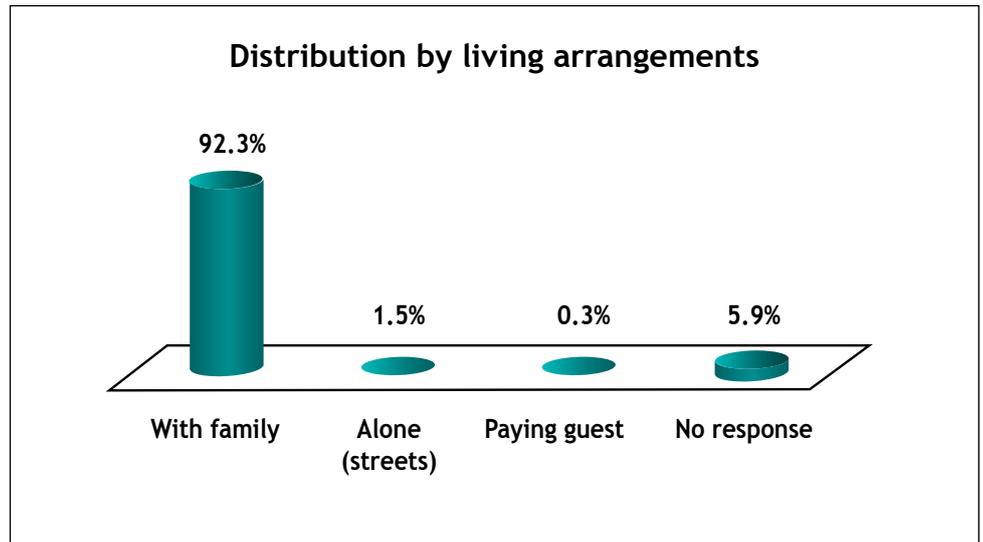


Fig 7: Distribution of sample by Living Arrangements

## DRUG USE RELATED PARAMETERS

At the time of inclusion in the study, the respondents were using injectable opioids, non-injecting opioids through oral and inhalational route and other drugs. The bar diagrams show the lifetime and current drug use (in the last one month). The injectable drugs used most commonly in the last one month were buprenorphine (48 percent) and heroin (46.4 percent). Most buprenorphine users used the drug along with a sedative (45.6 percent), while a small percentage used buprenorphine without sedatives (6.3 percent). Pentazocine was used by 3.2 percent and propoxyphene by 0.8 percent.

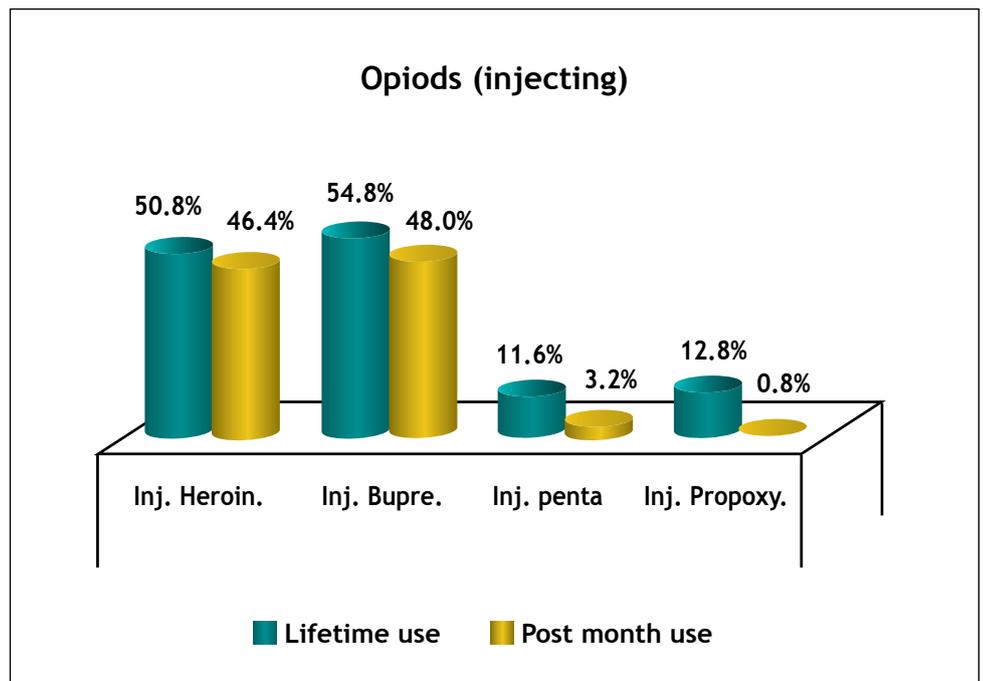


Fig 8: Bar diagram showing life time and past one month use of injectable opioids

Past month use of heroin by chasing was reported by 50.8 percent of the sample. Oral use of pharmaceutical opioids was reported by 23.6 percent and opium use by 16 percent of the respondents.

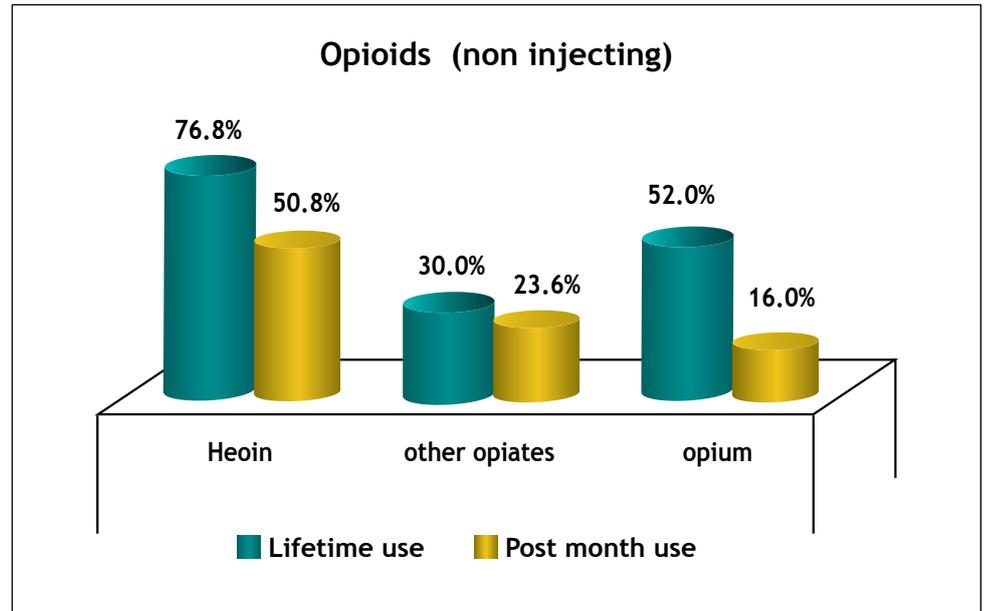


Fig 9: Bar diagram showing life time and past one month use of non-injectable opioids

Substances used besides opioids in the last one month included cannabis (36.8 percent), alcohol (35.6 percent), sedatives (26.4 percent) and inhalant use by a small percentage (1.2 percent).

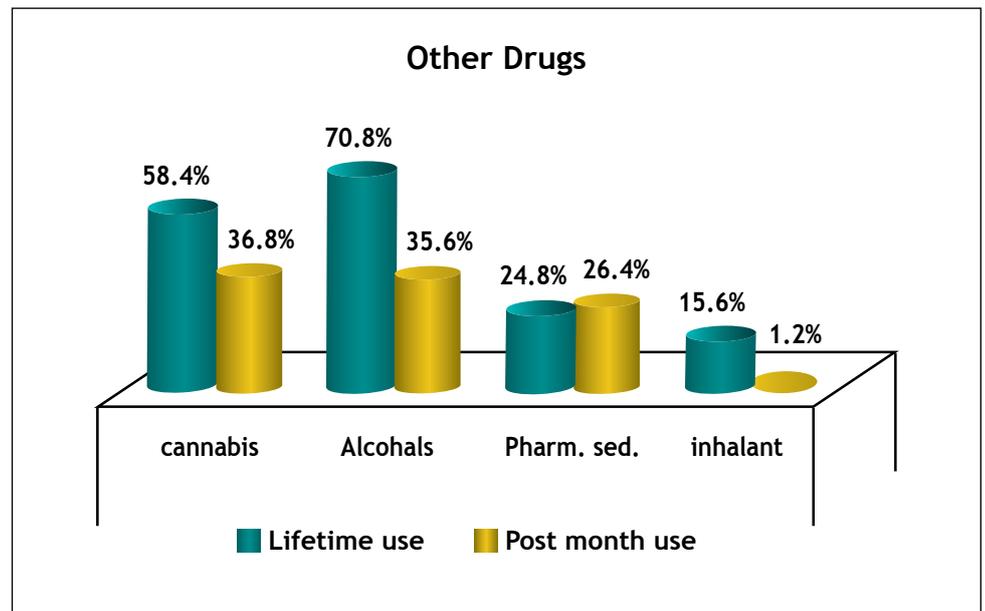
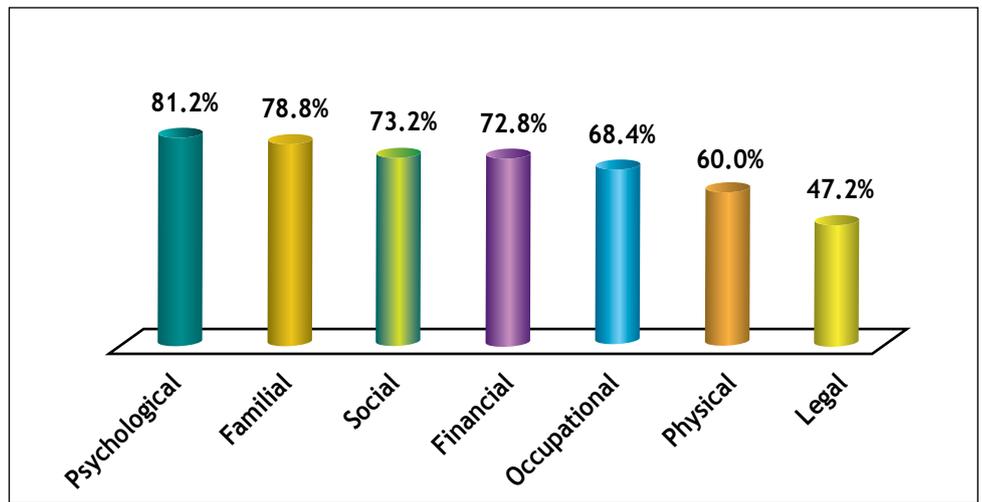


Fig 10: Bar diagram showing life time and past one month use of other drugs

### Complications due to substance use

Information on complications experienced and faced by the user due to substance use was ascertained. A large percentage reported psychological problems (81.2 percent), familial (78.8 percent), social (73.2 percent), financial (72.8 percent), occupational (68.4 percent), physical (60 percent) and legal (47.2 percent) problems. The users from Imphal (92.9 percent) and Delhi (86.5 percent) reported a particularly high percentage of legal problems.

Fig 11: Bar diagram showing the complications due to substance use



Past abstinence attempts were reported by 63.6 percent of the users, and multiple attempts had been made by 12.7 percent of the users. The reasons reported for relapse were peer pressure, experiencing withdrawal symptoms, psychological problems and craving.

## OUTCOME RELATED DATA

The retention rate of users in MMT is given in the graph. There was high variability in the retention rates across the five participating sites. The retention rate was 71 percent at the three-month follow-up, 60.5 percent at six months, 47.9 percent at nine months and 35.9 percent at the one-year follow-up.

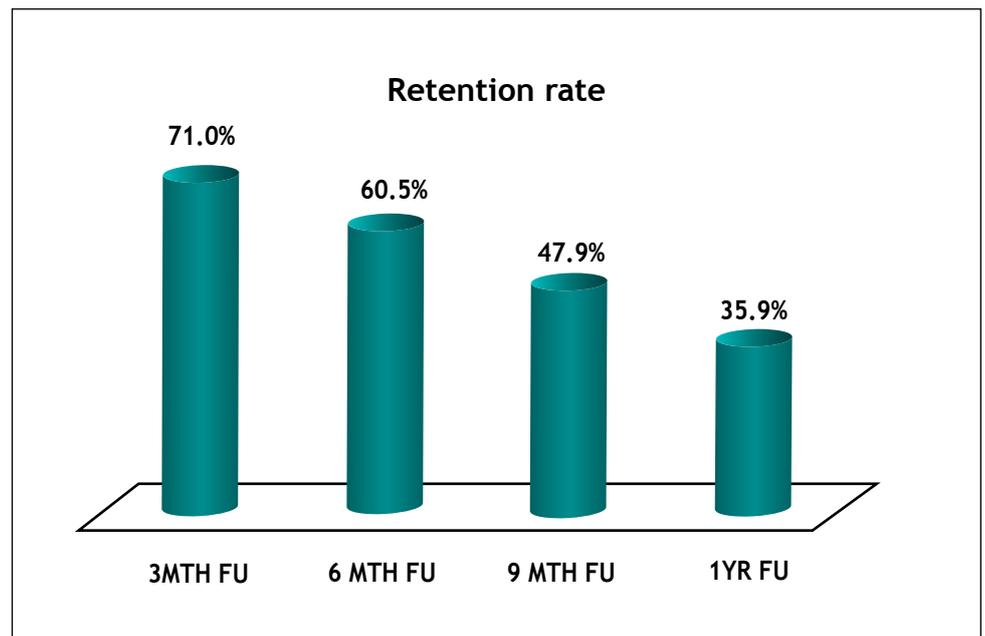


Fig 12: Bar diagram showing retention rate of MMT

### Dose and Compliance related data

The mean dose was 35 mg at one month, and 41 mg at 3 months; it remained about the same subsequently. The median dose was very similar to the mean dose. The dose range was very wide, as evident from the table, with a maximum dose of 125 mg and a very low minimum dose as there were users who were dropping out of and re-entering the treatment at different points of time. Therefore, at the time of each assessment, some users were in the initial stages of induction

## DOSE OF METHADONE

TABLE 3: Methadone Dose Details

VARIABLES	ONE-MONTH FOLLOW-UP	THREE-MONTH FOLLOW-UP
Mean Dose (mg/day)	35	41
Range (mg/day)	7.5 - 125	2.5 - 125
Median	35	40

The mean number of visits to the centres by the respondents during the one year period was 212.2 days, and the median was 251 days, with a wide range of two to 364 days (respondents who came daily). Compliance was calculated based on total days visited upon total days till a person was retained in treatment. Compliance also had wide variability, with a median percentage of 90.8 percent.

Table 4: Compliance On Methadone

VARIABLES	DAYS VISITED (NUMBER)	TOTAL DAYS ELIGIBLE FOR VISITS (NUMBER)	COMPLIANCE (%)
Mean	212.2	262.3	80.3
Range	2 - 364	2 - 365	2.8 - 100
Median	251	351	90.8%

## Number of days of drug use in the past month

The number of days of drug use in the last one month declined substantially over the first three months itself, with almost 80 percent of the respondents reporting no use in the last one month for heroin and other opioids at three months. Those reporting intermittent/frequent/daily use (>7 days/month) were almost nil at all follow-up assessments. The percentage of respondents reporting no use in the last one month further increased over subsequent follow-ups and more than 90 percent reported no use of other opioids at six months and thereafter.

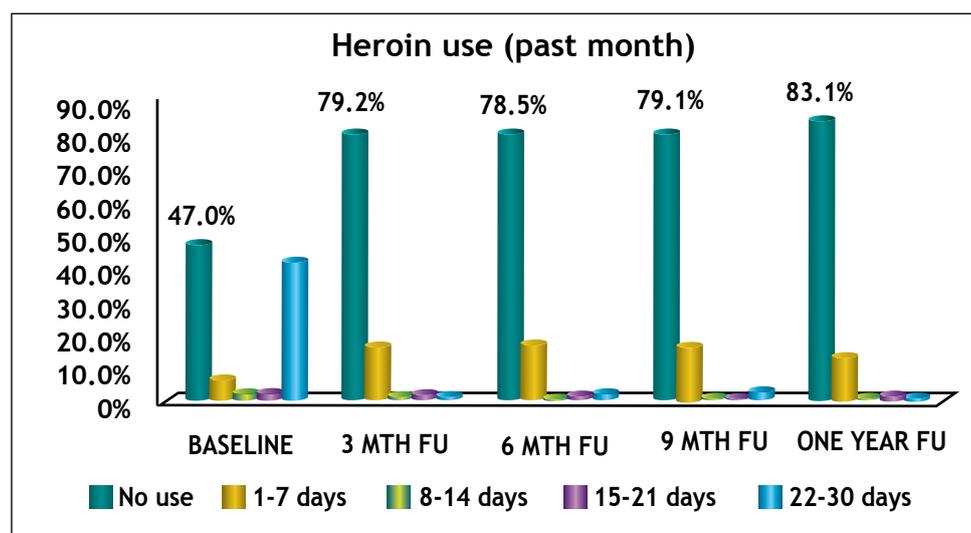


Fig 13: Bar diagram showing Heroin use in past one month after starting MMT

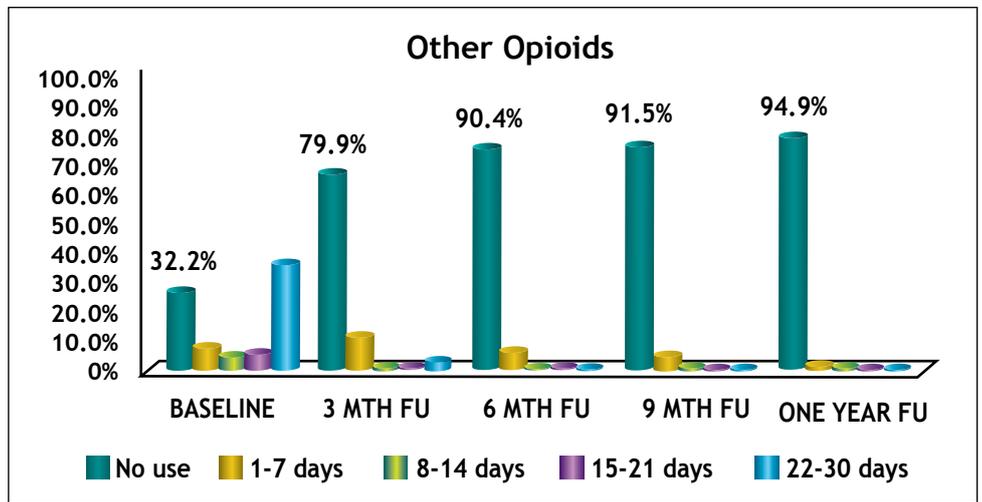


Fig 14: Bar diagram showing use of other opioids use in past one month after starting MMT

### Urine Screening Results

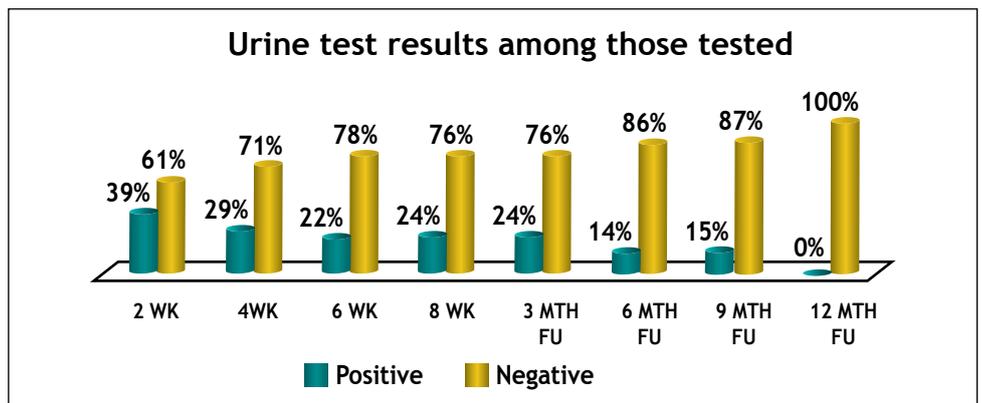


Fig 15: Bar diagram showing urine screening results

The urine screening results confirm that a vast majority of respondents had not used opioids recently. In fact, 61 percent of the results were urine negative within the first two weeks. This percentage increased further over subsequent follow-ups.

### Severity of Addiction

The severity of addiction as measured by the ASI composite domain score values at the time of each assessment show that at baseline, the most severe problems were in the area of 'employment status'. Other domains with severe problems were related to 'family/social relationship', 'drug' and 'psychological' aspects. The least impaired domain was 'alcohol use'.

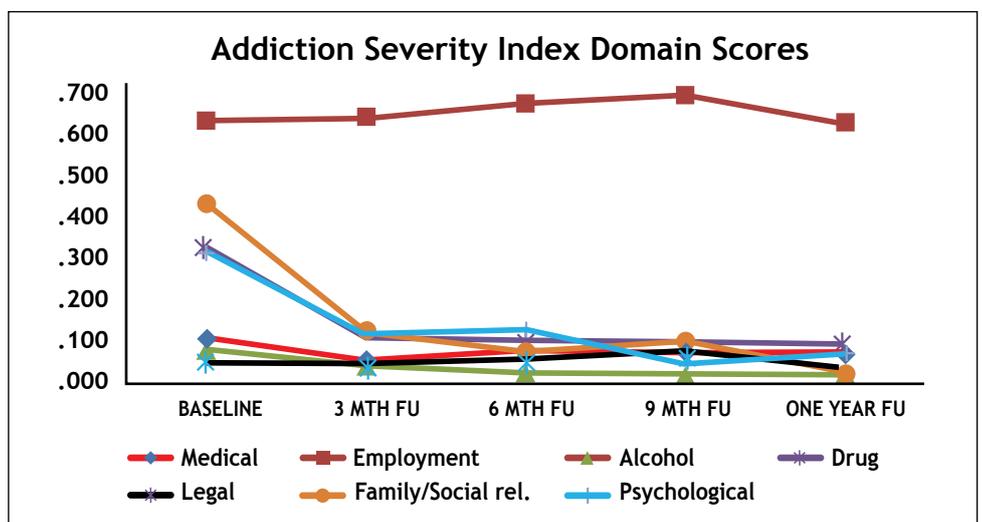


Fig 16: Graph showing addiction severity index domain scores

A general reduction was observed in scores, indicating lower severity of problems in all domains except 'employment' at three months, with continued reduction in problems even after three months in the 'family and social relationships' and 'psychological' domains. The 'employment' domain showed a more delayed reduction in severity, as the scores indicate.

### Quality of life

WHOQOL-BREF assesses an individual's perceptions of their quality of life in the context of culture and value systems, and their personal goals, standards and concerns. In addition, it is used to measure change in quality of life over the course of treatment.

The overall quality of life as assessed by a single item in WHOQOL-BREF was reported as poor/very poor by 62.2 percent at baseline and declined to 5.8 percent at the one-year follow-up. Simultaneously, the reporting of good/very good quality of life by 29.6 percent at baseline increased to 76.7 percent at one year.

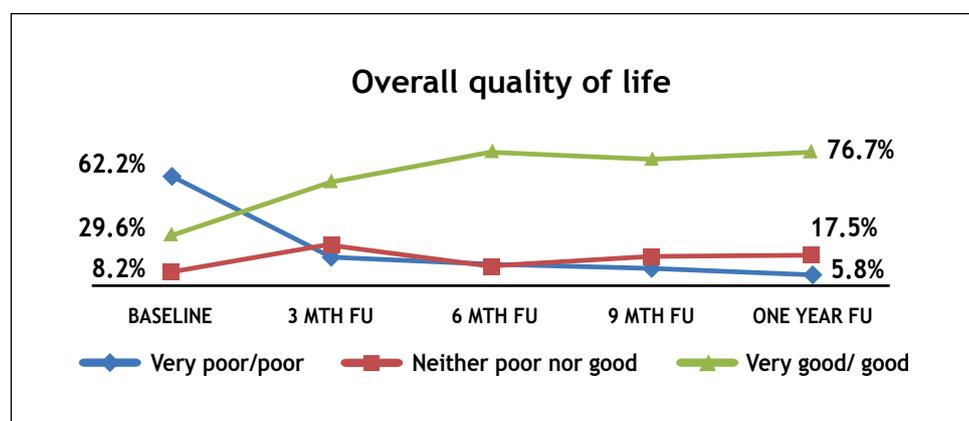


Fig 17: Graph showing overall quality of life

The four domain scores, taking into account multiple items in each domain, were based on the users' perception of their quality of life in each domain. Higher scores denote higher quality of life. The table below provides the WHOQOL-BREF domain scores for assessments carried out at different points of time. At baseline, the sample had low scores in all domains (physical, psychological, social relationships, environment). Thereafter, these scores increased within the first three months, with a further increase over the course of treatment.

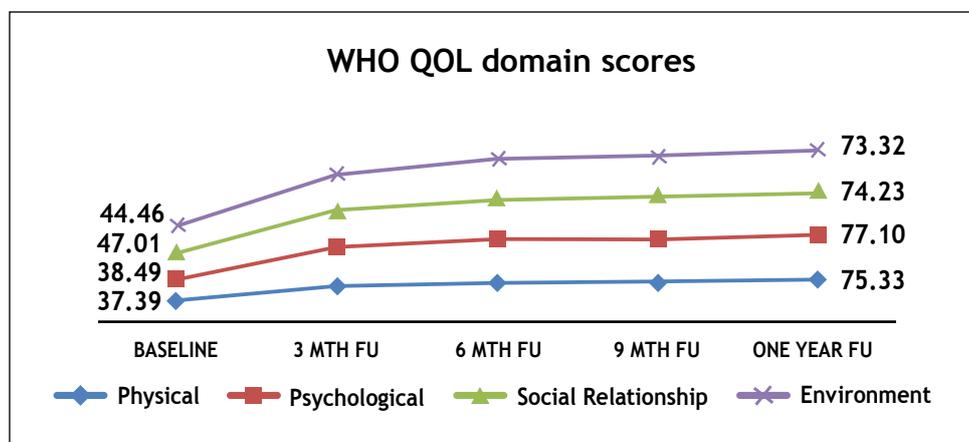


Fig 18: Graph showing WHOQOL domain scores

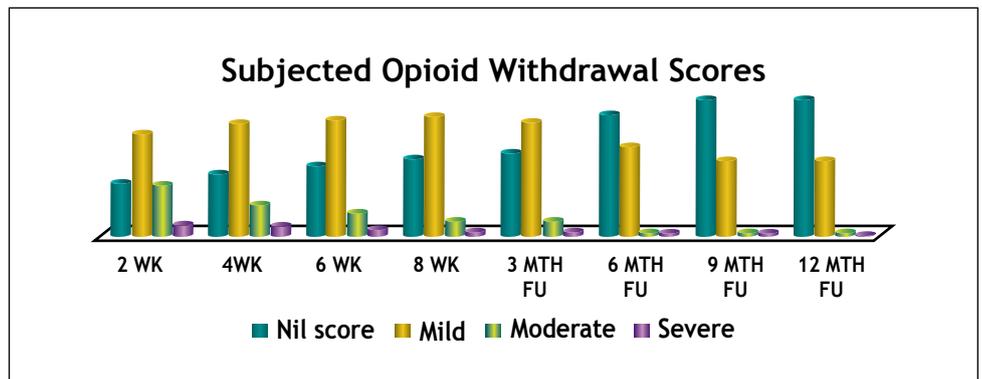
## Opiod Withdrawal Symptoms

It is important to assess the control of withdrawal symptoms by the prescribed dosage of methadone. The subjective and objective opioid withdrawal symptoms were assessed using the Subjective Opioid Withdrawal Scale (SOWS) and Objective Opioid Withdrawal Scale (OOWS).

Table 5: Subjective Opioid Withdrawal Scores

	Two week	Four week	Six week	Eight week	Three month	Six month	Nine month	One year
Nil score	78 24.5%	90 28.8%	100 32.7%	103 36.0%	105 38.3%	128 56.4%	115 62.8%	62 63.3%
Mild (1-10)	150 47.0%	163 52.2%	164 53.6%	157 54.9%	145 52.9%	93 41.0%	64 35.0%	35 35.7%
Moderate (11-20)	75 23.5%	44 14.1%	33 10.8%	21 7.3%	19 6.9%	3 1.3%	2 1.1%	1 1.0%
Severe (21-30)	16 5.0%	15 4.8%	9 2.9%	5 1.7%	5 1.8%	3 1.3%	2 1.1%	0 .0%

Fig 19: Bar diagram showing Subjective opioid withdrawal scores



About one fourth of the respondents experienced no withdrawal at two weeks; this proportion rose to one third of the respondents at six weeks and two thirds at the nine-month follow-up. More than half the respondents experienced mild withdrawal in the initial few months, and one third of them continued to report mild withdrawal at the one-year follow-up. Overall, 71.5 percent reported no/mild withdrawal at two weeks and this percentage increased to 80 percent at four weeks, 86.3 percent at six weeks and 90.9 percent at eight weeks. The percentage of respondents who experienced moderately severe withdrawal declined from 23.5 percent at two weeks to 14.1 percent at four weeks, and saw a further decline thereafter. The percentage of persons who reported severe withdrawals was low, overall, even at two weeks (5 percent).

Table 6: Objective Opioid Withdrawal Scores

OOWS score	Two week	Four week	Six week	Eight week	Three month	Six month	Nine month	One year
Mean±s.d.	3.6± 3.1	2.9±2.8	2.5±2.7	2.0±2.4	1.9±2.5	0.94±1.7	0.8±1.7	0.67±1.4
Median	3.0	3.0	2.0	1.0	1.0	0	0	0
(range)	(0-12)	(0-13)	(0-13)	(0-13)	(0-13)	(0-13)	(0-13)	(0-7)

The severity of objective opioid withdrawals remained low but showed variability with a median score of 3 at two weeks (maximum possible score was 13); this declined to a score of 2 at six weeks, 1 at eight weeks, and was down to a median score of 0 at six months.

### Side effects

Although side effects attributed to methadone were experienced by a large percentage of respondents, most of them were not of serious nature. The side effects reported after the first month include generalized weakness (50.5 percent), craving (38.2 percent), muscle aches (38.2 percent), constipation (36.4 percent), yawning (33.9 percent), anxiety (32.6 percent), lacrimation (28.2 percent), sleeplessness (27.6 percent), confusion (17.2 percent), light headedness (16.3 percent), nausea (14.4 percent), sense of high/happiness (14.4 percent), vomiting (13.8 percent), drowsiness (12.5 percent), blurred vision (11.0 percent), bloating (8.5 percent), loose stools (9.7 percent), giddiness (11.3 percent), double vision (8.2 percent), and some other minor side effects were seen less frequently. Most side effects were related to opioid withdrawal or intoxication. There was no report of death due to overdose at any of the five centres.

### High Risk Behaviours

The High Risk Behaviour Scale (HRBS) gives the drug use and sex behaviour score as well as a total high risk behaviour score. The maximum possible score is 30 in the drug use subscale, 25 in the sexual behaviour subscale, and the maximum possible total score is 55. High variability was observed in the drug use score, which was based on an assessment of injecting risk behaviour in this sample, which is why the median values and range are being discussed. The drug score had a median value of 3 at baseline (range 0-20) and it declined to 0 at the follow-up assessments (range 0-6). The sex score that measures sexual high risk behaviour did not show this variability and had a mean value of 3.53 at baseline. The mean values reduced minimally after the one-year follow-up. The median value of the total high risk score reduced substantially from baseline to three months, continued to decline thereafter, as was evident after the one-year follow-up.

Mean ±S.D. Median (Range)	Baseline	3 months follow-up	6 months follow-up	9 months follow-up	1 year follow-up
Drug Score	3.48 ±3.9 3.0 (0-20)	0.93 ±1.94 0 (0-10)	0.65 ±1.58 0 (0-11)	0.28 ± 0.98 0 (0-7 )	0.11 ± 0.65 0 (0-6)
Sex Score	3.53±1.63 3.0 ( 0-15)	3.57±1.64 3.0 (0-11)	3.32±1.37 3.0 (0-12)	3.09±1.04 3.0 (0- 8)	3.03±1.05 3.0 (0-7)
Total Risk Behaviour Score	7.0 ± 4.3 6.0 (0- 23)	4.5 ± 2.78 3.0 (0- 21 )	3.97 ± 2.02 3.0 (0-14)	3.37 ± 1.56 3.0 (0-12)	3.14 ± 1.23 3.0 (0-9)

Table 7: Scores On High Risk Behaviour Scale

All the respondents had injected at least once in the last three months, at baseline. However, 54.2 percent did not report having injected in the last one month, while 45.6 percent reported injection use in the past month. The frequency of use was less than daily for 29.1 percent, followed by one or more times per day for 16.5 percent. At the three-month follow-up, 92.4 percent were not injecting and this percentage increased in subsequent follow-ups.

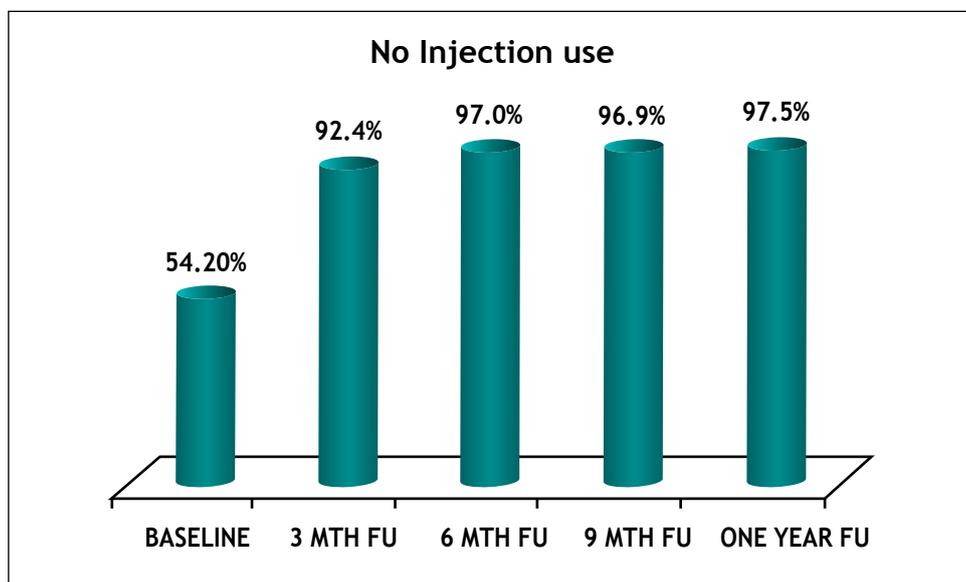


Fig 19: Bar diagram showing no injection use

Injection Sharing Behaviour	Baseline %	Three-monts %	Six-monts %	Nine-monts %	One-Year %
Not used a needle after someone else	82.3	99.6	99.0	100	100
No one used a needle before me	76.0	98.7	98.0	100	100
No one used a needle after me	68.5	96.6	96.0	98.8	100

Table 8: Frequency Of Borrowing And Lending

There was overall a reduction in borrowing and lending with almost no one reporting borrowing and lending at follow-up.

# DISCUSSION

This was the first pilot study to explore the feasibility and effectiveness of methadone in India. It is important to discuss the findings of this project as well as to look at the experiences in implementing it, in order to draw a road map for the future of MMT in India. In this section, we discuss the findings and experiences over the course of the project, along with future implications of scaling up MMT in India from project mode to programme mode.

## THE PROCESS OF IMPLEMENTATION

UNODC has been instrumental in introducing OST (both methadone and buprenorphine) in the South Asian region and making it part of the national programmes, together with the national governments and technical agencies. NDDTC, AIIMS, on the other hand, has had vast experience in using OST medicines for the treatment of opioid dependence as well as in training and research in the area of substance use disorder. The project was built on the combined experience and expertise of both these institutions/agencies. NDDTC, AIIMS was the lead technical and coordinating centre for implementing the MMT project. Four other institutional healthcare centres, with varying degrees of experience and expertise, were also identified as the implementing centres. All four centres (KEMH, Mumbai, RIMS, Imphal, Civil Hospital, Bathinda, and Civil Hospital, Kapurthala) were headed by experienced psychiatrists who had earlier been collaborators with NDDTC, AIIMS in other endeavours. This ensured that the process of implementing the project was smooth and all the stakeholders could work in tandem. Additionally, periodic meetings, visits and email-based consultations helped to ensure coordination.

Right from the outset, the project was planned in a manner that would render it easy to be incorporated in one of the ongoing national programmes, or that it could be scaled up to programme mode after the pilot phase was over. Thus the resources and inputs that went into the project were modest and allocated as per national norms. For instance, the staffing structure at the implementing site was kept at a minimum, in adherence to national programme norms. Similarly, for the process of procurement, the standard norms of government procedures were followed. Such planning ensured that the project did not become just a boutique or showcase project which is difficult to scale up or incorporate into other national programmes.

## EFFECTIVENESS

The data on effectiveness comes from a modest-sized sample. The sample size was determined primarily with logistical and feasibility aspects in mind. Other than NDDTC, AIIMS, none of the other sites had any other ongoing OST programme. Thus, before beginning the project, there were doubts regarding the ability of each project site to recruit a sufficient number of opioid dependent IDUs within the stipulated time frame. Additionally, since this was a pilot study and the investigators at none of the sites had any experience of using methadone, it was decided to restrict the sample size to a manageable level. Hence, a sample size of 50 clients at each site was decided on, and this number proved to be feasible at all the sites. However, the project eventually ended up with a total of 334 clients recruited across all sites. It is realized that in programme mode, the target number of clients who could be served at an MMT centre should be around 100 in order to utilize the resources most optimally as well as to have a public health impact.

Clients who entered the study displayed varying demographic profiles. The mean age ranged between around 26 years at Delhi to 35 years in Imphal. In terms of educational profile, too, the sample in Delhi tended to have the lowest level of education, while Imphal had the highest. Overall, about 55 percent were married and 40 percent were unmarried. About half were employed, though in Delhi, a large majority (80 percent) were unemployed. Thus the project managed to recruit a wide variety of clients from different parts of the country, thereby contributing to the generalizability of the results.

MMT clients differed from each other in terms of drug use parameters as well. Globally, MMT has mostly been provided to opioid dependent individuals, primarily dependent on heroin. In our study, the single largest category was of people injecting buprenorphine (48 percent), followed by heroin users (46 percent), making it a unique study. In fact, a substantial proportion was also using oral pharmaceutical opioids (24 percent) or opium (16 percent).

In terms of the severity of addiction, the highest severity was found in the domain of employment, which is not surprising considering the fact that just about half the clients were employed. Given that overall, just about one third of the clients reported current alcohol use, the alcohol use domain was least impaired, as per the Addiction Severity Index.

In general, retention in the treatment was only modest. Overall, at the one-year follow-up, data could be collected from around 36 percent of the clients who had entered the treatment. Some western studies have reported similar retention rates with MMT, while others have reported higher retention rates (D'Ippoliti et al., 1998; Peles et al., 2008). With buprenorphine-based OST, slightly higher rates of retention have been found in India (Dhawan A et al., 2009).

On the whole, when one compares international literature as well as recommendations of standard practice guidelines, the dose received by most of the clients in this study was on the lower side (Nice technology appraisal guidance, 2007; Federal guidelines for Opioid Treatment, 2013). The low mean dose of 35 mg at the end of one month of treatment is understandable since almost all the clients were going through the phase of induction. However, even from three months onwards and, subsequently, till one year of treatment, the mean and median dose hovered around 40 mg/day. There was a wide range: from a high of 125 mg/day to a low of 5 mg/day. Obviously, some clients were dropping out and then re-entering the treatment and, hence, were on different stages of induction throughout the one-year follow-up period. The experience of OST with buprenorphine in India suggests that the dose requirement for Indian clients is typically lower than that described in literature of western countries. Another interesting learning is that with greater experience of OST implementation, the average dose received by clients keeps increasing. The earliest studies with buprenorphine indicated that clients were maintained at a very low dose, while subsequent and more recent studies point towards a relatively high dose (Dhawan and Sunder, 2008; Rao R et al., 2012).

An indication of the adequacy of methadone dose comes from the data on withdrawal symptoms and side effects. Withdrawal symptoms were assessed much more frequently than other clinical indicators. As the duration of methadone treatment progressed, the proportion of clients reporting withdrawal symptoms declined. Thus, clearly, the dose was adequate to control withdrawal symptoms and, as the data on drug use shows, the dose also succeeded in achieving abstinence from illicit opioid use among most of the clients.

Even though the data on retention shows that just about 36 percent of the clients managed to complete their one-year assessment, those retained in the treatment were largely compliant. The median of the proportion of days that the clients

visited the clinic to receive their daily methadone dose was an encouraging 91 percent. This indicates that while some clients did entirely drop out of the treatment, others who stuck to the treatment kept visiting and taking their daily doses.

Among those who were retained in the treatment, substantial improvement was found. The number of days that heroin or other opioids were used in the prior month was significantly reduced at each of the follow-up assessments and came down to practically zero at the end of the one-year follow-up. The fact of reduced or no opioid use while on MMT, is confirmed by the results of the urine screening. Another way of assessing improvement with MMT is the Quality of Life score. While a majority (62 percent) had reported their quality of life to be poor/very poor at baseline, at one year, as many as 76 percent reported their quality of life to be good/very good. Such improvements in the quality of life of methadone clients have been reported from other Asian countries as well.

Since the outcome data was collected during follow-ups conducted at multiple points in time (after three months, six months, nine months and 12 months of treatment), we have the opportunity to look at the time frame for the changes observed following MMT. Data on ASI indicates marked improvements in most of the domains (except employment) at the three-month follow-up itself. This improvement was not noted in the employment domain, where hardly any improvement was noted throughout the follow-up period. This could be explained by the fact that the Daily Observed Treatment Strategy (DOTS) regimen of MMT prevented many clients from finding gainful employment, though their other problems (such as psychological problems of relationship with the family) were substantially improved. In the quality of life assessment, too, a dramatic improvement was observed at the three-month follow-up, after which the pace of improvement was slightly lower. The overall trend of improvement in quality of life was, however, maintained till the one-year follow-up.

Another important outcome was observed in the area of risk behaviours. The study sample showed dramatic improvement in the behavioural profiles of clients. While about 46 percent had reported injecting in the prior month at baseline, after one year of treatment, only about 3 percent reported so. At baseline, about 18 percent clients had reported borrowing a used needle and 32 percent had reported lending a used needle. This figure was reduced to zero at the one-year follow-up. On the high risk behaviour scale, the scores on drug related behaviour had been modest even at baseline (median score = 3, maximum possible score = 30). At the end of one year of treatment with methadone, this was reduced to zero. In the sex behaviour sub-scale, too, the scores had been low at baseline (median score = 3, maximum possible score = 25) and they remained so throughout the one-year follow-up period.

## IMPLEMENTATION ISSUES

As stated earlier, this being a feasibility study, the project was designed with scalability as an important consideration. Thus, a minimal amount of resources and inputs went into the project in order to assess whether it would be feasible to implement such an intervention in programme mode at a larger scale. Many of the processes followed were similar to the standard procedures for implementing the buprenorphine-based OST programme in India. This was made possible by the fact that the coordinating centre, NDDTC, AIIMS, had been implementing an OST programme of its own and was also instrumental in designing the OST programme for NACO.

The infrastructure requirement for implementing MMT was easily met, with only some refurbishment required at some centres. From the experience of this project, it can be safely surmised that any drug dependence treatment facility that can provide adequate space for a doctor, counsellor, nurse, a dispensing area, waiting area and storage space can host an MMT centre without much difficulty. Among the infrastructure requirements, only storage space for methadone requires special attention as it needs to be properly secured and is subject to inspection by the licensing authorities.

The staff strength for the project was kept at a minimum. While the implementation could be managed without the presence of a doctor exclusively dedicated to the project at four of the sites, it is realized that in future, smooth implementation can only be ensured by the presence of an exclusive doctor at each site. All the implementation sites were managed by senior and dedicated psychiatrists, which may not be the scenario when this programme is scaled-up. Additionally, being in project mode, the patient load at the MMT sites was modest (50 at each site). In programme mode, however, the optimal target would be around 100 clients at each MMT centre. For such a patient load, an exclusive doctor (with a minimum qualification of MBBS) would be essential. The same is true for the required nursing staff. This project managed with a nurse deputed to the MMT clinic from the existing nursing staff at the hospital. For an enhanced load of 100 clients, an exclusive nurse (with a back-up nurse from the general pool) would be necessary. In this project, the counsellor at each clinic doubled up as the research assistant and was tasked with collecting data on research tools, besides providing psychosocial interventions. In the programme phase, one counsellor per site would be necessary just for managing psychosocial interventions.

A variety of methods were employed to recruit clients in the treatment, of which linkages with NGOs providing Targeted Interventions are the most important. Once the critical mass of clients was reached, word-of-mouth publicity ensured a steady flow of new clients at most of the sites. The only exception was KEMH, Mumbai, where, despite the best attempts, the NGO TIs did not manage to refer the adequate number of clients to the MMT centre. Perhaps one of the factors responsible for this was the location of the MMT centre—deep inside the hospital and away from most of the IDU hotspots. This centre did, however, receive requests for MMT enrolment from a large number of non-injecting opioid dependent clients. Thus, one can infer that as a treatment modality for opioid dependence, MMT is likely to be well utilized by a large number of clients.

The threshold for entry into the methadone programme was fairly low. Despite being a research study, the inclusion and exclusion criteria were liberal. In fact, all the exclusion criteria were situations where methadone as a treatment cannot be provided anyway (rather than the exclusion criteria for a research study). Thus, the study sample was fairly representative of the universe of the opioid dependent population in India, and its findings can be generalized.

Service providers found it feasible to follow the guidelines for induction and maintenance. This was made possible by the thorough training programme that all of them had to attend. Subsequent hand-holding was provided through frequent telephone calls, quality assurance and mentoring visits and the annual refresher training. It may be noted here that all the implementing centres were headed by experienced psychiatrists who were generally well versed with the concept of OST. Additionally, the coordinating centre, NDDTC, AIIMS has rich experience in providing training on OST (both buprenorphine and methadone, in India as well as neighbouring countries) and in conducting quality assurance for OST programmes. The rich experience of UNODC in initiating methadone

treatment programmes in neighbouring countries (Bangladesh, Nepal and Maldives) also helped strengthen the initiative in India. Thus, it can be safely said that full technical capacity exists in India for capacity building and quality assurance of MMT, as and when the programme is scaled-up.

Clients, too, largely accepted the induction process well, which involved a gradual increase in the dose of methadone. Importantly, although a large proportion of clients were primarily using a partial agonist (buprenorphine through injecting route) the phenomenon of precipitation of opioid withdrawal (expected upon injecting buprenorphine while being under the influence of methadone) was not observed. Thus, methadone treatment appears suitable for opioid dependent people primarily using a pure agonist (like heroin, which was used by the sample from Delhi and Imphal) as well as a partial agonist (like buprenorphine, which was used by the sample from Kapurthala and Bathinda).

Very few clients among the study sample reached the 'termination' phase of treatment (i.e. a stage where their agonist maintenance treatment was deemed to be complete on the basis of attainment of treatment goals by clients and service providers both). Thus, the experience gained in terminating (gradual tapering of methadone dose to help the clients achieve an opioid free state) is rather limited. Even with this limited experience, however, it can be said that weaning the clients off methadone should be feasible in most routine clinical settings.

A major issue for the methadone programme was the fear of overdose and fatal outcomes related to overdose among MMT recipients. During the course of project implementation, there were one or two instances of overdose among the MMT clients, none of which resulted in a fatal outcome. Even other side-effects reported by the clients were mild in nature, and could be managed at the centre itself. Thus, the study shows that methadone is tolerable to the Indian population.

The package of psychosocial interventions developed for this project was not different from the routine psychosocial interventions provided in any OST program (say, in the buprenorphine-based OST programme for India). Since this was a research study, an attempt was made to standardize this package to bring about uniformity of intervention for all the clients at all sites. The experience from the study suggests that even the counsellors who were relatively inexperienced and did not possess any specific qualification for drug addiction related counselling, could be trained to execute the intervention package. Thus, the kind of human resources expected to be available in the country during scale-up, could very well be trained to implement the routine package of psychosocial interventions.

Thus, in terms of routine clinical aspects of the intervention (recruitment, assessment, medical intervention, psychosocial intervention), no significant challenge was encountered during the course of the project, owing to the past experience with buprenorphine-based OST. One issue that did pose a major challenge was the procurement of methadone. Given that methadone is classified as a scheduled, narcotic drug, stringent regulations have been put in place for its procurement, supply, storage and dispensing. The variation in these regulations in different states added to the problem. It is worth noting that four different states were involved in this project (Delhi, Maharashtra, Punjab and Manipur). In no two states was there any similarity in regulatory mechanisms and procedures. The only uniformity was in the tediousness of going through the procedures for obtaining a license in each state.

This challenge was minimized to some extent by the centralized procurement

## MMT IN INDIA: THE FUTURE

of methadone by NDDTC, AIIMS. Thus, while the supply order originated from one centre (AIIMS, New Delhi), the supplier was instructed to convey the supplies directly to the implementing centre. Despite functioning in project mode, with only five implementing sites, it was a substantial enough challenge to ensure that there was no stock-out situation. In programme mode, with a large number of implementing sites, this will surely be a formidable challenge for whichever agency that adopts the role of national coordinating agency. It is heartening to note, however, that during the project life itself, the NDPS Amendment Bill (2014) was passed. With this amendment the procedures governing essential narcotic drugs (including methadone, for the purpose of treatment of opioid dependence) are likely to be much smoother and, more importantly, are expected to be made uniform throughout the country. As of now, the notification of rules regarding the same is awaited.

A simple system of record-keeping was developed and tested during the project, which ensured that every drop of methadone was accounted for and could be traced from the point of origin to the point of consumption. This system succeeded in preventing diversion and not a single instance of diversion came to light from any of the centres.

This pilot project succeeded in achieving both its objectives viz. establishing that (a) methadone is effective in reducing opioid use and injecting related high risk behaviours in the Indian population; and that (b) it is feasible to implement a MMT programme in India using technical and human resources available and developed from within the country. There is no scope for any kind of hesitation in scaling-up this much required and awaited treatment programme for the lakhs of opioid dependent people in India.

Based upon the experiences of this project, two different approaches to scale-up the MMT programme in India could be recommended:

1. **MMT as a drug dependence treatment intervention (for all opioid dependent people); and**
2. **MMT as a HIV prevention intervention (for opioid dependent injecting drug users).**

It must be noted that these two recommended approaches are not mutually exclusive and could, in fact, also be adopted as two independent programmes.

### 1. **MMT as a drug dependence treatment intervention:**

India has a large network of drug dependence treatment centres (or 'de-addiction centres'). The Ministry of Health and Family Welfare (MOH&FW) has established around 124 such centres in association with medical colleges and civil/district hospitals throughout the country. Among these, the centres that are currently functional (i.e. those equipped with at least the minimum staff and infrastructure required) could potentially become sites for MMT centres. Indeed, along with MMT, such centres could also provide services to people suffering from other substance use disorders.

For this to be realized, some amount of resources as well as technical support and supervision would be required. Financial resources could be provided by the MOH&FW through its Drug De-Addiction Programme and technical expertise could be provided at the national level by NDDTC, AIIMS. Moreover, institutions that are relatively experienced (such as KEMH, Mumbai and RIMS, Imphal) could be roped in to function as regional resource centres. Indeed, some initiatives in this regard have been taken. A programme for establishing Drug Treatment Clinics

(which are expected to provide MMT as well as a host of other interventions) at all five sites of this project is also slated to commence soon.

## 2. MMT as a HIV prevention intervention:

The OST programme of NACO is already on its way to being scaled-up, with about 160 functional OST centres in various government hospitals and NGOs throughout the country, all of which currently provide buprenorphine based OST services. Elaborate mechanisms for capacity building, quality assurance, ensuring uninterrupted supply-chain have already been established. Thus, it should be feasible to incorporate MMT as another type of OST under the OST programme of NACO. Experienced resource institutions such as UNODC and NDDTC, AIIMS (which have provided extensive inputs to the buprenorphine-based OST programme of NACO, and which now have the additional experience of coordinating and implementing MMT) could be roped in to provide technical inputs.

### Areas of future research

There is a need for greater clinical and research experience with MMT in India. The optimum dose for Indian clients can be worked out only after a sizable number of clients, with a variety of clinical profiles and from a variety of places in India, have received MMT. Similarly, it is difficult in the present context to decide between the suitability of buprenorphine versus methadone for each client. It is only with more experience and research comparing both the medications that new insights will emerge.

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# APPENDICES

## List of Tables

Table 1: List of records to be maintained at individual MMT centre and the staff responsible

Table 2: Tools Used In MMT Research

Table 3: Methadone Dose Details

Table 4: Compliance On Methadone

Table 5: Subjective Opioid Withdrawal Scores

Table 6: Objective Opioid Withdrawal Scores

Table 7: Scores on High Risk Behaviour Scale

Table 8: Frequency of Borrowing and Lending

## List of Figures

Fig 1: India map showing Study sites

Fig 2: Methadone Dispenser

Fig 3: Distribution of sample by age groups

Fig 4: Distribution of sample by Educational Status

Fig 5: Distribution of sample by Marital Status

Fig 6: Distribution of sample by Religion

Fig 7: Distribution of sample by Living Arrangements

Fig 8: Bar diagram showing life time and past one month use of injectable opioids

Fig 9: Bar diagram showing life time and past one month use of non -injectable opioids

Fig 10: Bar diagram showing life time and past one month use of other drugs

Fig 11: Bar diagram showing the complications due to substance use

Fig 12: Bar diagram showing retention rate of MMT

Fig 13: Bar diagram showing Heroin use in past one month after starting MMT

Fig 14: Bar diagram showing use of other opioids use in past one month after starting MMT

Fig 15: Bar diagram showing urine screening results

Fig 16: Graph showing addiction severity index domain scores

Fig 17: Graph showing overall quality of life

Fig 18: Graph showing WHOQOL domain scores

Fig 19: Bar diagram showing Subjective opioid withdrawal scores

Fig 19: Bar diagram showing no injection use

